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Assessment Group's Report

Adjunctive colposcopy technologies for assessing suspected cervical abnormalities: a systematic review with meta-analysis and economic evaluation

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

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List of abbreviations

CHE	Centre for Health Economics
CI	Confidence interval
CIN	Cervical intraepithelial neoplasia
CRD	Centre for Reviews and Dissemination
DOR	Diagnostic Odds Ratio
DSI	Dynamic spectral imaging
DYSIS	Dynamic Spectral Imaging System
EIS	Electrical impedance spectroscopy
FN(R)	False negative (rate)
FP(R)	False positive (rate)
HG	High grade
HPV	Human papillomavirus
hrHPV	High-risk human papillomavirus
HSIL	High-grade squamous intraepithelial lesion
HSROC	Hierarchical summary receiver operating characteristic
ICER	Incremental cost-effectiveness ratio
ITT	Intention-to-treat
LBC	Liquid-based cytology
LG	Low grade
LLETZ	Large-loop excision of the transformation zone
lrHPV	Low-risk human papillomavirus
LSIL	Low-grade squamous intraepithelial lesion
NHSCSP	NHS cervical screening programme
NICE	National Institute for Health and Care Excellence
NA	Not applicable
NPV	Negative predictive value
NR	Not reported
PPV	Positive predictive value
QALY	Quality-adjusted life-year
QoL	Quality of life
QUADAS	Quality assessment of diagnostic accuracy studies
RR	Relative risk

Glossary

Acetowhitening: Whitening effect following application of acetic acid to epithelial tissue, used to identify zones of squamous cell change for biopsy.
Adjunctive DYSIS: DYSISmap used as adjunct to DYSIS colposcope
Adjunctive ZedScan: ZedScan used as adjunct to standard colposcope
Cervical intraepithelial neoplasia: Abnormal changes in the squamous epithelial cells of the cervix. This pre-cancerous disorder is graded according to its pathological progress, from CIN1 to CIN3.
Colposcope: An instrument producing an illuminated, magnified view of cervical and vaginal tissues designed to facilitate visual inspection and biopsy of the cervix.
Cost-effectiveness analysis: An economic analysis that converts effects into health terms and describes the costs for additional health gain.
Decision modelling: A theoretical construct that allows the comparison of the relationship between costs and outcomes of alternative health-care interventions
DYSIS: A digital video colposcope using dynamic spectral imaging to assist in detecting cancerous and precancerous cervical tissue.
DYSISmap: A colour coded image of the cervix indicating the intensity of epithelial acetowhitening.
Dyskaryosis: Abnormal cytologic changes of squamous epithelial cells. Synonym to dysplasia. Classified into degrees of severity: low grade (including borderline or mild cellular changes) and high grade (moderate and severe changes).
Electrical impedance spectroscopy: A form of spectroscopy assessing different patterns of electrical conductivity to assess tissue composition.
False negative: Incorrect negative test result – an affected individual with a negative test result.
False positive: Incorrect positive test result – an unaffected individual with a positive test result.
Histology/Histopathology: The microscopic study of tissue samples to enable diagnosis of cancerous and pre-cancerous cells
Human papillomavirus: A type of virus that can infect the skin and the mucuous membranes. Some types of human papillomavirus can cause dyskaryosis in the cells of the cervix and are strongly associated with cancer.
Incremental cost-effectiveness ratio: The difference in the mean costs of two interventions in the population of interest divided by the difference in the mean outcomes in the population of interest.
Index test: The test whose performance is being evaluated.
Liquid-based cytology: A method of preparation for microscopic examination of smear test samples. This method superseded Pap tests in the NHS cervical cancer screening programme.

Markov model: An analytical method particularly suited to modelling repeated events or the progression of a chronic disease over time.

Meta-analysis: Statistical techniques used to combine the results of two or more studies and obtain a combined estimate of effect.

NHS Cervical Screening Programme: The programme set up in the UK aimed at detecting and treating cervical abnormalities and hrHPV infection to prevent future cases of cervical cancer.

Opportunity costs: The cost of forgone outcomes that could have been achieved through alternative investments.

Positive predictive value: Probability that people with a positive test result truly have the disease.

Negative predictive value: Probability that people with a negative test result truly do not have the disease.

Receiver operating characteristic curve: A graph which illustrates the trade-offs between sensitivity and specificity that result from varying the diagnostic threshold.

Reference standard: The best currently available diagnostic test against which the index test is compared.

See-and-treat: The removal of an abnormal area during a colposcopy examination.

Sensitivity: Proportion of people with the target disorder who have a positive test result.

Specificity: Proportion of people without the target disorder who have a negative test result.

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

True negative: Correct negative test result – an unaffected individual with a negative test result.

True positive: Correct positive test result – an affected individual with a positive test result.

ZedScan: A device which utilises electrical impedance spectroscopy to make judgements on the status of cervical tissue

Abstract

Background

DYSISmap and ZedScan I are two technologies that can be used adjunctively with conventional colposcopy which may improve detection of CIN and cancer.

Objectives

To systematically review the evidence on the diagnostic accuracy, clinical effectiveness and implementation of DYSISmap and ZedScan I as adjuncts to standard colposcopy, and to develop a cost-effectiveness model.

Methods

We performed four parallel systematic reviews of: diagnostic accuracy, other clinical effectiveness issues, implementation issues, and economic analyses. We searched MEDLINE and other databases to April 2017 for studies where DYSISmap or ZedScan were used adjunctively with standard colposcopy to detect CIN or cancer in women referred to colposcopy. Risk of bias was assessed with QUADAS-2.

Summary estimates of diagnostic accuracy were calculated using bivariate and other regression models where appropriate. Other outcomes were synthesised narratively.

We developed a de-novo decision model to evaluate the cost-effectiveness of DYSISmap and ZedScan I under either HPV triage or the HPV primary screening algorithm. Sensitivity and scenario analyses were undertaken to explore the robustness of the results to changes in the parameter inputs, structural assumptions of the model and the time horizon.

Results

Eleven studies were included in the diagnostic review (nine of DYSIS, two of ZedScan), three in the clinical effectiveness review (two DYSIS, one ZedScan) and five in the implementation review (four DYSIS, one ZedScan).

Adjunctive DYSIS use was found to have higher sensitivity for detecting CIN2+ lesions (81.25%, 95% CI 72.2 to 87.9) than standard colposcopy alone (57.91%, 95% CI 47.2 to 67.9) but lower specificity (70.40%, 95% CI 59.4 to 79.5) than colposcopy (87.41%, 95% CI 81.7 to 91.5). [redacted]

[redacted]There was very little data on other clinical outcomes associated with DYSIS or ZedScan. The implementation review suggested DYSIS may be acceptable to both patients and clinicians.

The base case cost-effectiveness results showed that adjunctive DYSISmap routinely dominated standard colposcopy (less costly and more effective). The only exception was for HG referrals in a Watchful waiting clinic setting, where the incremental cost-effectiveness ratio (ICER) of DYSISmap varied between £675 and £1095 per QALY under HPV triage and primary protocols. The ICER for ZedScan I varied between £272 and £4922 per QALY. ZedScan I also dominated colposcopy alone for HG referrals in See and treat clinics. These findings appeared robust to a wide range of sensitivity and scenario analyses.

Limitations

Most studies were at high risk of bias. There was no evidence directly comparing ZedScan I with standard colposcopy. No studies directly compared DYSIS and ZedScan. Very little data on participant subgroups was available. There was very limited evidence relating to the clinical effectiveness of adjunctive DYSIS or ZedScan.

Conclusions

The use of adjunctive DYSIS increases sensitivity for detecting CIN2+ when compared to colposcopy alone, so it increases the number of high-grade CIN cases that are detected. However it also reduces specificity when compared to colposcopy, so more women with no or low-grade CIN will be incorrectly judged as possibly having high-grade CIN. The limited evidence precludes any definitive conclusions regarding the diagnostic accuracy of ZedScan I, although it appears, like DYSIS, to increase sensitivity and decrease specificity compared to colposcopy alone. The cost-effectiveness of both adjunctive technologies compared to standard colposcopy, under both the HPV triage and primary screening algorithms, appears favourable when compared against conventional thresholds used to determine value in the NHS.

Plain English Summary

Cervical cancer is the twelfth most common cancer among women in the UK. In order to prevent this cancer women in England and Wales used to receive a cervical smear test, typically every three to five years, although this will be replaced with a human papilloma virus (HPV) test in the future. If a smear test suggests there may be abnormal cells or HPV infection is detected a women will be offered a colposcopy examination. This is a test where a physician visually examines the cervix using a special device called a colposcope to identify areas that may be affected by pre-cancerous changes called cervical intraepithelial neoplasia (CIN). If this is suspected further tests may be performed, or the affected area removed.

DYSISmap and ZedScan are two new methods designed to improve colposcopy. DYSISmap provides a colour coded map to make it easier to identify areas affected by CIN; ZedScan uses a small current applied to the cervix to detect CIN. This report assesses whether DYSISmap and ZedScan are improvements on standard colposcopy, in terms of ability to detect CIN and cancer and in reducing costs. This was achieved by a thorough review of all studies examining the potential benefits of the DYSISmap and ZedScan technologies, and a new model to assess the economic value of using the technologies.

The review found that both DYSISmap and ZedScan successfully detect more women with CIN or cancer, but more women who do not have CIN or cancer will undergo unnecessary further testing or treatment. However the data reported for ZedScan is limited and further studies are needed to confirm its added value.. Although both methods are more expensive to use than standard colposcopy, the additional CIN and cancers cases detected means that both DYSIS and ZedScan are likely to represent good value for money for the NHS.

1 Scientific Summary

1.1 Background

Colposcopy is used to detect cervical intraepithelial neoplasia (CIN) and cervical cancer in women with abnormal results from a cervical smear test or with high-risk human papilloma virus (HPV) infection. DYSISmap and ZedScan I are two technologies that can be used as adjunct to conventional colposcopy which may improve detection of CIN and cancer.

1.2 Objectives

The purpose of this assessment was to assess the clinical and cost-effectiveness of adjunctive colposcopy technologies (DYSIS with DYSISmap and ZedScan I) for assessing suspected cervical abnormalities in people referred for colposcopy as part of the NHS cervical screening programme under either the HPV triage screening algorithm (including test-of-cure), or the HPV primary screening algorithm as recommended for use in the sentinel sites (including test-of-cure).

1.3 Methods

1.3.1 Assessment of clinical effectiveness

Three systematic reviews were conducted. A range of bibliographic sources including MEDLINE and EMBASE were searched from inception to April 2017 for published and unpublished literature.

For diagnostic accuracy outcomes, we included prospective cohort studies of DYSIS with DYSISmap (DYSIS Medical) or ZedScan (Zilico Ltd) reporting sufficient data to allow the calculation of diagnostic accuracy estimates. For clinical effectiveness outcomes, we included any study in which DYSIS with DYSISmap or ZedScan were used that reported relevant clinical outcomes such as adverse events. For implementation outcomes, we considered all publications reporting issues related to implementation of DYSIS with DYSISmap or ZedScan.

For all reviews, the eligible population were patients who were referred to colposcopy through a cervical screening programme due to a suspected abnormality identified via liquid-based cytology, Pap smear test, positive high-risk HPV test. Follow-up referrals were also eligible for inclusion.

The index tests were DYSIS with DYSISmap or ZedScan as an adjunct to colposcopy used for the diagnosis of CIN or cervical cancer. The reference standard was histopathology based on excisional or treatment biopsies.

Two researchers independently screened the titles and abstracts of all reports identified by the bibliographic searches and of all full-text papers subsequently obtained for assessment. Data extraction and quality assessment were performed by at least one researcher and checked by a second. Risk of bias of diagnostic accuracy studies was assessed using a modified version of the QUADAS-2

checklist.

For diagnostic accuracy outcomes, bivariate models were fitted to calculate summary estimates of sensitivity and specificity with 95% confidence intervals (CIs). Additional diagnostic accuracy results that could not be pooled in a meta-analysis, as well as results from studies included in the clinical effectiveness and implementation review were reported narratively.

1.3.2 Assessment of cost-effectiveness

A range of bibliographic databases were searched to identify relevant cost-effectiveness evidence. Only full economic evaluations were considered for review. Study characteristics and design issues were extracted and critically appraised using a published checklist. The main findings of existing economic evaluations were narratively summarised and important structural assumptions and areas of uncertainty highlighted.

The review also informed the development of a *de-novo* decision analytic model (the 'York model'). The York model used a patient-level state-transition modelling approach to estimate the cost-effectiveness of adjunctive colposcopy technologies (DYSIS with DYSISmap and ZedScan I) for people who are referred for colposcopy through the NHS Cervical Screening Programme under either HPV triage (including test of cure) or the HPV primary screening algorithm (including test of cure).

The model provides a link between diagnostic test accuracy and final health outcomes expressed in terms of Quality-Adjusted Life Years (QALYs). This is necessary in order to provide decision makers with an indication of the health gain achieved by adjunctive colposcopy technologies, relative to their additional cost, in units which permit comparison with other uses of health service resources. This requires 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 also includes the impact of the technologies on unnecessary biopsies and excisions which may increase the risk of adverse obstetric outcomes.

The model was populated using results from the systematic clinical and cost-effectiveness reviews, routine sources of cost data, expert clinical opinion and data provided by the manufacturers and other investigators. A time horizon of 60 years (lifetime) was used and costs and outcomes discounted at a rate of 3.5%. A 2015/2016 price year was used.

In the base-case and in scenario analysis, analyses were run separately for each routine screening model (HPV triage protocol and HPV primary protocol), different types of clinic (See and treat, Watchful waiting) and for different reason for referral (all referrals, low grade (LG) and high grade

(HG)). The incremental cost-effectiveness of adjunctive colposcopy technologies (DYSIS with DYSISmap and ZedScan I), compared to conventional colposcopy alone, were determined based on an assessment of long-term NHS and Personal Social Service costs and QALYs. Sensitivity and scenario analyses were undertaken to explore the robustness of the results to changes in the parameter inputs, structural assumptions of the model and the time horizon.

1.4 Results

1.4.1 Diagnostic accuracy

Eleven studies were included in the diagnostic review, including nine of DYSIS, two of ZedScan. Five studies were conducted in England, and one in Wales. Of those, three only included patients referred with high-risk HPV as part of the NHS HPV-primary screening programme.

Only one study was at low risk of bias overall and the remaining ten studies were considered at high risk of bias. Significant applicability concerns were raised for five of the nine DYSIS studies, and for both ZedScan studies.

Adjunctive DYSIS use was found to have higher sensitivity (81.25%, 95% CI 72.2 to 87.9) than standard colposcopy alone (57.91%, 95% CI 47.2 to 67.9) but lower specificity (70.40%, 95% CI 59.4 to 79.5) than colposcopy (87.41%, 95% CI 81.7 to 91.5).

Only two included studies investigated ZedScan. Both were performed by the same researchers in Sheffield. One was a study of the ZedScan I and did not report full diagnostic accuracy results for colposcopy alone. The other was a study of a pre-commercial ZedScan prototype. These issues significantly limited our ability to assess the diagnostic accuracy of ZedScan. [redacted]

Data on participant subgroups, including women with high-risk HPV or high-grade referrals were limited. The results suggested that colposcopy alone has poor sensitivity to detect high-grade CIN in women with low-grade referrals (e.g. mild dyskaryosis). Adjunctive DYSIS and ZedScan appeared to improve diagnosis in low-grade referral cases. There was some limited evidence that the diagnostic accuracy of adjunctive DYSIS may be greater in women with high-risk HPV infection.

Sensitivity analyses identified that the specificity of all methods was strongly dependent on what reference standard was used in women with no colposcope-detected high-grade CIN. Specificity was much higher where no biopsies were performed in those women, suggesting a possible verification bias due to under-diagnosis of high-grade CIN. This means that the actual diagnostic accuracy of

colposcopy and adjunctive colposcopy is uncertain, as it depends on the use of the reference standard. However the comparative results are valid, because any possible bias affects all methods equally.

Test failure rates ranged from 2.9% to 16.7% in studies evaluating a commercial version of DYSIS. The ZedScan I study reported a low test failure rate (5.6%), although this should be interpreted with caution since it excluded patients with non-fully visible transformation zone.

1.4.2 Clinical effectiveness

Three studies (two of DYSIS, one of ZedScan) were included in the clinical effectiveness review and reported very limited data on adverse events. No data were reported on other clinical outcomes, including morbidity and mortality associated with treatment and biopsies or with cervical cancer in studies of DYSIS and ZedScan. No data of outcomes related to health-related quality of life, pain and anxiety using standardised scales were found.

1.4.3 Implementation

Five studies (four of DYSIS, one of ZedScan) were included in the review of implementation, including two in England, and one in Wales. There is some evidence that DYSISmap as an adjunct to colposcopy is generally well received by patients referred for colposcopy (2 studies). There is evidence that adjunctive DYSIS was consistently perceived by clinicians to improve accuracy of colposcopy and confidence in their diagnostic decisions and biopsy site selection (2 studies). There is evidence that additional time required to use ZedScan is minimal in experienced colposcopists. No further evidence was provided for ZedScan.

1.4.4 Cost-effectiveness

Two studies were included in the review of cost effectiveness. One was an independent assessment of the cost-effectiveness of DYSIS developed for the previous NICE DG4 assessment. The other study was a company funded assessment of a prototype version of ZedScan. Neither study fully informed the current decision problem which includes the current HPV triage protocol (including test of cure) and also the proposed HPV primary screening protocol.

The main results of the base case analysis from the York model under HPV triage protocol can be summarised as follows:

- DYSIS routinely dominated colposcopy alone, regardless of the type of clinics or the reason for referral. The only exception was for HG referrals in Watchful waiting clinic setting, where DYSIS was more costly and more effective with an associated ICER of £675 per QALY.

- ZedScan also dominated colposcopy alone in See and treat clinics. However, in Watchful waiting clinics, ZedScan was always more effective than colposcopy alone but also more costly. The ICER for ZedScan in Watchful waiting clinics ranged from £272 (LG referrals) to £4070 per QALY (HG referrals).
- The indirect comparison between ZedScan and DYSIS showed that ZedScan routinely appeared more effective but also more costly than DYSIS. The ICER for ZedScan ranged from £109 per QALY for HG referrals in See and treat clinics to £9918 per QALY for HG referrals in Watchful waiting clinics.

The main results of the base case analysis from the York model under HPV primary protocol can be summarised as follows:

- In most instances, DYSIS dominated colposcopy alone except for HG referral in Watchful waiting clinics where the ICER was estimated to be £1095 per QALY (Table 58).

- Results for ZedScan were more varied. ZedScan only dominated colposcopy alone for HG referral in a See and treat clinic. In all other cases, ZedScan was more effective but also more costly than colposcopy alone. The ICER ranged from £417 per QALY for LG referrals in See and treat clinics to £4922 per QALY for HG referrals in Watchful waiting clinics (Table 59).

- ZedScan was always more effective but also more costly than DYSIS. The ICER ranged from £426 per QALY for HG referrals in See and treat clinics to £8190 per QALY for HG referrals in Watchful waiting clinics (Table 60).

The results appeared robust to a variety of sensitivity and scenario analyses. Only in one of the analyses did the ICER exceed a £20,000 per QALY threshold. This arose in a sensitivity analysis for Zedscan where the diagnostic performance of colposcopy was derived from a separate study to the base case analysis and only for HG referrals in a Watchful waiting clinic.

The York model was specifically developed to address the limitations of existing studies and concerns regarding the generalisability to both the HPV triage and HPV primary screening protocols. The main strength of the decision model is the linkage between the diagnostic accuracy of a given identification strategy, the impact on subsequent treatment decisions and the ultimate effect on health outcomes and costs. There remains uncertainty regarding the cost-effectiveness of ZedScan given the challenges of comparing it to colposcopy. In the absence of a direct comparison between the alternative technologies, an indirect comparison was performed. However, these results should be considered exploratory in nature given the lack of a robust direct comparison and the challenges identified more generally arising from the limitations in the evidence base for ZedScan.

Finally, the cost-effectiveness results presented for the HPV primary screening protocols also require careful consideration. Our analysis is based on the current protocol and that the final HPV primary screening protocol may alter prior to HPV primary screening being rolled out nationally. Furthermore, key input data were derived from unpublished and preliminary results collected in the HPV pilot sites. Data collection is still ongoing and selection issues may limit the generalisability of the data used. Hence, the results under the HPV primary screening protocol should be considered exploratory and further analyses should ideally be undertaken when data collection has been completed and the implications of any selection effect is clearer.

1.5 Discussion

Extensive literature searches were conducted with an attempt to maximise retrieval of potentially relevant studies. These included electronic searches of a variety of bibliographic databases as well as screening of clinical trial registers and conference proceedings to identify unpublished studies. The search strategy did not restrict by study design. The device manufactures and study authors were contacted to provide additional data, and the review includes additional data from published studies and data from as yet unpublished studies. The review process followed recommended methods to minimise the potential for error and/or bias. The quality of the included studies was assessed and accounted for when interpreting the review results. Appropriate synthesis methods were employed by taking into account the heterogeneity of study characteristics.

Only one study of the current version of ZedScan was available, limiting the ability to compare it to colposcopy. No studies directly compared DYSIS and ZedScan. Very little data on participant subgroups was available. In particular there was little data on diagnostic accuracy in women with high-risk HPV.

There was very limited evidence relating to the clinical effectiveness of adjunctive DYSIS or ZedScan, with little reporting of any potential adverse effects.

1.6 Conclusions

The use of adjunctive DYSIS (DYSISmap with DYSIS video colposcope) increases sensitivity when compared to colposcopy alone, so it increases the number of high-grade CIN cases that are detected. However it also reduces specificity when compared to colposcopy, so more women with no or low-grade CIN will be incorrectly judged as possibly having high-grade CIN. This could lead to an increase in the number of unnecessary diagnostic biopsies, excisions and “see and treat” cases, although evidence as to whether this is actually the case is limited. It might therefore increase

unnecessary anxiety, and complications in subsequent pregnancies in women who did not require treatment.

The limited evidence precludes any definitive conclusions regarding the diagnostic accuracy of ZedScan I, although it appears, like DYSIS, to increase sensitivity and decrease specificity compared to colposcopy alone, when using the currently implemented ZedScan I assessment algorithm. There is currently too little evidence to assess whether ZedScan is or is not superior to DYSIS.

The cost-effectiveness of both adjunctive technologies compared to standard colposcopy, under both the HPV triage and primary screening algorithms, appears favourable when compared against conventional thresholds used to determine value in the NHS. However, the limitations and uncertainties in the evidence base identified for ZedScan need to be carefully considered. The cost-effectiveness of both adjunctive technologies under the HPV primary screening protocol should also be reassessed when additional data becomes available from the pilot sites.

Given the limited number of studies of ZedScan, further and well-conducted diagnostic accuracy studies of ZedScan I are needed, particularly to compare its diagnostic accuracy to standard colposcopy, and in groups independent of the manufacturers. Diagnostic accuracy studies comparing DYSIS and ZedScan directly may also be useful.

As most current studies have been in women referred to colposcopy on the basis of cytology screening, diagnostic accuracy studies in women referred from HPV primary screening (or specifically in women with high-risk HPV) are needed to assess whether the new screening programme will alter diagnostic accuracy.

1.6.1 Study registration

The protocol for this review is registered on PROSPERO CRD42017054515

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2 Background

2.1 Description of health problem

In 2014, 3,224 people were diagnosed with cervical cancer in the UK, making it the 12th most common cancer in women, and 890 people died as a result of the disease. More than 80% of people diagnosed with cervical cancer in England and Wales will survive for one year or more and almost 65% will survive ten years or more after their diagnosis.(1) The mortality rate is low due to NHS cervical screening programmes, and because it is preventable if detected in its early stages.(2) However mortality rates are higher for those living in the most deprived areas.

People will develop detectable changes in the cervix many years before progression to cancer. The cells lining the surface of the cervix may go through a series of changes called cervical intraepithelial neoplasia (CIN). The neoplasia is often harmless and may resolve itself without intervention; however, sometimes these changes can become cancerous.(3)

CIN is classified in one of three grades as CIN 1, 2 or 3, according to the depth of abnormal cells within the surface layer of the cervix observed on a diagnostic or excisional (treatment) biopsy:

- CIN 1 – one third of the thickness of the surface layer of the cervix is affected
- CIN 2 – two thirds of the thickness of the surface layer of the cervix is affected
- CIN 3 – full thickness of the surface layer of the cervix is affected

CIN 1 is associated with benign viral replication and in most cases will regress spontaneously.(4) CIN 3 is considered to be pre-cancerous with the potential to progress to invasive cancer. (5) CIN 2 is also generally considered and managed as pre-cancerous, although the average regression rate of CIN 2 to normal/negative hrHPV in adult people is significant, with estimates of 21% over 12 month in a pooled analysis of three studies.(6) and approximately 40% regression over two years in a large US trial.(7)

Cervical cancer typically develops from precancerous changes over a period of 10 to 20 years. The most common types of cervical cancer cases are squamous cell carcinomas (approximately 90%) and adenocarcinomas.(8)

One of the strongest risks factors for cervical cancer is high risk human papillomavirus (hr-HPV) infections. There are around 13 types of hr-HPV.(9)(10) Of those, HPV 16 and HPV 18 are associated with changes in the cervical cells leading to abnormalities (pre-cancerous changes or CIN) which can progress into cervical cancer (around 70% in the UK). However, most HPV infections will not progress to CIN as the virus is usually cleared without any treatment.(11) Certain risk factors are

associated with the progression of HPV infection to CIN; in particular the HPV genotype, smoking, other sexually transmitted infection, early age at first intercourse, and numbers of different sexual partners.(12)

There is evidence to suggest that cellular changes caused by HPV16 may be more apparent on colposcopy examination than cellular changes caused by other hr-HPV genotypes.(13) Therefore the accuracy of colposcopy, and the adjunctive technologies, may differ in these subgroups.

2.2 Current service provision and care pathways

In England, women aged 25 to 49 years of age are offered screening every three years, and women aged 50 to 64 are offered screening every five years under the NHS Cervical Screening Programme (14, 15). If there is an abnormal cytological test result, or symptoms that are suggestive of cervical cancer, women will be referred for colposcopy.

2.2.1 HPV immunisation

Since September 2008 all girls aged 12 to 13 have been offered HPV vaccination against HPV 16 and 18 genotypes (a catch-up programme was initially implemented for girls between 14 and 18 years old).(14) This cohort is now entering the NHS cervical screening programme, but may not be fully protected against HPV 16 and 18. The relative sizes of subgroups with HPV 16 and 18 may change in the future as people who are vaccinated enter the NHS Cervical Screening Programme.

The full impact of HPV vaccination on the screening programme is therefore not fully understood at present, and the prevalence of disease is likely to change over time as partially vaccinated and fully vaccinated cohorts enter screening and colposcopy services.

As HPV immunisation is new, very few immunised people will have entered the cervical screening programme or will have developed CIN or cervical cancer.

2.2.2 Cervical screening

Cervical screening is conducted by taking a sample of cells brushed from the cervix (liquid-based cytology).(14) These cells are tested for possible changes that may or may not develop into cancer. Cytological assessment is performed to detect nuclear abnormalities, referred to as dyskaryosis; which is graded according to severity.(15) Grading systems for cervical cytology differ by country and the current system used in the NHS is shown in Table 1.

Table 1 Cervical cytology reporting terminology

BSCC 1986 (previous NHS system)	ABC3 (current NHS system)	Bethesda system (used in the US)
Inadequate	Inadequate	Unsatisfactory for evaluation
Negative	Negative	Negative for intraepithelial lesion or malignancy
Borderline change	Borderline change in squamous cells	ASC-US: Atypical squamous cells of undetermined significance (ASC-US)
	Borderline change in endocervical cells	
Mild dyskaryosis	Low-grade dyskaryosis	LSIL: Low grade squamous intraepithelial lesion
Borderline change with koilocytosis		
Moderate dyskaryosis	High-grade dyskaryosis (moderate)	HSIL: high grade squamous intraepithelial lesion ASC-H: cannot exclude high-grade squamous intraepithelial lesions (HSIL)
Severe dyskaryosis	High-grade dyskaryosis (severe)	
Severe dyskaryosis suspected invasive	High grade dyskaryosis /?invasive squamous carcinoma	Squamous cell carcinoma
Suspected glandular neoplasia	Suspected glandular neoplasia of endocervical type	Endocervical carcinoma in situ Adenocarcinoma endocervical
	Suspected glandular neoplasia (non-cervical)	Adenocarcinoma: Endometrial Extrauterine Not otherwise specified

Sources: NHS cervical screening programme (2013) (16) and Solomon (2004)(17)

In 2015-16 a total of 4.21 million people aged 25 to 64 were invited for screening of which 3.1 million (around 73%) attended and 3.25 million samples were examined. Of all people with an adequate test, 94.5% had a negative result and 5.5% had an abnormal result (from borderline change through to potential cervical cancer). 1.1% of people tested had a result that showed a high-grade abnormality. (18)

2.2.3 High-risk HPV triage

The current HPV triage management protocols for cervical cytology and management options for patients are outlined in Table 2. Under the high-risk HPV (hrHPV) triage protocol, people whose cervical samples shows borderline change or low-grade dyskaryosis (abnormal cell changes) are given a reflex hrHPV test. If the test is HPV positive, the people will be invited to attend a colposcopy clinic. If the test is HPV negative, they will be returned to routine screening. People with high-grade dyskaryosis or worse are referred straight to colposcopy without an hrHPV test.(15) National implementation of hrHPV triage for people with borderline or low-grade cytology results and hrHPV test of cure was completed in 2013. From 1 April 2014, hrHPV triage has been implemented across England.(19)

Table 2 HPV triage management protocol

Result	Management recommendation
Inadequate - insufficient cells were available for analysis	Repeat in 3 months, refer to colposcopy after 3 consecutive inadequate samples.
Negative - adequate sample with no abnormal cells	Return to routine recall (3 or 5 years depending on age)
Borderline change in squamous cells	Test residual sample for high risk-HPV: High risk-HPV detected – refer for colposcopy High risk-HPV not detected – return for routine recall.
Borderline change in endocervical cells	
Low-grade dyskaryosis	
High-grade dyskaryosis (moderate)	Refer for colposcopy
High-grade dyskaryosis (severe)	
High-grade dyskaryosis/ suspected invasive squamous carcinoma	
Suspected glandular neoplasia of endocervical type	
Suspected glandular neoplasia (non-cervical)	Refer to gynaecology

Source: NHSCSP publication 20(20)

2.2.4 HPV primary screening

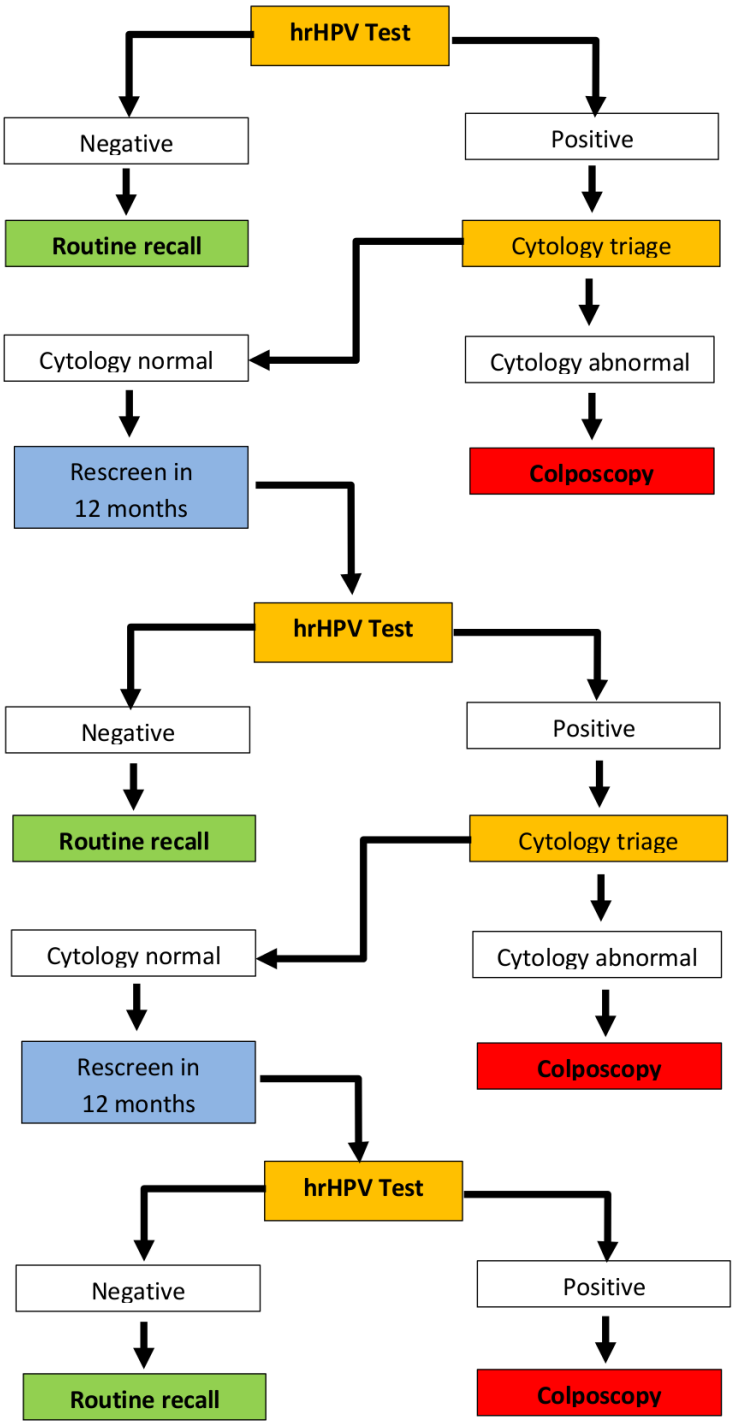
Following the piloting of HPV primary screening which commenced in six sites in England in 2013-2014, (21) the Department of Health announced a change to the cervical screening process in July 2016.(20) In several sites in England, where HPV primary screening was piloted, it has now been adopted as the standard of care.

In HPV primary screening a cervical cytology sample is first tested for the presence of hrHPV, prior to cytology triage. The algorithm for the HPV primary screening pilots is shown below in Figure 1. In general, primary screening with hrHPV testing detects over 90% of all cases of CIN2, CIN3, and invasive cancer. It is reported as 25% more sensitive in detecting borderline changes or worse compared to liquid-based cytology, though it is about 6% less specific.(22)

Where genotyping tests are used, people testing HPV 16 or 18-positive and cytology-normal at baseline and at their first 12 month follow up test can be referred to colposcopy without further repeat tests.

The patient group of interest for this assessment is people referred for colposcopy through the NHS Cervical Screening Programme under HPV triage screening algorithm (with test of cure) or HPV primary screening algorithm as currently recommended for use in pilot sites (with test of cure). People 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.

Figure 1 HPV Primary Screening algorithm (pilot sites)



Adapted from: Public Health England (23)

2.2.5 Colposcopy management and treatment

Standard binocular colposcopy, with directed biopsy/treatment when necessary, is the current usual management for people referred with abnormal cytology results. The colposcopist applies solutions such as acetic acid or Lugol's iodine, to the surface of the cervix. These help to highlight any areas of abnormality on the cervical epithelium. Video colposcopy may also be used, particularly for DYSIS where the DYSISmap is overlaid onto a video colposcopic image, and it is unlikely that a separate binocular colposcopy will be performed.

Colposcopy involves a significant amount of subjective assessment and the final histological diagnosis depends on the training, experience, and the volume of patients seen and also the ability of the colposcopist to identify the most appropriate sites for biopsies.(24-26) (25-27) (25-27) (24) (25) (26) Details of referral cytology results, HPV status, other clinical information, the type of management available, and the number of biopsies taken may also be relevant when interpreting the results of colposcopy.

NHSCSP publication 20(15) recommends that where successful colposcopy has been performed the positive predictive value to detect high-grade lesions (CIN2+) should be at least 65%. It also recommends that treatment at first visit to colposcopy should not be offered to patients referred with borderline or low-grade dyskaryosis. It also recommends that unless an excision is planned, a diagnostic biopsy should be performed when cytology results indicate high-grade dyskaryosis (moderate) or worse, and always when a recognisably atypical transformation zone is observed. In some circumstances, such as the presence of low-grade colposcopic change and high grade dyskaryosis (severe), an excisional form of biopsy (rather than punch biopsy) is recommended.

Results of biopsies are used to guide treatment decisions. Typically, areas of CIN2 or worse would usually be treated, although CIN2 may be managed more conservatively if only part of the transformation zone is affected, and in younger women who have not completed their family. Treatment options during the colposcopy examination include excising the area of abnormal cells, If an abnormality is detected during the colposcopy examination, the colposcopist may treat an abnormality during the first clinic appointment ("see and treat") by excising the area of abnormal cells where high grade changes are suspected, or in rarer cases, by destroying them in situ (ablation).(15)

The aim of excision is to remove all abnormal tissue. Excision is usually performed with a thin electrically-heated looped wire in a procedure called a large loop excision of the transformation zone (LLETZ) under local anaesthesia. The excised tissue is sent to histopathology to confirm the extent of the abnormality and inform further management. In some cases, notably where glandular abnormalities are present (CGIN), a deeper excision (cone biopsy) is required which is likely to be

performed under general anaesthesia. The depth of the excision depends on the nature of the cervical transformation zone.(15)

A number of ablative techniques exist, including laser ablation, cryocautery and cold coagulation. NHSCSP publication 20 recommends that ablative treatments are only performed when the entire transformation zone is visible, there is no evidence of glandular abnormality or invasive disease, and there is no major discrepancy between cytology and histology.

If cervical cancer is identified, treatment options include cone biopsy (very early stage), trachlectomy, hysterectomy, radiotherapy and chemotherapy. Conservative treatment may also be offered. Further details are reported elsewhere.(27)

2.2.5.1 NHS colposcopy and treatment

There were 188,179 referrals for colposcopy in 2015-16; 65.6% of these were as a result of screening and 23.1% were clinically indicated, 11.3% were referred for other reasons (e.g. CIN treatment follow-up). In 2015-16, 61% of all people referred to colposcopy in England underwent a procedure or treatment at their first appointment. Diagnostic biopsy was the most common procedure (47%), followed by an excision (12%). Only a small percentage of all referrals underwent ablation (0.6%).(18)

Treatment patterns vary significantly at local and regional level. In 2015-2016, the percentage of all women receiving some treatment or procedure in England at their first appointment ranged from 53.5% in the North West to 70.5% in the North East. For people diagnosed with high-grade abnormalities, the percentage of patients who received a diagnostic biopsy ranged from 21.7% in the West Midlands to 71.1% in London; for low-grade abnormalities, rates ranged from 51.6% in the East to 80.9% in the North East. The percentage of patients with high-grade abnormalities who underwent excision ranged from 11.6% in London to 65.4% in the North West. However, it is likely that most people presenting with high-grade abnormalities and reported as having either no treatment or a diagnostic biopsy at their first attendance went on to receive therapeutic treatment at a subsequent appointment.(18)

2.2.6 Follow-up and test of cure

Post-colposcopy follow-up depends on whether treatment has been performed or whether surveillance has been recommended. Surveillance can be done within the colposcopy service or within the community.

NHSCSP publication 20 recommends that people referred with low-grade dyskaryosis or less and hr-HPV positive who have a satisfactory and normal colposcopic examination can be returned to community-based recall.(15) People with a low-grade lesion based on colposcopy may be followed up at 12 months in the colposcopy clinic or the community. If the lesion has not resolved within two years of referral to colposcopy a biopsy should be taken. For people referred with high-grade dyskaryosis who do not have treatment, surveillance with colposcopy and cytology at 6 months is recommended even if no abnormality is seen with colposcopy. For patients who are not treated following a colposcopic diagnosis of a low-grade lesion, multiple directed biopsies should be performed. Treatment is recommended for people with high-grade cytology at follow-up,

Where CIN1 or less is confirmed, colposcopy and cytology at 6 months is recommended. Follow up for people referred under the HPV primary screening pilot algorithm is described in more detail elsewhere.(28)

Under the hr-HPV 'test of cure protocol', patients who have previously received treatment for CIN (all grades) are invited for screening six months after treatment for a repeat cervical sample in the community (Figure 2). Under HPV triage, a woman whose sample is reported as negative, borderline change, or low-grade dyskaryosis is given an hr-HPV test. If the HPV test is negative, the woman is recalled for a screening test in three years (irrespective of age) and can be returned to routine recall if the subsequent cytology test result is negative. Hr-HPV positive patients are referred back to colposcopy. People whose cytology is reported as high-grade dyskaryosis or worse are referred straight to colposcopy without an hr-HPV test.(15) Under HPV primary screening, test of cure differs and is described in the NHS cancer screening programme's pilot.(28)

During 2015-16 in England, a total of 433,624 appointments were reported at colposcopy clinics, of which 163,859 (37.8%) were follow-ups.

2.2.7 Current service cost

Currently the NHS spends around £21million a year to treat cervical cancer, mostly from women diagnosed at stage 2 (the cancer has grown beyond the cervix and uterus, but has not spread to the walls of the pelvis or the lower part of the vagina) or above.(29)

2.3 Description of technologies under assessment

Following a previous diagnostic assessment report (DG4)(30), NICE Diagnostics guidance (DG4)(31) recommended using DYSIS as an adjunct to colposcopy. ZedScan, previously known as APX100, was not included in the final guidance as it had not received its CE mark prior to publication. Both DYSIS and ZedScan are now being used in several hospitals in England and Wales.

DYSIS with DYSISmap (DYSIS Medical)

The Dynamic Spectral Imaging System (DYSIS) is a high resolution digital video colposcope. It also uses spectral imaging technology and an inbuilt algorithm to produce an adjunctive map of the cervical epithelium which is known as the DYSISmap (or pseudo-colour imaging). The DYSISmap is intended to be used as an adjunct to colposcopy to assist clinicians in the diagnosis, biopsy and treatment of CIN.

DYSISmap maps the whitening effect following application of acetic acid (aceto-whitening) on the epithelium of the cervix, to aid diagnosis, as well as 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 DYSISmap is produced during the period of the aceto-whitening reaction. An inbuilt algorithm assigns each area of the cervix a colour on the DYSISmap which corresponds to the likelihood of an abnormality being present. The DYSISmap is displayed on the screen, overlaid on a live image of the cervix. The colour spectrum ranges from cyan which represents weak aceto-whitening to white which represents intense aceto-whitening; the greater the intensity of the measured aceto-whitening reaction, the greater the likelihood of an abnormality. Imaging typically takes 3 minutes, and the average duration of use per examination is less than 15 minutes.

The manufacturer claims that new users can be trained to use DYSIS in 2–4 hours.[personal communication] Imaging takes 3 minutes and it can be stopped manually, however the company recommends at least 125 seconds of imaging to allow the system to calculate and display the DYSIS map.(32) The list price for the latest version of DYSIS (DYSIS Touch colposcope) is £24,000.[personal communication] This is around twice the cost of a standard colposcope. The 5 years maintenance plan is an additional £6500, and the viewer licence is £650 in the first year and £500 per year in the following years. DYSIS includes a colposcope and no additional equipment is needed. Costs for specula are £3.50 per examination. (33)

DYSIS is CE marked and is developed by DYSIS Medical. The currently available version of DYSIS is DYSIS version 3, but the company intends that it will be superseded by the DYSIS touch and

DYSIS ultra colposcopes in early 2017. Each updated version of the system has had modifications to both the hardware and software, but the DYSISmap algorithm has remained unchanged.

ZedScan I (Zilico)

ZedScan is an electrical impedance spectroscopy (EIS) device. It is designed to be used as an adjunct to colposcopy to aid in the diagnosis, biopsy and treatment of high-grade CIN. It applies a small alternating current at different frequencies to the cells lining the cervix and measures the resulting voltage. By using electrical impedance spectroscopy, it measures the resistivity of cervical epithelial cells to distinguish between normal and abnormal tissue. Electrical impedance is measured at 14 different frequencies and a spectrum is produced which varies according to the structure and properties of the tissue. The degree of impedance is related to tissue structure, which is classed as normal, pre-cancerous or cancerous. A handset displays a diagram of the measurement zone by coloured circles which indicate the location and results from each measurement point.(34)

- Clear/white – no reading
- Green - high-grade CIN is unlikely to be present
- Amber – high-grade CIN is likely to be present
- Red – the highest likelihood that high-grade CIN is present

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 device is also designed to indicate the location of high-grade CIN for biopsy.

The manufacturer estimates that each cervical scan using the ZedScan takes 2–3 minutes. The device can also be used in a single point mode to help select sites for diagnostic biopsy after the initial 10-12 readings have been taken. The manufacturer states that it takes approximately 2 hours to train the new users. ZedScan is CE marked and is developed by Zilico Ltd. ZedScan was previously known as APX100, which was the name used in the previous assessment (DG4). The ZedScan costs £3000, including computer software. The cost per case with the ZedScan is approximately £30 plus clinician time. There are no routine maintenance costs.

The previous assessment (DG4)(30) found evidence to suggest that DYSIS with DYSISmap had higher sensitivity but lower specificity than colposcopy alone for detecting CIN2+ disease, and limited evidence for other adjunctive technologies (LuViva and Niris).

3 Definition of decision problem

Women in England between the ages of 25 and 64 are invited for regular cervical screening every three to five years in order to detect abnormal cells in the cervix. Screening is conducted using liquid-based cytology; women may also be tested for high-risk human papillomavirus.

Depending on the results of the cervical screen, people may be referred for a colposcopy examination. Colposcopy is largely a subjective examination, and diagnosis will partly depend on the opinion and expertise of the colposcopist. The DYSIS digital video colposcope with DYSISmap (DYSIS Medical) and the ZedScan I device (Zilico Ltd) have been developed to be used alongside colposcopy. They aim to help the colposcopist to find abnormal cells more accurately. The DYSIS system provides a coloured map of the cervix on a computer screen, where different colours show different risks of there being abnormal cells. ZedScan uses an electrical current to distinguish between normal and abnormal cells, and shows coloured circles on a diagram ranging from green (low risk of abnormal cells) to red (high risk).

These technologies have previously been reviewed in the DG4 assessment (30). However, additional information on the technologies and recent changes in the NHS cervical screening programme mean that the relative value of using these new tests is uncertain.

This report, undertaken for the NICE Diagnostics Assessment Programme, examines the clinical and cost effectiveness of DYSISmap and ZedScan used adjunctively alongside regular colposcopy for women referred for colposcopy as part of the cervical cancer screening programme.

3.1 Decision problem in terms of PICOS and other key issues

The primary population of interest is women referred for colposcopy as part of the NHS cervical screening programme under either:

- The HPV triage screening algorithm (including test of cure), or
- The HPV primary screening algorithm as recommended for use in the sentinel sites (including test of cure).

All women who have been referred to colposcopy on the basis of a positive cytology test or because of the presence of high-risk HPV infection will be considered, bearing in mind that, outside the UK, algorithms for deciding who should be referred for colposcopy may differ from those listed above.

The tests of interest are the DYSISmap system (DYSIS Medical), which generates a coloured map representing the level of aceto-whitening of the cervix, and ZedScan I (Zilico) which uses electrical impedance spectroscopy to detect abnormal cervical tissue. Both technologies should be used

alongside standard colposcopy; DYSIS video colposcopy is used with DYSISmap and binocular colposcopy with ZedScan. The combination of tests is referred to as adjunctive colposcopy.

The key comparator of interest is standard colposcopy alone, whether using a binocular or video colposcope.

When assessing diagnostic accuracy the accepted reference standard is histopathological diagnosis of CIN or cancer based on cells extracted from the cervix by punch biopsy or excision.

Key outcomes of interest are the diagnostic accuracy of adjunctive colposcopy (i.e. sensitivity, specificity and related measures), its clinical effects, ease of implementation and cost-effectiveness. Given this any prospective study reporting data on any of these outcomes was considered for inclusion in this review.

3.2 Overall aims and objectives of assessment

The aim of the project is to determine the clinical and cost-effectiveness of adjunctive colposcopy technologies (DYSISmap and ZedScan I) for assessing suspected cervical abnormalities in people who are referred for colposcopy through the NHS Cervical Screening Programme under either HPV triage (including test of cure) or the HPV primary screening algorithm (including test of cure). To achieve this, the following objectives are proposed:

1. To perform a systematic review and meta-analysis of the diagnostic accuracy of adjunctive colposcopy technologies (DYSISmap and ZedScan I) in conjunction with standard colposcopy for the examination of the uterine cervix of the people who are referred for colposcopy
2. To perform a systematic review of the clinical impacts and implementation of adjunctive colposcopy. This will include assessment of the associated mortality and morbidity, patient-centred outcomes, adverse events, acceptability to clinicians and patients and compliance.
3. To perform a systematic review of published cost-effectiveness studies of adjunctive colposcopy technologies (DYSIS with DYSISmap and ZedScan I) for assessing suspected cervical abnormalities in people who are referred for colposcopy.
4. To develop a decision model to estimate the cost-effectiveness of adjunctive colposcopy technologies (DYSIS with DYSISmap and ZedScan I) for people who are referred for colposcopy through the NHS Cervical Screening Programme under either HPV triage (including test of cure) or the HPV primary screening algorithm (including test of cure).

This report is considered in two parts: Clinical effectiveness (covering objectives 1 and 2) is discussed in Section 4. Cost effectiveness (objectives 3 and 4) is discussed in Sections 5 and 6.

4 Assessment of Clinical Effectiveness

The review of clinical effectiveness of adjunctive colposcopy was broken down into the following three systematic reviews.

1. A review of the diagnostic accuracy of adjunctive colposcopy technologies (DYSISmap and ZedScan I) in conjunction with standard colposcopy for the examination of the uterine cervix of the people who are referred for colposcopy
2. A review of the clinical effects of adjunctive colposcopy technologies, including assessment of the associated mortality and morbidity, patient-centred outcomes, adverse events
3. A review of the implementation of adjunctive colposcopy technologies, including acceptability to patients and clinicians.

The methodology of these reviews is described below.

4.1 Methodology of the clinical effectiveness review

The systematic reviews were conducted following the general principles recommended in the Centre for Reviews and Dissemination (CRD) guidance (35), and the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement (35).

4.1.1 Searches

The literature searches aimed to systematically identify research related to the clinical and cost effectiveness of DYSIS with DYSISmap and ZedScan.

The search strategy was developed in MEDLINE (Ovid) and was based on the search strategy used for the previous HTA review of adjunctive colposcopy by Wade (2013).(30) The original strategy was checked and updated to reflect the changed scope of the current review. Updates were also necessary to account for changes to the database search interface or provider and where new subject headings had been introduced or changed since the date of the previous searches.

The strategy consisted of a set of terms for cervix, which were combined using the Boolean operator AND, with a set of terms for the two adjunctive colposcopy technologies. A date limit was applied to the search strategy to restrict retrieval to those studies published since 2000. No further limits relating to language or study design were applied. The MEDLINE strategy was adapted for use in all other resources searched.

The searches were carried out during January 2017, with a further update search undertaken on 10th April 2017. The following databases were searched: MEDLINE (including: Epub Ahead of Print, In-

Process & Other Non-Indexed Citations, Ovid MEDLINE Daily and Ovid MEDLINE), Cochrane Central Register of Controlled Trials **(**CENTRAL), Cochrane Database of Systematic Reviews (CDSR), CINAHL Plus, Database of Abstracts of Reviews of Effects (DARE), EMBASE, Health Management Information Consortium (HMIC), Health Technology Assessment (HTA) Database, NHS Economic Evaluation Database (NHS EED), PubMed and the Science Citation Index.

In addition, ongoing studies, and unpublished and grey literature was identified using the following resources: ClinicalTrials.gov, Conference Proceedings Citation Index: Science, EU Clinical Trials Register, PROSPERO, WHO International Clinical Trials Registry Platform portal, technology manufacturer websites, and Health and Social Care Information Centre (HSCIC) data. Data was requested and obtained from the NHSCSP HPV screening pilot (Sentinel Sites). Data submitted to NICE by manufacturers as a part of this assessment was also used. Abstracts from recent relevant conferences, including the British Society for Colposcopy and Cervical Pathology (BSCCP) and the International Federation for Cervical Pathology and Colposcopy (IFCPC) were also consulted.

Relevant guidelines were identified through searches of the following resources: National Institute for Health and Clinical Excellence (NICE), NHS Evidence, National Guideline Clearinghouse, Scottish Intercollegiate Guidelines Network (SIGN), Public Health England, British Society for Colposcopy and Cervical Pathology (BSCCP), Royal College of Obstetricians and Gynaecologists, and the TRIP database.

Search results were imported into EndNote X8 (Thomson Reuters, CA, USA) and deduplicated against the results from the previous 2013 HTA review of adjunctive colposcopy.(30) Full details of search strategies can be found in Appendix 10.1.

Additional searches

Due to the lack of evidence found in the review of clinical effectiveness, additional pragmatic PubMed searches were conducted to identify recent systematic reviews reporting on the adverse effects of CIN treatments on fertility, pregnancy and neonatal outcomes.

4.1.2 Selection criteria

Two researchers independently screened the titles and abstracts of all reports identified by the bibliographic searches and full-text papers were subsequently obtained for assessment and screened by at least two researchers. Disagreements were resolved by consensus.

4.1.2.1 Types of studies

Diagnostic Accuracy

Prospective cohort studies in which the index test (DYSISmap or ZedScan performed as an adjunct to colposcopy) and reference standard test (histopathology) were performed independently in the same group of participants, and which reported sufficient data to calculate diagnostic accuracy (sensitivity and specificity).

Effectiveness and implementation

Any experimental or observational study where adjunctive DYSIS and/or adjunctive ZedScan testing was used were included. Since no studies included a parallel control group which underwent standard colposcopy alone, non-comparative studies that only recruited people who received adjunctive colposcopy were included.

The following types of report were excluded: editorials and opinions, case reports, reports focusing only on technical aspects of the technologies (such as technical descriptions of the testing process or specifications of machinery). Where multiple reports for a particular study were identified, all studies were included, with the most recent or most complete report included as the main study selected for inclusion. Authors of studies were contacted in cases where the most appropriate paper for inclusion was unclear.

4.1.2.2 Participants

Eligible studies included participants who were referred to colposcopy through a cervical screening programme due to a suspected abnormality identified via liquid-based cytology, Pap smear test, or positive hrHPV test. People referred for colposcopy as follow-up after a previous CIN diagnosis (including test-of-cure) were also eligible for inclusion.

4.1.2.3 Intervention

DYSISmap (DYSIS Medical) or ZedScan I (Zilico Ltd) as an adjunct to binocular or video colposcopy used for the diagnosis of CIN or cervical cancer was the intervention of interest. Studies on all versions of these tools (including prototypes) were considered for inclusion.

4.1.2.4 Comparators

Standard colposcopy was the comparator of interest; however, data from standard colposcopy alone did not need to be reported for a paper to be eligible. Both binocular and video colposcopy were included.

4.1.2.5 **Reference standard**

Histopathology based on excisional or treatment biopsies, used to classify samples into three CIN grades or cervical cancer.

Studies that did not perform biopsies to confirm absence of disease where colposcopic examination did not reveal any abnormalities were included.

4.1.2.6 **Outcomes**

The following outcomes were eligible for inclusion:

- diagnostic accuracy: including sensitivity and specificity, or sufficient data to calculate these
- test failure rates (and reasons for test failure)
- number of biopsies (and type) performed
- diagnostic results of biopsies
- number of treatments and treatment type
- number of 'see and treat' procedures
- duration of colposcopy examination
- number of people discharged from colposcopy

Eligibility depended on the study reporting results from both the index test and the reference standard. Only studies reporting results in terms of graded CIN, differentiating between mild dysplasia or less (≤CIN 1 i.e. negative diagnostic result), and moderate dysplasia or worse (CIN 2 or greater, i.e. positive diagnostic result) were included.

The following clinical outcomes were also eligible:

- morbidity and mortality associated with treatment and biopsies conducted as part of the colposcopy examination (including subsequent obstetric outcomes such as miscarriage and infertility)
- morbidity and mortality associated with cervical cancer (in studies of DySIS and ZedScan)
- health-related quality of life (HRQoL)
- pain and anxiety associated with colposcopic examination, biopsies, treatment and waiting for results
- any other adverse event that may have an impact on resource use or quality of life (e.g. infection, infertility, miscarriage)

Outcomes related to the implementation of the interventions of interest and related practical issues were eligible:

- Acceptability of the adjunctive technologies (to clinicians and patients)
- Patient satisfaction
- Successful database and record management
- Training requirements
- Capacity to perform colposcopies
- Uptake and compliance

4.1.3 Data extraction

A standardised data extraction form was designed, piloted and finalised to extract data relating to study design, patient characteristics, index, comparator, and reference standard tests, and outcome data were extracted by one reviewer and independently checked for accuracy by at least one other reviewer. Disagreements were resolved through discussion until consensus was achieved, or with involvement of an additional reviewer if necessary.

For studies reporting diagnostic accuracy data, the number of true positives, true negatives, false positives and false negatives for each index test evaluated in each study were extracted to construct 2 x 2 tables. Otherwise, we calculated the number of true positives, true negatives, false positives and false negatives from the summary estimates of sensitivity and specificity of the index test, if available. Where available, the number of patients in diagnostic categories (normal, CIN1, CIN2, CIN3, or cancer) was also extracted. Where only a subgroup of patients included in a study was eligible, we extracted, analysed and presented data for this subgroup only. Manufacturers and corresponding authors were contacted for all included studies to obtain additional data on diagnostic accuracy.

Diagnostic accuracy data were extracted using Excel software. Data on study characteristics, and results informing the reviews of effectiveness and implementation were extracted using EPPI Reviewer.

4.1.3.1 Additional data from manufacturers and study authors

For all studies additional data on diagnostic accuracy were requested. Requests were made to device manufacturers (DYSIS Medical or Zilico) for studies in which they had direct involvement, or to the first author of the primary publication where manufacturers were not involved in the study.

Diagnostic accuracy data for both colposcopy and adjunctive colposcopy (with either DYSISmap or ZedScan) were requested as a 5x5 table, with results categorised as <CIN1, CIN1, CIN2, CIN3 and cancer. Also requested were 2x2 tables of diagnostic accuracy in the following participant subgroups:

- Participants with high risk HPV (HPV 16/18)
- with low risk HPV or no HPV infection
- referred to colposcopy with high grade dyskaryosis or worse
- referred to colposcopy with low grade dyskaryosis or less
- with a previous history of CIN or cervical cancer (including test-of-cure)

4.1.4 Critical appraisal

Risk of bias of all included studies included in the diagnostic accuracy review was performed using a modified version of the Quality Assessment tool of Diagnostic Accuracy Studies (QUADAS-2) checklist. The modified version of the QUADAS-2 tool used in Wade (2013)(30) and further described elsewhere (36) to assess risk of bias in comparative diagnostic accuracy studies (i.e. a comparison of the index test with both standard care and the gold standard) was used. Futher questions were added to inform judgments about study quality in the following domains: index/comparator test, flow and timing, and other concerns. Further details are presented in Appendix 10.7. The quality of survey studies included in the implementation review was assessed using guidance from Burns (2008)(37) and Center for Evidence Based Management (2014).(38) Due to the limited evidence the quality of studies included in the effectiveness review were not formally assessed.

Risk of bias assessments were performed by one reviewer, and independently checked by a second. Disagreements were resolved through consensus, and if necessary, a third reviewer was consulted.

4.1.5 Methods of data synthesis

4.1.5.1 Statistical analyses

Estimates of sensitivity and specificity were calculated using diagnostic accuracy data from the constructed 2x2 tables or the 5x5 tables supplied by manufacturers, and presented as both forest plots and in the receiver operating characteristic (ROC) space to examine the within and between study variability of diagnostic test accuracy. Positive and negative predictive values were also calculated, as were diagnostic odds ratios.

Where equivalent clinical thresholds were used to diagnose CIN/cancer in three or more studies, the hierarchical bivariate model described by Reitsma (2005)(39)was fitted, providing summary estimates of sensitivity and specificity, and associated 95% confidence intervals. The hierarchical summary ROC (HSROC) model (40) was also fitted to provide summary ROC curves. As the bivariate model

does not account for the fact that different diagnostic tests may be performed in the same study further logistic regression analysis (41) was performed to meta-analyse sensitivity and specificity accounting for the fact than standard colposcopy and adjunctive colposcopy were performed on the same participants. Unless otherwise specified, all analyses used the threshold of CIN2 of higher as the cut-off for defining a positive diagnostic test.

If at least two studies reported on the same clinical or implementation outcome, results were pooled if reporting was consistent enough for feasible analysis; otherwise, results were synthesised narratively. Meta-analyses were performed using standard random-effects DerSimonian-Laird methods.

Analyses were conducted in the R software package.

Investigation of heterogeneity and subgroup analyses

Visual inspection of forest plots and ROC space was performed to check for between-study heterogeneity of diagnostic accuracy results. Sources of heterogeneity were investigated by performing meta-analyses of diagnostic accuracy within defined study subgroups, and, where there were sufficient studies, by incorporating covariates in the logistic regression models of diagnostic accuracy. Heterogeneity was assessed using the I^2 statistic and through visual inspection of forest plots. Subgroup analyses and meta-regression were used where feasible. The following potential sources of heterogeneity were accounted for in the interpretation of the results:

- Presence of high-risk HPV genotype, stratified by: HPV16+; other high-risk HPV; and no high-risk HPV
- Cytology results, stratified by: low grade dyskaryosis or less; and high-grade dyskaryosis (moderate) or worse
- People with a previous diagnosis or history of CIN or cervical cancer

Sensitivity analyses

Study quality based on QUADAS domain results was planned as a basis for conducting sensitivity analyses for diagnostic accuracy studies. This involved exclusion of studies thought to have a high risk of bias in each particular domain, using this to explore the robustness of results. Results from the Cochrane risk of bias tool, and study date (reflecting improvements in technology) were also used as a basis for analyses.

The impact of excluding studies which only performed biopsies in those patients with suspected high-grade lesions (rather than in all patients) was explored.

Studies suspected of recruiting a substantial proportion of its population from another study cohort were excluded from analysis to examine the effect of overlap on outcomes. Only the study with the most reliable or complete reporting was included in the main analyses.

4.1.5.2 **Narrative and qualitative syntheses**

Qualitative synthesis was performed for outcomes pertaining to implementation. Summary information relating to implementation outcomes, the conclusions of these studies, consequences of colposcopy, recommendations for practice, and suggested needs for further research were tabulated and summarised.

Narrative summaries were also performed for outcomes where meta-analyses or other statistical analyses were not deemed feasible. This included tabulation or plotting of results as reported, which were then narratively described and compared.

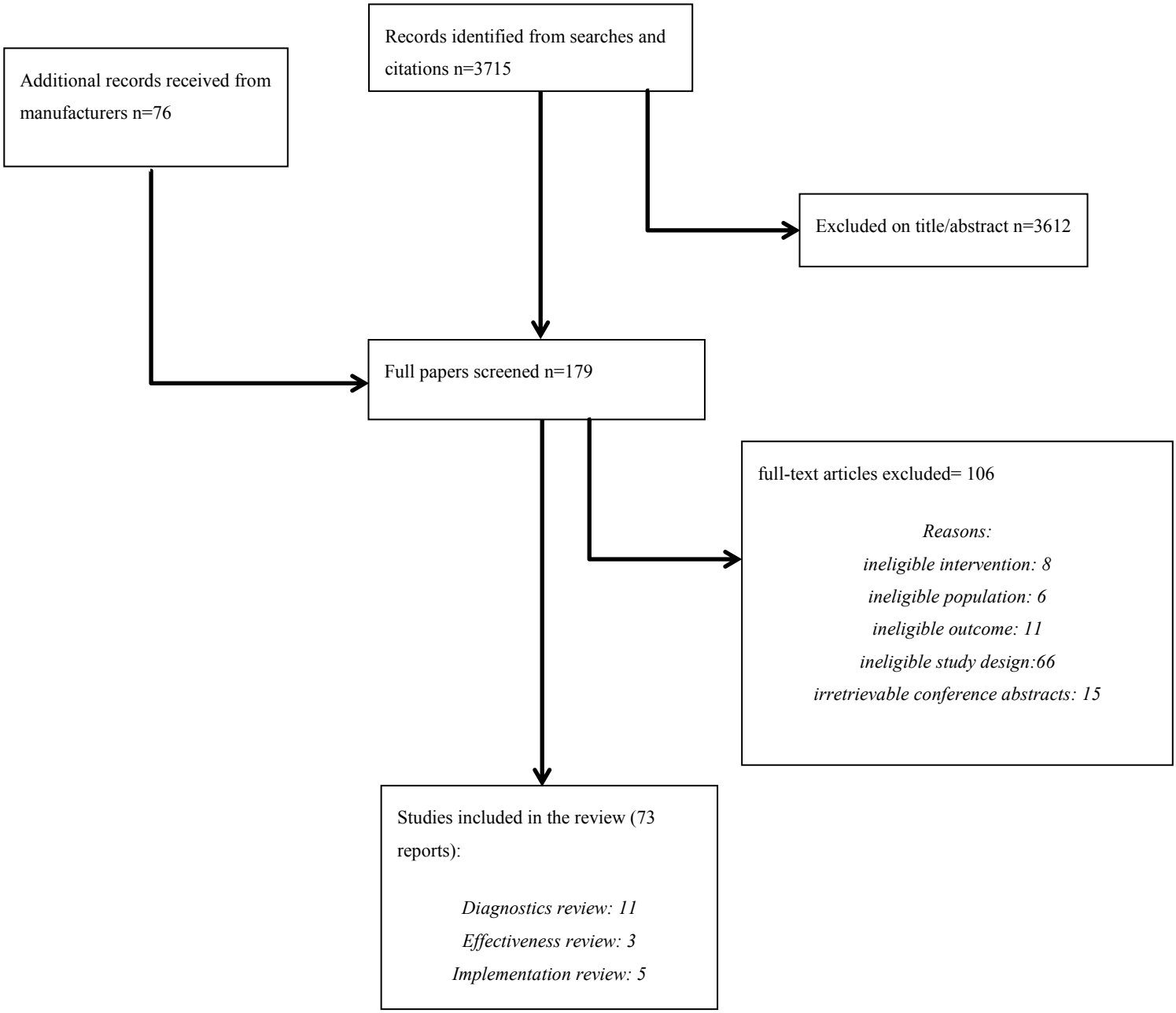
4.2 Summary of clinical effectiveness evidence

This chapter is structured as follows. The next section provides information on the quantity of research available, including characteristics and risk of bias of the included studies. This is then followed by the results sections with diagnostic accuracy, clinical effectiveness and implementation of DYSISmap and ZedScan as adjunctive technologies presented separately.

4.2.1 Number of studies included

The literature searches of bibliographic databases identified 3617 references. After initial screening of titles and abstracts, 179 were considered to be potentially relevant and were ordered for full paper screening. In total eleven studies were included in the diagnostic review, three studies were included in the clinical effectiveness review, and five studies were included in the review of implementation (from a total of 73 reports). Figure 2 shows a flow diagram outlining the screening process with reasons for exclusion of full-text papers.

Figure 2 Flow diagram: Study selection process



Most studies were reported in several papers and abstracts, with considerable overlaps in data and reporting. For each study and each review we selected the paper with the most up-to-date and complete data, which was treated as the main paper. Consequently some papers were included in more than one review, and some papers (mostly conference abstracts with limited or outdated data) were not included in any analysis. Table 3 presents an overview of these studies; their included studies and how papers were included in each review. Appendix 10.2 presents a list of all included references.

4.2.2 Excluded studies

A list of full-text papers that were excluded along with the reasons for their exclusions is given in Appendix 10.3. These papers were excluded because they failed to meet one or more of the inclusion criteria in terms of the type of study, participants, test, reference standard or outcomes reported. This includes four studies of electrical impedance spectroscopy for the diagnosis of CIN,(115-118) which were identified by the bibliographic database searches and were also submitted by Zilico. These studies were excluded as their focus was on demonstrating the potential of spectroscopy for detecting CIN and calculating impedance levels that could be used to diagnose CIN2+, rather than formal diagnostic accuracy assessment.

Table 3 Overview of included studies

Study (country)	Number of full text papers	Number of conference abstracts	Studies included in the review			
			Diagnostic accuracy (full/main paper)	Clinical effectiveness (full/main paper)	Implementation (full /main paper)	Linked conference abstracts
Budithi 2016, (42) Wales	1	4	Budithi 2016 (42)	None	Budithi (2016)(43)*	Budithi (2016)(44); Budithi (2015)(45); Budithi (2015)(46)
Coronado (2016),(47) Spain	1	2	Coronado (2016)(47)	None	Coronado (2014)(48)	Coronado (2014)(49); Coronado (2013)(50)
Founta (unpublished),(51) England	1	5	Founta (unpublished) (51)	None	None	Founta (2014) (52); Founta (2014) (53); Founta (2015)(54); Founta (2015)(55); Founta (2015)(56)
Louwers (2011),(57) Netherlands	5	9	Louwers (2011)(57); Louwers (2015) (58); Zaal (2012)(59); Zaal (unpublished)(60)	Louwers (2011)(57)	Louwers (2015)(61)	Louwers (2013)(62); Louwers (2009)(63); Louwers (2010)(64); Louwers (2010)(65); Louwers (2011)(66); Louwers (2013)(67); Zaal (2012)(68); Louwers (2014)(69); Louwers (2013)(70);
Lowe (2016),(71) England	0	3	None	None	Lowe (2016)(71)*	Lowe (2016)(72) Brady (2016)(73)
Natsis (2016),(74) England	0	5	None	None	None	Natsis (2016),(74) Founta (2014)(75); Founta (2014)(76); Founta (2015)(77); Natsis (2015)(78)
Roensbo (2015),(79)	1	0	Roensbo (2015)(79)	None	None	None

Denmark						
Salter (2017),(80) USA	0	8	None	None	None	Salter (2017),(80); Salter (2016)(81); Livingston (2016)(82); Papagiannakis (2016)(83); Livingston (2016)(84); Weinberg (2017)(85); Cholkeri (2016)(86); DYSIS Medical(87)
Soutter (2009),(88) England	1	5	Soutter (2009)(88)	Soutter (2009)(88)	None	Soutter (2009)(89); Balas (2007)(90); Soutter (2007)(91); Soutter (2008)(92); Soutter (2010)(93)
Tidy (2013),(94) England & Ireland	2	7	Tidy (2013)(94); Tidy (2011)(95)	Tidy (2013)(94)	None	Tidy (2012)(96); Tidy (2011)(97); Tidy (98); Tidy (2012)(99); Tidy (2011)(100); Tidy (2011)(101); Tidy (2013)(102)
Tidy (forthcoming), (103) England	4	5	Tidy (forthcoming)(103); Macdonald (submitted EJGO)(104); Palmer (2016)(105); Zilico (2013)(106)	None	Palmer (2016)(105)	Tidy unpublished(107); Macdonald (2015)(108); Tidy(109); Tidy(110); Tidy (2016)(111)
Tsetsa (2012),(112) Greece	0	3	None	None	None	Tsetsa (2012),(112) ; Tsetsa (2010)(113); Tsetsa (2011)(114)

* Conference abstract

4.3 Results: assessment of diagnostic accuracy

4.3.1 Characteristics of the included studies

Table 4 presents the summary information of characteristics of the included diagnostic accuracy studies. There were 11 studies included in the diagnostic review, including nine studies of DYSIS (42, 47, 51, 57, 74, 79, 80, 88, 112) and two studies of ZedScan.(94, 103) A total of six studies were unpublished, included three full text studies (42, 51, 103) and three studies only reported as conference abstracts.(74, 80, 112)Two studies were ongoing but reported sufficient preliminary diagnostic accuracy data to be included in this review.(74, 80) The manufacturer was involved in the design, conduct and/or interpretation of all ZedScan studies and all DYSIS studies except two.(47, 79)

All included studies were conducted in hospital-based colposcopy clinics and used a prospective cohort design. All patients underwent colposcopy with an adjunctive colposcopy technology, except for participants included in two DYSIS two-arm studies that included a separate parallel control group examined with colposcopy alone.(74, 80) Six studies were conducted in more than one centre.(42, 57, 74, 80, 88, 94)

Five studies were conducted in England.(51, 74, 88, 94, 103) Of those, one also recruited patients in Greece(88) and one involved a clinic in Ireland.(103) Other studies were conducted in Wales,(42) the Netherlands,(57) Spain,(47) Denmark,(79), the USA(80) and Greece.(112)

The sample size of studies (defined as the total number of participants analysed) ranged from 54 to 1237. Mean/median age of participants ranged from 29 to 37 years where reported. Prevalence of high-risk HPV was reported in only five studies, and ranged from 37.5% to 100%, (47, 51, 57, 74, 103) and three studies included patients with hr-HPV exclusively.(51, 74, 103)

The majority of patients included in the studies were referred to colposcopy due to an abnormal cytology/smear test, although one study only included test-of-cure patients referred with negative cytology who tested positive for hr-HPV either 6 months after LLETZ or in the context of the NHS catch-up programme.(51) All patients included in Tidy (forthcoming)(103) were referred to colposcopy through the NHS HPV-primary screening pilot.(21) A sub-study of Tidy (forthcoming)(103) included 613 patients with known-hr-HPV genotype already included in Tidy (forthcoming)(103), as well as an additional 226 (26.9%) patients, of which most (187, 82.7%) had a persistent HPV test and cytology negative result. (104) No other study included patients referred through HPV-primary screening.

Where reported, the percentage of low and high-grade referrals varied widely across the studies. One study of test-of-cure patients reported a high prevalence of high-grade referral (84.7%),(51) and

another study only included patients with low-grade cytology and hr-HPV.(74) In other studies, between 17.1% and 52.8% of participants were referred to colposcopy with high grade dyskariosis or worse, and 9.5% to 82.9% of participants were referred with low grade dyskaryosis or less. The prevalence of histology confirmed CIN2+ varied widely, from [redacted](51) to 45.2%. Further details on histology confirmed CIN and cancer prevalence are reported in Appendix 10.4.

One study excluded women with type 3 transformation zone.(103) Five studies excluded pregnant women(42, 57, 88, 94) and two studies also excluded women with active menstruation.(94, 103) Further details on patient selection criteria and exclusions are reported in Appendix 10.5.

Of the nine DYSIS studies, all evaluated DYSISmap as an adjunct to colposcopy except one which only reported the diagnostic accuracy of DYSISmap alone against colposcopy(79) Four studies evaluated the accuracy of DYSISmap both alone and as an adjunct to colposcopy. (47, 80, 88, 104) Both ZedScan studies used ZedScan as an adjunct to colposcopy. All DYSIS studies used a DYSIS video colposcope, and both ZedScan studies used a binocular colposcope.

Six studies evaluated a commercial version of the DYSIS map, of which three used DySIS v3(42, 47, 51, 74) (80) and one used DySIS v2.1.(57) One study evaluated a pre-commercial prototype version (FPC-03)(80), and two studies did not report which version of DYSIS map was used.(74, 112) Most studies of DYSIS reported using the upper end of the acetowhitening scale of the colour-coded DySIS map to identify predicted high-grade lesions (red/yellow/white).(47, 51, 57, 80, 88) One study also included areas with weaker acetowhitening (coloured as dark blue and green, in addition to the standard red, yellow and white) as potential high-grade lesions,(79) and three studies did not report which part of the colour-coded scale was used to predict CIN2+.(42, 74, 112) Following request for information from NICE, the manufacturer stated that the DYSIS map algorithm had not changed after the FPC-03 version, and that DYSIS v3 had undergone improvements in the following areas compared with earlier versions: increased image resolution, ergonomic set-up allowing flexible positioning, working distance to allows easier biopsy and treatment, improved software usability and availability of single-use specula.

One ZedScan study was a two-phase study evaluating a pre-commercial version of the tool (3rd generation prototype);(94) in phase 1, 12 colposcopically guided ZedScan measurements were taken from the cervix: and analysed from a group of 214 people on a per-point basis to determine cut-offs for the detection of CIN2+. The cut-offs were then used in a second phase to evaluate the diagnostic accuracy of adjunctive ZedScan with colposcopy alone, and conduct further analyses to test and determine further cut-offs.

The more recent ZedScan study, Tidy (forthcoming)(103) evaluated a commercial version of ZedScan.(103) Clarification from the manufacturer indicated that [redacted]

[redacted]SUPERSEDED –

SEE ERRATUM

Table 4 Study and population characteristics

Study	Country	Sample size (N analysed)	Number of centres involved	Recruitment dates	Adjunctive technology	Age (yrs)	Hr-HPV prevalence	Reason for referral	Low grade dyskaryosis or less	High-grade dyskaryosis
Budithi 2016(42)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Coronado (2016)(47)	Spain	443	1	03/2012-02/2014	DYSIS (DySIS v3)	Mean 36, SD 1[redacted]9	37.5%*	Abnormal pap-smear	82.9%	17.1%
Founta (unpublished) DyS-CO1(51)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Louwers (2011)(57)	Netherlands	239	3	07/2008-09/2009	DYSIS (DySIS v2.1)	Mean 36.7, Median 35.3, Range 18.7-62.6	66.1%£	Abnormal cytology: 91.6% ; follow-up of untreated CIN1-2: 8.4%	66.1%	33.9%
Natsis (2016)(74) (conference abstract, ongoing study)	England Gatsehead & Taunton	287 (+948 parallel standard colposcopy control group)	2	NR	DYSIS (DySIS v3)	NR	100%	Low-grade cytology & hr-HPV	100%	0

Roensbo (2015)(79)	Denmark	239	1	12/2013-01/2014	DYSIS (version NR)	Mean 34.3, SD 11.5	NR	Abnormal cytology	NR	NR
Salter (2017)(80) (conference abstract, ongoing study, IMPROVE-COLPO)	USA	210 (+ 1788 retrospective standard colposcopy control group)~	2	NR	DYSIS (DySIS v3)	Median 31, range 21-62	NR	Abnormal cytology/pap (99%), test-of-cure (1%)	74%+	25%++
Soutter (2009)(88)	England (London), Greece	308	3	05/2004-07/2005	DYSIS (FPC-03 prototype)	Median 37, IQR 29-46	NR	Abnormal Pap test: 96.1%; symptoms 3.9%	NR	NR
Tidy (2013)(94)(phase 1)	England (Sheffield)	214 (phase 1)	2	04/2009-05/2011	ZedScan (3rd generation protoype)	Median 32.8 range 20-60	NR	Abnormal cytology	47.2%	52.8%
Tidy (2013)(94) (phase 2)	England (Sheffield), Ireland	196 (phase 2)	3	04/2009-05/2011	ZedScan (3rd generation protoype)	Median 29.5 range 20-64	NR	Abnormal cytology	56.3%	43.7%
Tidy (forthcoming)(103)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Macdonald (2017)(104) (linked to Tidy (forthcoming) (103)^	England (Sheffield)	839	1	01/2014-12/2015	ZedScan (commercial version)	Mean 32.9, range 20.3–66.1	100%	Known hr-HPV genotype (100%), abnormal cytology (73.1%),^ persistent hr-HPV/negative cytology (22.3%), follow-up (4.2%),	49.0%	24.1%

								clinical indication (0.6%)		
Tsetsa (2012)(112) (conference abstract, unpublished completed study)	Greece	57 (54)	1	NR	DYSIS (version unknown)	NR	NR	Abnormal cytology	NR	NR

[+] LSIL, ASC-US/HPV, persistent HPV and HPV16/18; [+] HSIL, AGC and ASC-H * Low-risk HPV:31.8%; not determined 30.[illegible]%; [#] 5.[illegible]% unknown/inadequate; [£] low-risk HPV: 30.5%; not determined: 3.3%; [illegible] details and results of retrospective arm only reported in linked separate study of LSIL and ASC-US/hrHPV(83)

4.3.2 Risk of bias of the included studies

All eleven included studies were assessed for risk of bias and applicability using a modified version of the QUADAS-2 tool. Table 5 presents a summary of the results for the risk of bias across all studies in the five main risk of bias domains: patient selection, index test, comparator test, reference standard, and flow and timing. Appendix 10.7 presents complete results of quality assessment with justifications for decisions where appropriate.

4.3.2.1 **DYSIS studies**

Only one study was considered at low risk of bias overall.(57) and the remaining eight studies were at high risk of bias. Significant applicability concerns were raised for five of the nine DYSIS studies.(47, 57, 79, 88, 112)The main source of bias in DYSIS studies was related to verification bias. Only three studies conducted biopsies in all patients analysed.(57, 79, 88) [redacted] The remaining two DYSIS studies were conference abstracts and did not report sufficient data to assess the risk of verification bias.(80, 112)

The DYSIS technology used in the earlier study by Soutter (2009) was a pre-commercial model (FPC-03).(88) The study reported technical issues relating to the software, speculum and a batch of faulty disposable nozzles, leading to the exclusion of a large proportion of eligible participants (31%) from the analyses. Therefore the applicability of the results of this study may be limited.

4.3.2.2 **ZedScan studies**

Both studies of ZedScan were considered at high risk of bias overall,(94, 103) and significant applicability concerns were raised for both studies.

Neither study conducted biopsies in participants with normal cervical transformation zone to confirm absence of CIN, and so both were considered at high risk of verification bias. Risk of study selection bias was considered high in both studies, notably due to the exclusion of patients with transformation zone type 3 in whom colposcopy may be harder to perform.(103)

[redacted] However, the study did collect data on whether biopsy would have been taken with colposcopy alone regardless of the ZedScan result, and diagnostic accuracy results for standard colposcopy were reported in a linked sub-study.(104) Therefore the ZedScan I results were considered at high risk of reporting bias.

[redacted] and most patients included in Tidy (2013)(94) were examined in a single centre (Sheffield) by colposcopists highly experienced with ZedScan, and the extent to which the results of this study are applicable to other settings is uncertain.

4.3.2.3 **Risk of bias associated with the reference standard**

In all included studies, nearly all histology was performed based on samples collected from punch biopsies rather than from deeper treatment biopsies. Although it is obviously unethical to perform treatment biopsies where not clinically indicated, samples from punch biopsies may be less accurate.(119) Therefore the risk of bias associated with the reference standard was classed as high across all studies.

Table 5 Results of the QUADAS2 assessment of diagnostic accuracy studies

	Risk of bias					Applicability concerns			
Short Title	**Patient selection**	**Index test**	**Comparator test**	**Reference standard**	**Flow and timing (incl. verification bias)**	**Patient selection**	**Index test**	**Comparator test**	**Reference standard**
Budithi (unpublished)(42)	*	*	*	*	*	*	*	*	*
Coronado (2016)(47)	+	+	?	-	-	-	+	+	+
Founta (unpublished)(51)	+	?	+	-	-	+	+	+	?
Louwers (2011)(57)	+	+	+	-	+	-	+	-	+
Natsis (2016)(74)	?	?	?	-	-	+	?	?	?
Roensbo (2015)(79)	?	-	-	-	-*	?	-	-	+
Salter (2016)(80)	?	?	?	-	?	?	?	?	?
Soutter (2009)(88)	?	+	+	-	-*	?	-	-	+
Tidy (2013)(94)	-	-	+	-	-	-	-	+	+
Tidy (forthcoming)(103)	*	*	*	*	*	*	*	*	*
Tsetsa (2012)(112)	?	?	?	-	?	?	-	-	?

*Considered at low risk of verification bias, although other significant concerns were raised regarding flow and timing (see Appendix 10.7 Table 69)

4.3.3 Additional data provided by the manufacturers

[redacted]

[redacted]

In all analyses, this additional data was used in preference to published results. For studies where additional data was not provided the data extracted from publications was used.

We intended to further analyse the 5x5 diagnostic data provided. [redacted] it was decided that more detailed analysis of this additional analysis was not appropriate, as it may be biased by the availability and structure of the data provided.

4.3.4 Statistical synthesis of diagnostic accuracy

Initial meta-analyses of diagnostic accuracy were based on data presented in the publications listed in Table 3. Two studies were excluded from these analyses because they were conducted in very specific subpopulations: [redacted] and one other(74) because it was conducted only in women with both a high risk HPV infection and low-grade cytology results. The statistical analyses therefore included eight studies, six of DYSIS and two of ZedScan.

In performing the analyses we made the following assumptions: we assumed that the DYSIS video colposcope (used in DYSIS studies) was equivalent, in diagnostic accuracy, to a binocular colposcope (used in ZedScan studies). In one study(80) DYSIS was used but it was not clear whether this was DYSISmap alone (without colposcopy) or adjunctive to colposcopy. We have assumed the latter, since it is assumed the colposcopists must have seen the video colposcopic image as part of the assessment. One study (79) reported whether the colposcopists agreed or disagreed with the DYSISmap result, rather than the result of adjunctive colposcopy. We have assumed that when either the colposcopists or the DYSISmap result found CIN2 (or greater) to be present then the test was taken to be positive for CIN2. This differs from the interpretation in the original paper.

The threshold used for colposcopy in all publications was CIN2 or greater, and that has been used in these analyses. Only one paper (47)reported diagnostic accuracy at CIN1 or greater.

Only two ZedScan studies were available for analysis, one was of the current ZedScan I device (103)and the other (94)was of a ZedScan prototype. We have therefore not performed meta-analyses of these studies; instead, we report diagnostic accuracy results on ROC plots without meta-analytic summary results.

4.3.4.1 **DYSIS**

Forest plots of diagnostic accuracy

In this section we present diagnostic accuracy results from the studies of DYSIS in the form of forest plots.

Figure 3 shows estimates of sensitivity and

Figure 4 estimates of specificity. Colposcopy alone has moderate sensitivity (58.4%, 95% CI 50.3 to 66.5) but high specificity [redacted] colposcopy therefore misses many women who do have CIN2 or greater, but produces relatively few false-positive test results. DYSISmap alone has similar performance [redacted] For adjunctive DYSIS use the sensitivity rises to [redacted] ; so using DYSISmap in addition to colposcopy correctly identifies more CIN2 cases, but with a higher false-positive rate, which may mean performing biopsies in a larger proportion of women who do not have CIN2 (or greater).

Figure 3 Forest plot of diagnostic sensitivity of DYSIS [AIC]

Figure 4 Forest plot of diagnostic specificity of DYSIS [AIC]

Figure 5 Diagnostic odds ratios from the DYSIS studies [AIC]

Figure 5 presents the diagnostic ratios (DORs) for each study. The diagnostic ratio is a combination of sensitivity and specificity (formally, log odds of sensitivity minus log odds of specificity) which increases as the overall diagnostic accuracy of a test increases. The results show almost no difference between colposcopy and adjunctive DYSIS [redacted] suggesting that DYSISmap does not improve the diagnostic accuracy of colposcopy when defined in terms of diagnostic odds ratios.

Figure 6 and Figure 7 show the positive and negative predictive values (PPV/NPV) in the studies, respectively. These are harder to interpret as PPV and NPV vary with prevalence, which is different across the studies. The PPV for adjunctive colposcopy is lower than for colposcopy alone [redacted] so fewer than half of all women who receive a DYSIS-guided biopsy will have high-grade CIN. The summary PPV, and the estimated PPV in most studies, is lower than the 65% level recommended by UK guidance.(15) The NPV is slightly higher with adjunctive DYSIS [redacted] so fewer high-grade CIN cases will be missed.

Figure 6 Positive predictive values in the DYSIS studies [AIC]

Figure 7 Negative predictive values in the DYSIS studies [AIC]

Table 6 Heterogeneity I2 in the diagnostic meta-analyses

	Colposcopy only	**DYSISmap only**	**DYSISmap+Colposcopy**
Sensitivity	62.7	94.4	0
Specificity	90.2	91.5	94.5
Diagnostic odds ratio	78.6	92.7	74.4
Positive pred. value	64.9	79.4	88.4
Negative pred. value	94.8	97.7	89.8

Heterogeneity was substantial in almost all meta-analyses. The I^2 values are summarised in Table 6. All but one analysis had an I^2 above 60%.

Bivariate and regression models of diagnostic accuracy

The analyses presented so far have not accounted for the correlation between sensitivity and specificity. Formal bivariate meta-analysis of diagnostic accuracy should be used to account for this correlation (39). Nor have they accounted for the fact that colposcopy and DYSIS are performed in the same study on the same participants. Full individual level-data would be needed to properly account for within-person correlation between test results. This was not available, but extensions to the bivariate model can account for the fact that the tests were compared within the same study.(41)

Figure 8 shows the sensitivity and specificity for all included studies. It can be seen that, for all studies, adjunctive DYSIS has higher sensitivity, but lower specificity, than using colposcopy alone. Using DYSISmap alone generally falls somewhere between the two.

Figure 8 Sensitivity and Specificity for all DYSIS studies in ROC space [AIC]

Table 7 shows the results of bivariate meta-analyses;

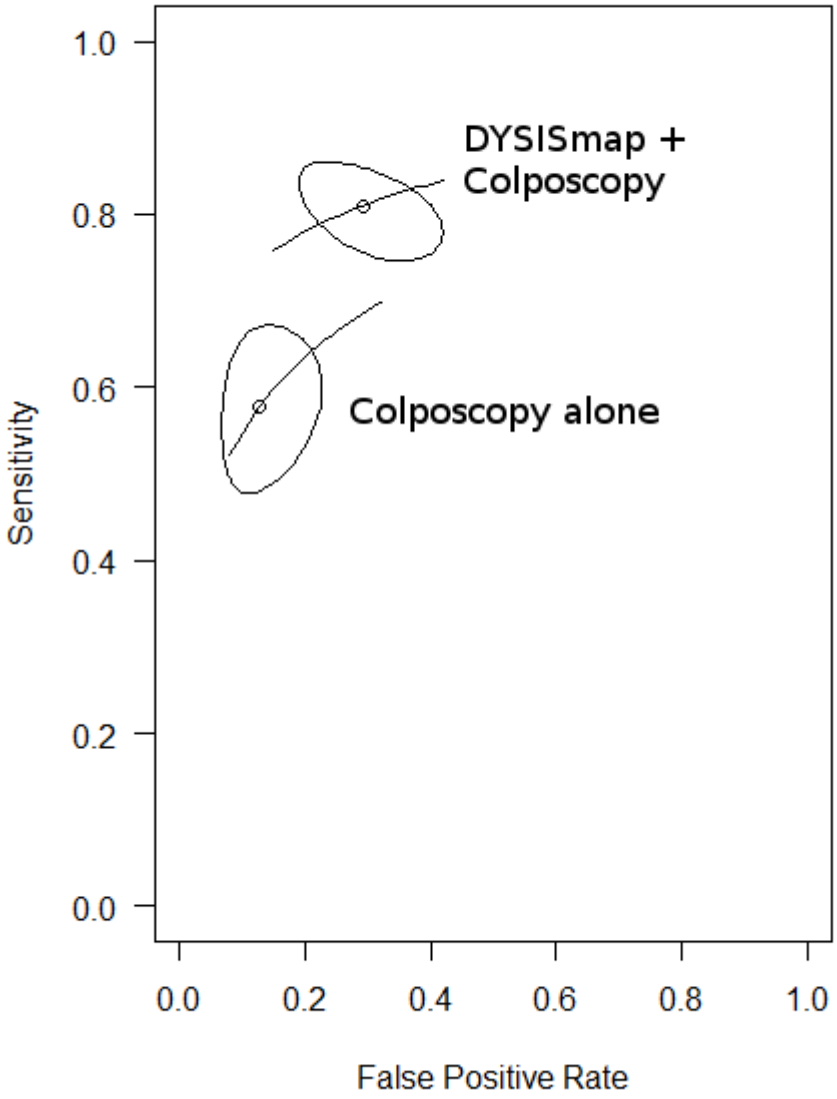
Figure 9 shows the results in ROC space, including 95% confidence regions (the ellipses) and summary ROC curves. The results are consistent with those seen in the forest plots of diagnostic accuracy (Figure 3 and

Figure 4), and show that using adjunctive DYSIS increases sensitivity when compared to colposcopy alone, but at the cost of reduced specificity. As only three studies reported use of DYSISmap alone, no bivariate model was fitted for that test.

Table 7 Results of bivariate diagnostic meta-analyses

	Sensitivity (95% CI)	**Specificity (95% CI)**
Colposcopy alone	57.74% (49.7 to 63.4)	87.34% (79.7 to 92.4)
DYSISmap + Colposcopy	80.97% (76.0 to 85.1)	70.90% (60.8 to 79.3)

Figure 9 Summary ROC plot from bivariate models



The bivariate model analyses colposcopy and adjunctive DYSIS separately, and does not account for the fact that they are measured in the same studies. To correct for this we fitted logistic regression models including study-level parameters, to account for possible correlation between test results within studies (see Methods section for details).

The summary results for this regression model are shown in Table 8. The results are similar to the standard bivariate model in Table 7. This model also permits direct comparison of colposcopy and adjunctive DYSIS. This found evidence of a difference in specificity between the tests (Difference in log odds of specificity: 1.33, SE 0.33, p-val <0.0001) but no evidence of a difference in diagnostic accuracy (Difference in log diagnostic odds ratios: 0.04, SE 0.20, p-val 0.84). This suggests that using

DYSIS changes the test threshold for diagnosis of CIN2 such that more women go on to receive biopsy, but is not improving diagnostic accuracy (in terms of diagnostic odds ratio) when compared to colposcopy alone.

To confirm this we also fitted a regression model which constrains adjunctive DYSIS and colposcopy to have the same diagnostic accuracy (but permits differences in specificity). The Bayes information criterion (BIC) is used when comparing regression models; generally a lower BIC suggests a better-fitting and more parsimonious model. This new model had a BIC of 198.3, lower than the previous model, which had a BIC of 201.5. This confirms that assuming DYSIS and colposcopy have the same diagnostic accuracy is reasonable.

Table 8 Results from logistic regression model of diagnostic accuracy

	Sensitivity (95% CI)	Specificity (95% CI)
Colposcopy alone	57.91% (47.2 to 67.9)	87.41% (81.7 to 91.5)
DYSISmap + Colposcopy	81.25% (72.2 to 87.9)	70.40% (59.4 to 79.5)

4.3.4.2 **ZedScan**

Two studies of ZedScan are included in this analysis. The most recent(103)reported data for adjunctive ZedScan only, using the current ZedScan I device, with no data on the performance of colposcopy alone. The other (94) was a study of a ZedScan prototype which assessed diagnostic accuracy at six different cut-off points of the ZedScan algorithm. This was compared to two colposcopy cut-offs: "Colposcopic impression" (CI), where the colposcopy was considered to have a positive finding if it judged that high-grade CIN was present; and "Disease present" (DP) where colposcopy was considered to have given a positive result if at least one measurement point was suggested for biopsy. The six ZedScan cut-offs were selected such that one had the same sensitivity as Colposcopy (CI or DP), one so that it had the same specificity as colposcopy, and the third as a trade-off between sensitivity and specificity. Because only two studies were available, the differences between the pre-commercial device and ZedScan I, and how results were presented, no meta-analysis was performed. Instead the sensitivity and specificity data from the studies is shown in ROC space in Figure 10. The black lines show summary ROC curves for adjunctive ZedScan and for colposcopy. The sensitivity and specificity results from the two studies are also presented in Table 9.

These results suggest that adjunctive ZedScan may have better diagnostic accuracy than colposcopy alone. In the prototype study ZedScan had greater sensitivity for the same specificity as colposcopy or greater specificity for the same sensitivity. Greater diagnostic accuracy for ZedScan is also suggested

by the summary ROC curve for ZedScan having greater sensitivity than that for colposcopy. However, the small size of the study, and the wide confidence intervals, mean that it is uncertain whether this difference is clinically meaningful. Fitting a logistic regression model to the data from the prototype study found that the improvement in diagnostic accuracy was not quite statistically significant (difference in log diagnostic accuracy: 0.488, SE 0.28, p-val 0.078).

[redacted]

[redacted]

Figure 10 ROC presentation of results from ZedScan studies [AIC]

[redacted]

Table 9 Diagnostic accuracy data from ZedScan studies

Study	Colposcopy cut-off	Colposcopy alone		ZedScan cut-off	ZedScan + Colposcopy	
		Sensitivity (95% CI)	**Specificity (95% CI)**		**Sensitivity (95% CI)**	**Specificity (95% CI)**
Tidy (forthcoming)(103)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tidy (2013)(94)	Colposcopic Impression (CI)	73.6% (64.3 to 82.8)	83.5% (76.5 to 90.5)	1.321	73.6% (64.3 to 82.8)	90.8% (85.4 to 96.2)
				1.083	78.2 % (69.5 to 86.8)	83.5% (76.5 to 90.5)
				1.568	62.1% (51.9 to 72.3)	95.4% (91.5 to 99.3
	Disease Present (DP)	88.5% (81.8 to 95.2)	38.5% (29.4 to 47.7)	0.768	88.5% (81.8 to 95.2)	65.2% (56.2 to 74.1)
				0.390	96.6% (92.7 to 100)	38.5% (29.4 to 47.7)
				0.568	92.0% (86.2 to 97.7)	51.4% (42 to 60.8)

4.3.4.3 **Test positive rates**

Figure 11 shows the test positive rate (the proportion of women where colposcopy or adjunctive colposcopy suggests presence of high-grade CIN) for each test in each study of DYSIS. In every study adjunctive use of DYSIS increases the positive rate compared to colposcopy alone, often substantially. In the Louwers study for example use of DYSIS increase the positive rate from 33.1% to 55.5%.(57) Hence the use of DYSIS will substantially increase the number of women who receive biopsies after colposcopy. Results for ZedScan are shown in Figure 12. These suggest that the positive rate for ZedScan is similar to that for colposcopy alone, regardless of the cut-off used. The Disease present (DP) cut-off, unsurprisingly, produces higher positive rates than the colposcopic impression (CI) cut-off.

Figure 11 Percentage of positive test results in DYSIS studies [AIC]

Figure 12 Percentage of positive test results in ZedScan studies [AIC]

4.3.4.4 Subgroup analyses

Some of the studies provided diagnostic accuracy data for key identified subgroups namely:

- High grade and low grade cytology referral
- High risk HPV (including HPV16) and low risk HPV
- The "test-of-cure" population

We include here data on these subgroups provided by the manufacturers or study authors, data from primary publications, and data from secondary reports of primary studies where those papers included subgroup data not reported in the original study publication. Table 10 provides an overview of the subgroups reported in each study.

Table 10 Overview of patient populations and results reported in diagnostic accuracy studies

Study	Comparisons	Subgroups reported	Primary source of data
DYSIS studies			
Budithi 2016 (unpublished) (44)	[redacted]	[redacted]	[redacted]
Coronado (2016)(47)	DYSISmap+Colposcopy DYSISmap alone Colposcopy alone	High risk HPV	Publication (47)
Louwers 2011 (57)	DYSISmap+Colposcopy DYSISmap alone Colposcopy alone	[redacted]	[redacted]
		Low grade referral High grade referral	Linked publication (Louwers 2015) (58)
		Positive hrHPV test and BMD, or high-grade cytology* BMD cytology and a hrHPV positive test or high grade cytology, irrespective of the hrHPV test result**	Linked publication (Zaal 2012) (59)
Founta (unpublished) DyS-CO1(51)	[redacted]	[redacted]	[redacted]
Natsis (2016)(74)	DYSISmap+Colposcopy Colposcopy alone Colposcopy alone (contemporaneous control group)	High risk HPV with low grade referral	Conference abstract (74)
Roensbo (2015)(79)	DYSISmap alone Colposcopy+random biopsies	None	Publication (79)
Salter (2016) IMPROVE-COLPO(80)	DYSISmap+Colposcopy DYSISmap alone Colposcopy alone (matched control)	Initial results from 2 clinics	Conference abstract Salter 2016 (80)
		LG Pap smear	Conference abstract: Papagiannakis 2016 (83) Weinberg 2017 (85)
Soutter (2009)(88)	DYSIS+Colposcopy Colposcopy alone DYSISmap alone	LG Pap smear HG Pap smear	Publication Soutter 2009 (88) Soutter 2009 (89)
Tsetsa (2012)(112)	DYSIS+Colposcopy	3% acetic acid treatment 4% acetic acid treatment 5% acetic acid treatment	Conference abstract (120) (112)
ZedScan studies			
Tidy 2013 (94)	ZedScan+Colposcopy Colposcopy alone	[redacted]	[redacted]

Tidy (forthcoming)(103)	ZedScan+Colposcopy Colposcopy alone	[redacted]	[redacted]
		Low risk HPV High risk HPV	Linked manuscript(104)

* Referred through cytology based screening, but retrospectively treated as HPV-primary with cytology; ** Cytology based, with exclusion of hrHPV negative BMD

Figure 13 shows sensitivity and specificity forest plots by subgroup for colposcopy alone, Figure 14 shows the same analyses for adjunctive DYSIS and Figure 15 for adjunctive ZedScan. Summary meta-analyses are not presented because of the small number of studies in each subgroup.

Colposcopy appears less sensitive than average at detecting high grade CIN in women with low-grade referrals. This may partly be a consequence of interpretation bias: the colposcopic results are analysed with more caution if a woman is known to have a high-grade referral, or it may be because lesions are harder to detect in women with a low-grade referral. The same applies to women who have low- grade referrals combined with high-risk HPV. This difference is not observed when using DYSIS or ZedScan: in both cases sensitivity and specificity are similar for both low and high-grade referrals. This suggests that adjunctive colposcopy may improve detection of high grade CIN in women with a low grade referral (i.e. mild dyskaryosis).

There is no convincing evidence that diagnostic accuracy differs between women with and without high-risk HPV, however data are limited. For women with high risk HPV infection both sensitivity and specificity are higher than average (see Figure 3 and Figure 4) when using adjunctive DYSIS, suggesting that high grade CIN is easier to detect in women with high risk HPV. The sensitivity appears higher among women with high-risk HPV when using adjunctive DYSIS than with colposcopy alone. This suggests that adjunctive DYSIS may improve detection of high grade CIN in women with high risk HPV.

Results for ZedScan are more limited, with no apparent evidence of differences between subgroups.

We note that all these conclusions are based on small subgroups generally of only one to three studies, and so the results should be considered as speculative only.

Figure 13 Diagnostic accuracy of colposcopy by subgroup[AIC]

Figure 14 Diagnostic accuracy of adjunctive DYSIS by subgroup [AIC]

Figure 15 Diagnostic accuracy of adjunctive ZedScan by subgroup [AIC]

Meta-analyses were generally not possible within subgroups as only one or two studies reported data for each subgroup. For high and low-grade referrals for DYSIS a logistic regression model (as in Table 8) was fitted in each subgroup to meta-analyse diagnostic accuracy within these subgroups as there were two DYSYIS studies for each subgroup. The results of this analysis are shown in Table 11. These results suggest that for colposcopy alone the sensitivity to detect CIN2 among low-grade referrals is much lower than for high grade referrals, for a similar specificity. This difference was not quite statistically significant (p=0.072), because of the limited data available. There was no evidence of any difference between types of referral when using adjunctive DYSIS, suggesting that adjunctive DYSIS may be preferable to colposcopy for women with a low-grade referral. Similar regression models did not find any evidence of differences between HPV subgroups.

Table 11 Diagnostic accuracy according to referral grade

Test	Referral grade	Sensitivity (95% CI)	Specificity (95% CI)
Colposcopy alone	Low-grade	38.27% (18.9 to 62.4)	75.57% (53.4 to 89.3)
	High-grade	64.06% (42.2 to 81.3)	71.49% (50.5 to 86.0)
DYSISmap + Colposcopy	Low-grade	80.53% (57.9 to 92.5)	53.36% (28.6 to 76.3)
	High-grade	83.16% (58.4 to 94.6)	57.00% (30.7 to 79.8)

4.3.4.5 **Sensitivity analyses**

The study by Roensbo(79) differed from the other included studies as it did not assess DYSIS as an adjunct to colposcopy directly, but only whether a colposcopist agreed or disagreed with the DYSISmap result. As noted in section 4.3.1, the study also used the DYSISmap more conservatively

than other DYSIS studies, by interpreting areas with weaker acetowhitening on the coloured map (including dark blue and green) as "suspicious for high-grade disease".

We performed a sensitivity analysis of the logistic regression model in Table 8 for sensitivity and specificity, excluding this study. The results are shown in Table 12. There is little change when excluding Roensbo (2015)(79), with all estimates being similar to when the study was included.

Table 12 Sensitivity bivariate analysis excluding Roensbo (2015)

	Sensitivity (95% CI)	Specificity (95% CI)
Colposcopy alone	56.4% (47.5 to 64.9)	90.2% (86.3 to 93.1)
DYSIS + Colposcopy	82.9% (75.0 to 88.7)	72.9% (63.3 to 80.7)

A particular concern identified during quality assessment was that different studies had different practices when neither colposcopy nor adjunctive DYSIS or ZedScan identified any abnormal areas requiring biopsy: three studies(42, 47, 74) (80)performed no biopsy in those women, two studies typically performed a single randomly located biopsy(57, 88) and one performed multiple biopsies.(79) One study did not provide sufficient information.(80) Table 13 shows the results of meta-analyses categorised by the type of biopsy performed in the DYSIS studies. These results suggest that specificity and sensitivity tend to decline the more biopsies that are performed on colposcopy-negative women, as we might expect if verification bias is present and studies not performing biopsies are missing high-grade CIN cases. This is true for colposcopy alone and adjunctive DYSIS. Despite these differences the comparison between colposcopy and adjunctive DYSIS is unchanged: using DYSISmap as an adjunct to colposcopy increases sensitivity, but decreases specificity in all cases.

Table 13 Results of diagnostic meta-analyses according to number of additional biopsies performed

	Colposcopy alone		Adjunctive colposcopy	
	Sensitivity (95% CI)	Specificity (95% CI)	Sensitivity (95% CI)	Specificity (95% CI)
No additional biopsy (3 studies)(42, 47) (74, 80)	[redacted]	[redacted]	[redacted]	[redacted]
One additional biopsy (2 studies)(57, 88)	50.27 (43.0 to 57.5)	86.22 (79.1 to 93.3)	78.7 (72.6 to 85.6)	70.02 (57.9 to 82.2)
Multiple additional biopsies (1 study)(79)	67.65 (56.5 to 78.8)	67.25 (60.2 to 74.3)	75.00 (64.7 to 85.3)	57.31 (49.9 to 64.7)

4.3.4.6 Comparison of DYSIS and ZedScan

All analyses so far have considered DYSIS vs colposcopy and ZedScan vs colposcopy. Here we briefly consider a comparison of all three technologies.

As no studies in the review included both DYSIS and ZedScan a direct comparison is not possible. Instead we consider an indirect comparison of the technologies. This is less reliable than a direct comparison as there are differences in study populations and conduct which may alter diagnostic accuracy over and above the differences in diagnostic technology used.

Table 14 presents what we consider the best estimates of diagnostic accuracy. For DYSIS these are sourced from the logistic regression model comparing adjunctive DYSIS to colposcopy (Table 8). [redacted] When comparing ZedScan to colposcopy the situation is more complex as the most recent study did not report colposcopy diagnostic data. If we are willing to assume that binocular and video colposcopes have the same diagnostic performance than the best evidence is that found from the DYSIS studies. Only the ZedScan prototype study(94) has reported diagnostic accuracy data for binocular colposcopy, so an alternative estimate is the "Colposcopic Impression" cut-off from that study, as that cut-off is closest to that used to diagnose high-grade CIN.

These results show that both adjunctive DYSIS and adjunctive ZedScan substantially increase sensitivity, but also have substantially reduced specificity when compared to colposcopy. It would appear that adjunctive ZedScan even further favours high sensitivity, with a corresponding loss of specificity, when compared to adjunctive DYSIS, but this is an indirect comparison.

Table 14 Best-evidence estimates of diagnostic accuracy

Technology	Sensitivity (95% CI)	Specificity (95% CI)	Source
DYSIS + Colposcopy	81.25% (72.2 to 87.9)	70.40% (59.4 to 79.5)	Regression model (Table 8)
ZedScan + Colposcopy	[redacted]	[redacted]	Tidy (forthcoming)(103)
Colposcopy (DYSIS video colposcope)	57.91% (47.2 to 67.9)	87.41% (81.7 to 91.5)	Regression model (Table 8)
Colposcopy (binocular colposcope)	57.91% (47.2 to 67.9) OR 73.56% (64.3 to 82.8)	87.41% (81.7 to 91.5) OR 83.49% (76.5 to 90.5)	Regression model (Table 8) OR Tidy (2013) ZedScan prototype (CI cut-off)

We also performed a further logistic regression model to indirectly compare all three diagnostic tests. This model included all diagnostic data from all DYSIS and ZedScan studies, and accounted for the fact that tests were conducted in the same studies, and the differing cut-offs used in the ZedScan prototype study. When comparing adjunctive tests to colposcopy alone, adjunctive DYSIS no

improvement in diagnostic odds ratios over colposcopy (difference in log DOR: 0.06, p-val 0.74) but adjunctive ZedScan did improve diagnostic odds ratios (difference in log DOR: 0.84, p-val 0.003). Hence, when comparing DYSIS to ZedScan, ZedScan had greater diagnostic odds ratio (difference in log DOR: 0.59, p-val 0.003). This suggests that ZedScan could have better diagnostic accuracy than DYSIS, but the exact benefit would depend on the choice of cut-off and the corresponding sensitivity and specificity values.

4.3.5 Narrative synthesis of further diagnostic accuracy results

Six studies reported diagnostic accuracy data that could not be included in the statistical synthesis, including five DYSIS(51, 59, 74, 83, 112) and one ZedScan study.(104) Three of these studies were linked to studies also included in the meta-analyses(59, 83, 104), and three studies could only be reported in the narrative synthesis.(51, 74, 112) Table 16and Table 17 report the results of the studies of DYSIS and ZedScan respectively.

4.3.5.1 **DYSIS**

Overall, the results of the five DYSIS studies included in this section confirm the results of the meta-analysis. Adjunctive DYSIS improves sensitivity for detecting CIN2+ compared with colposcopy alone, although this is associated with a reduction in specificity. [redacted]

Louwers (2015)(58) was a secondary analysis of Louwers (2011)(57) which aimed to re-analyse the performance of DSI and conventional colposcopy to determine the difference between low-grade cytology (BMD) referrals and high-grade cytology referrals. The study also aimed to re-analyse the performance of DSI and conventional colposcopy by retrospectively assigning them to two referral strategies, based on their initial cytology and hr-HPV test results: 1) hrHPV-testing as primary screening test and cytology as triage (including patients with a positive hrHPV test and BMD, or high-

grade cytology); 2) reflex hrHPV-testing in patients with BMD cytology (including patients with BMD cytology and a hrHPV positive test or high grade cytology, irrespective of the hrHPV test result). Compared with standard colposcopy, the sensitivity of adjunctive DYSIS was higher and specificity was lower in both referral strategies. Diagnostic accuracy estimates were similar between HPV primary and cytology primary referral strategies for adjunctive DYSIS (sensitivity 81% vs. 80%; specificity 64% vs. 61%) and for colposcopy alone (sensitivity 53% vs 54%; specificity 82% vs. 78%).

Natsis (2016)(74) estimated the accuracy of adjunctive DYSIS in a population of 287 hr-HPV positive patients with low grade cytology. Initial colposcopy impression and potential biopsy sites were recorded before and after the appearance of the DYSISmap. Colposcopy alone had low sensitivity (27%) but high specificity (91%) for detecting CIN2+. Incorporation of DYSISmap improved sensitivity (82%) but reduced specificity (36%).

Salter (2016)(80) reported some preliminary data from two colposcopy clinics as part of a large cohort of US community-based colposcopy clinics using adjunctive DYSIS. Consistent with other studies, the addition of DYSISmap increased sensitivity compared to colposcopy alone (83.9% with adjunctive DYSIS compared with 61.3% for colposcopy alone) but was associated with a reduction in specificity (75.4% vs. 91.1%).

Tsetsa (2012)(112) was a single centre prospective diagnostic cohort study that assessed the performance of adjunctive DYSIS in three different concentrations of acetic acid solution (3%, 4% and 5%). The study was only reported in conference abstracts, and enrolled 57 patients with abnormal cytology, of which 54 were analysed. Each patient was examined with DYSIS colposcope and DYSISmap in three successive examinations. Biopsies were collected from sites corresponding to the most atypical indications of the coloured map and sent for histology. The diagnostic performance of adjunctive DYSIS was highest in examinations that used 3% concentration (sensitivity 86%; specificity 81%), compared with 4% concentration (sensitivity 79%, specificity 77%) and 5% (sensitivity 82%, specificity 77%), although the study was small and it is not clear whether these differences were statistically significant. The authors noted that morphological characteristics, such as mosaic pattern and atypical vessels, were better highlighted when the 5% concentration was used.

Cervical cancer (>CIN3)

Six studies reported on the prevalence of cervical cancer (>CIN3). [redacted] All were studies evaluating DYSIS. Of those, three identified at least one histology confirmed patient (a total of 15 cases) with the disease and reported sufficient data to evaluate the number of additional cases identified with DYSISmap as an adjunct to colposcopy. [redacted] Only one of these studies indicated that the addition of the DYSISmap to colposcopy helped to identify additional cancer cases

(two additional cases).(84) Table 15 summarises the ability of colposcopy and adjunctive DYSIS to identify the cancer cases. There is no clear evidence from these data that adjunctive DYSIS improves the detection of cancer cases.

Table 15 Cervical cancer reporting in DYSIS studies

	Number (%) of confirmed cases of cervical cancer	Number identified by DYSISmap+ colposcopy	Number identified by colposcopy alone	Number of additional cases identified DYSISmap
Louwers(57)[personal communication]	[redacted]	[redacted]	[redacted]	[redacted]
Coronado(47)[personal communication]	[redacted]	[redacted]	[redacted]	[redacted]
Livingston (2016) IMPROVE-COLPO(84)*	7/1839 (0.4%)	3 (of 5 recorded)	1 (of 5 recorded)	2

*Conference abstract of ongoing cohort study linked to Salter (2016) that included a total of 1839 patients across two arms: one prospective arm undergoing colposcopy with adjunctive DYSIS and one retrospective arm undergoing standard colposcopy. The number of participants in each arm was not reported.

4.3.5.2 **ZedScan**

[redacted]

Macdonald (2017)(104) evaluated the diagnostic accuracy of ZedScan in patients with known hr-HPV and compared its performance between HPV-16 and other hr-HPV genotypes. The study included 839 participants, of which 607 (72%) had abnormal cytology and were included in Tidy (forthcoming)(103) An additional 226 cases were included, of which most 82% had a persistent HPV test and cytology negative result. The sensitivity of adjunctive ZedScan was high (100%) regardless of the hr-HPV genotype. Sensitivity of colposcopy alone was also high, and slightly higher in patients

with HPV-16 genotype (86.9%) that in other high risk genotypes (79.7%) although this difference may not be significant due to overlapping confidence intervals. Specificity estimates were not reported in this study.

Table 16 Results of diagnostic accuracy studies of DYSIS included in the narrative synthesis (cut-off CIN2+)

Study	Population	N	Comparisons	Sensitivity% (95% CI)	Specificity% (95% CI)	PPV% (95% CI)*	NPV% (95% CI)*
Founta (unpublished) DyS-CO1(51)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
			[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Louwers (2015)(58), subgroup of Louwers 2011 (57)	Referral strategy 1: HPV primary with cytology triage (subgroup with a positive hrHPV test and BMD, or high-grade cytology)	165	DYSISmap+Colposcopy	8[illegible] (72-89)	64 ([illegible]-74)	71.7 (62.8-80.6)	74.2 (63.7-84.8)
			DYSISmap alone	68 (58-78)	69 (58-79)	71.4 (61.8-81.1)	65.4 (55.1-75.8)
			Colposcopy alone	53 (43-64)	82 (73-90)	77.0 (66.5-87.6)	60.6 (51.2-70.0)
	Referral strategy 2: Cytology primary with hr-HPV triage (subgroup with BMD cytology and a hrHPV positive test or high grade cytology, irrespective of the hrHPV test result)	180	DYSISmap+Colposcopy	8[illegible] (73-88)	[illegible] (51-71)	6[illegible].0 (60.5-77.6)	74.0 (63.9-84.0)
			DYSISmap alone	65 ([illegible]-74)	[illegible] (59-78)	6[illegible].2 (59.7-78.7)	64.2 (54.6-73.9)
			Colposcopy alone	54 (44-64)	78 (69-86)	72.2 (61.9-82.6)	60.5 (51.6-69.5)
Natsis (2016)(74)	LG cytology, hr-HPV+	287	DYSISmap+Colposcopy	82 (71.2-92.8)*	36 (29.9-42.1)*	20.9 (15.1-26.6)	90.7 (84.8-96.5)
			Colposcopy alone	27 (14.6-39.4)*	91 (87.4-94.6)*	38.2 (22.0-54.4)	85.8 (81.5-90.1)
		814	Colposcopy alone (contemporaneous control group)	36 (28.5-43.5)*	88 (85.7-90.3)*	37.1 (29.4-44.8)	87.5 (85.2-89.8)
IMPROVE-COLPO(80, 83)	Abnormal cytology/pap (99%), test-of-cure (1%) from 2 colposcopy clinics (subgroup)	210	DYSISmap+Colposcopy	83.9 (70.9-96.8)*	75.4 (69.1-81.7)*	37.1 (25.8-48.5)	96.4 (93.4-99.5)
			DYSISmap alone	74.2 (58.8-89.6)*	60.3 (53.1-67.5)*	24.7 (16.0-33.5)[@]	93.1 (88.5-97.7)

			Colposcopy	61.3 (44.1-78.4)*	91.1 (86.9-95.2)*	54.3 (37.8-70.8)[@]	93.1 (89.4-96.9)
	LG Pap smear[&] (subgroup), 44 colposcopy clinics	1857	DYSISmap+Colposcopy	NR	NR	13.3 (11.4-15.1)	NR
		1788	Colposcopy (retrospective matched control)	NR	NR	10.1 (8.4-11.7)	NR
Tsetsa (2012)(112)	Abnormal cytology	54	DYSIS+Colposcopy (3% acetic acid)	86	81	NR	NR
			DYSIS+Colposcopy (4% acetic acid)	79	77	NR	NR
			DYSIS+Colposcopy (5% acetic acid)	82	77	NR	NR

* Calculated; [@]study reported 17.1% for DYSISmap and 16.9% for colposcopy alone; [&]LSIL and ASC-US/hrHPV; [+] Results for a further subgroup of 20 patients with >BMD and hrHPV negative was reported

Table 17 Results of diagnostic accuracy study of ZedScan included in the narrative synthesis (cut-off CIN2+)

Study	Population	N	Comparisons	Sensitivity% (95% CI)	Specificity% (95% CI)	PPV	NPV
Macdonald (2017)(104), sub-study of Tidy (forthcoming)(103)	All known hr-HPV genotype (subgroup)	839	ZedScan+Colposcopy	100	NR	NR	NR
			ZedScan alone	96.2 (93.1-98.0)	NR	NR	NR
			Colposcopy alone	83.4 (78.4-87.4)	NR	NR	NR
	All known HPV-16 (subgroup)	303	ZedScan+Colposcopy	100	NR	NR	NR
			ZedScan alone	95.6% (90.6-98.2)	NR	NR	NR
			Colposcopy alone	86.9 (80.1-91.6)	NR	NR	NR
	All known hr-HPV other than HPV-16 (subgroup)	536	ZedScan+Colposcopy	100	NR	NR	NR
			ZedScan alone	96.9 (91.9-99.0)	NR	NR	NR
			Colposcopy alone	79.7 (71.9 - 85.8)	NR	NR	NR
Tidy (2016)(111), sub-study of Tidy (forthcoming)(103)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

4.3.5.3 **HPV-primary screening**

[redacted]

4.3.5.4 **Test failures**

Table 18 presents rates of and reasons for test failures. Reported rates of test failure varied widely across the studies. One study of a prototype version of DYSIS reported a high rate of failure (31.4%), primarily due to unsatisfactory view and issues with faulty disposable nozzles through which the acetic acid was delivered. Studies of more recent version of DYSIS reported lower failures rates, ranging from 2.9% to 16.7%, with lack of/poor quality imaging being the most common reasons. Failure rates in the ZedScan I and ZedScan prototype studies were [redacted] and 13.4% respectively. [redacted]

Table 18 Test failure rates and reasons

Study	Number (%) test failure	Reasons for test failure
Budithi (unpublished)(42)	[redacted]	[redacted]
Coronado (2016)(47)	36 (8.1%)	36 Excessive movements during the measurement
Founta (unpublished)(51)	[redacted]	[redacted]
Louwers (2011)(57)	33 (12.1%)	7 DYSIS did not start, 9 no map, 9 exam data not saved, 5 no available histology, 3 no DYSIS colposcopy after signing informed consent
Roensbo (2015)(79)	48 (16.7%)	48 women were excluded due to: - Biopsies not sent separately (n=28). - Not possible to classify the biopsy (n=6). - Technical difficulties (n=9). - Others (n=5).
Soutter (2009)(88)	139 (31.4%)	Software problems (15), no biopsy (23), unsatisfactory view (45) in 45 women, not eligible (6), 5% acetic acid (1), lost data form (1), lost biopsy slides (5), blood or mucus (1), biopsies from wrong point (3), excessive movement (2), problem with acetic acid-faulty nozzles (37)
Tidy (2013)(94)	Phase 1: 33 (13.4%); phase 2: 19 (13.6%)	Phase 1: 31 "as part of training", 2 incomplete clinical data. Phase 2: Biopsy not coincident with EIS reading or inadequate for histology (14), failure of EIS device (5)
Tidy (forthcoming)(103) [personal communication]	[redacted]	[redacted]

4.3.5.5 **Diagnostic and treatment biopsies**

All included diagnostic accuracy studies reported some data on diagnostic and treatment biopsies performed. However, due to limited data, the impact of adjunctive technology on the rates of diagnostic biopsies and treatment (including unnecessary treatments) is uncertain.

Table 19 presents the number of diagnostic biopsies and treatment biopsies performed in the diagnostic accuracy studies.

Three studies performed biopsies in all patients as reported previously.(57, 79, 88) In other studies, the proportion of adjunctive colposcopy patients biopsied ranged from [redacted] (80, 103) The mean number of biopsies varied widely,(57, 83, 88, 94) [redacted] to up to five in Roensbo (2015)(79) where reported. Only four studies reported on number of treatments performed during or after the examination, which were nearly always conducted as loop excisions.(57, 79, 94, 103) See-and-treat cases ranged from 0 in Roensbo (2015)(79) to [redacted]

Only three studies provided data on the number of additional biopsies performed associated with the use of adjunctive colposcopy. These results are however limited due to the lack of randomised evidence comparing adjunctive colposcopy with standard colposcopy in parallel groups.

[redacted]Papagniannakis (2016)(83) found that the addition of DYSIS led to an increase of approximately one additional biopsy per five patient (from 1.03 biopsy per patient with standard colposcopy to 1.25 with adjunctive colposcopy), although this result is derived from a non-randomised comparison with a retrospective arm. Natsis (2016) reported that the proportion of patients undergoing biopsies was lower in patients undergoing colposcopy with adjunctive DYSIS (80.8%) than in a parallel group of patients undergoing colposcopy alone (85.9%).

Table 19 Treatments performed

	Total number of patient analysed	**Number of patients (%) receiving diagnostic/treatment biopsies**	**Number of diagnostic biopsies (punch biopsies) performed**	**Number (%) of patients receiving treatment biopsies**	**Number of treatment biopsies performed**	**Mean number of biopsies per patient**
Budithi (unpublished)(42)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Coronado (2016)(47)	443	372 (84.0%)	332	59 (13.3%)	NR	NR
Founta (unpublished)(51)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Louwers (2011)(57)	239	239 (100%)	NR (≥332[+])[@]	84[+]	NR (≥84[+])	2.27[+]
Natsis (2016)(74)	DYSIS+colpo 287 Colpo alone: 948	DYSIS+colpo: 232 (80.8%) Colpo alone: 814 (85.9%)	NR	NR	NR	NR
Roensbo (2015)(79)	239	239 (100%)	NR	NR	NR	3 to 5
Salter (2016)(80)	210	173 (82.3%)	NR	NR	39	NR
Papagiannakis (2016)(83)	DYSIS+colpo : 1857 Colpo alone: 1788	NR	DYSIS+colpo: 2332 Colpo alone: 1846	NR	NR	DYSIS+colpo: 1.26 Colpo alone: 1.03
Soutter (2009)(88)	308	308 (100%)	603	86 (27.9%)	86	1.96
Tidy (2013)(94)	196 (phase 2)	NR	[redacted]	[redacted]	[redacted]	[redacted]
Tidy (forthcoming)(103)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tsetsa (2012)(112)	54	NR	NR	NR	NR	NR

[redacted] only reported for the according to protocol (ATP) cohort; [£] in linked Palmer (2015) study, which included all 1237 participants plus an additional 333 patients: 746 biopsies were taken with an average of 1.08 biopsies per biopsied patient. More than one biopsy was taken in 53 patients; [@] In the ATP cohort (n=183),153 control biopsies were taken from apparently normal tissue of which 39 (25.5%) were classed as CIN2+; [redacted]

4.4 Results: assessment of clinical effectiveness

The review of clinical effectiveness aimed to evaluate the following outcomes in studies of DYSIS and ZedScan:

- morbidity and mortality associated with treatment and biopsies conducted as part of the colposcopy examination (including obstetric outcomes such as miscarriage and infertility);
- morbidity and mortality associated with cervical cancer; health-related quality of life;
- pain and anxiety associated with the colposcopy examination, biopsies, treatment and waiting for results;
- any other adverse event that may have an impact on resource use or quality of life.

Only three studies reported data on clinical effectiveness outcomes. All three were also included in the review of diagnostic accuracy.(57, 88, 94) Characteristics and quality assessment of the studies are reported in Tables 2 and 3.

4.4.1 Results of studies on clinical effectiveness

Three studies reported data on adverse events.(57, 88, 94) One study of ZedScan(94) reported one serious adverse event and two adverse events following colposcopy, including one patient who "felt unwell" and two issues with bleeding after biopsies. It is not clear which of these three events was serious, and whether any of these adverse events could be attributed to the use of adjunctive colposcopy. Both studies of DYSIS reported that no patients experienced adverse events following colposcopy.(57, 88) No further data on adverse events were reported.

No data were reported on morbidity and mortality associated with treatment and biopsies conducted as part of the colposcopy examination or associated with cervical cancer in studies of DYSIS and ZedScan. No data of outcomes related to health-related quality of life were found. Data on pain and anxiety associated with colposcopy examination with DYSIS were only collected in patient surveys using non-validated scales, and these results are reported in Section 4.4.2(review of implementation).

4.4.2 Systematic reviews of adverse outcomes of CIN treatment

Due to the limited evidence identified by the review of clinical effectiveness, a pragmatic search for recent good quality systematic reviews on the impact of CIN treatment on adverse fertility, pregnancy, and obstetric outcomes was conducted. Two relevant systematic reviews with meta-analysis were identified.(121, 122) This section provides a critical summary of these reviews.

4.4.2.1 **Kyrgiou (2015)**

Kyrgiou (2015)(121) assessed the effect of excisional or ablative CIN treatment on fertility and early pregnancy outcomes (<24 weeks gestation). The review included studies that compared fertility and early pregnancy related outcomes (before 24 weeks of gestation) in women with a history of CIN treatment to women who had not received treatment. Any types of excisional and ablative treatments were included.

The review included 15 studies (2,223,592 participants, 25,008 of whom received treatment for CIN. All included studies were non-randomised, and heterogeneity was high. The quality of the evidence for early pregnancy outcomes was low (GRADE classification). The results of the meta-analysis showed that CIN treatment did not have an adverse effect on fertility outcomes. The overall pregnancy rate was higher for treated women than those who were untreated (43% and 38% respectively; RR 1.29, 95% CI 1.02 to 1.64; 4 studies). There was no statistically significant difference in pregnancy rates in treated and untreated women with an intention to conceive and women requiring more than 12 months to conceive. There was no increase in total miscarriage rate or first trimester miscarriage rate between the treated and untreated groups; however, CIN treatment was associated with an increased risk of miscarriage in the second trimester (1.6% versus 0.4%, RR 2.60, 1.45 to 4.67; 8 studies). Ectopic pregnancies (1.6% versus 0.8%, RR 1.89, 1.50 to 2.39, 6 studies) and terminations (12.2% versus 7.4%, RR 1.71, 1.31 to 2.22, 7 studies) were also more frequent in treated women. The authors concluded that CIN treatment is unlikely to have an adverse effect on fertility, and there was a slight increase in risk of miscarriage in the second trimester associated with treatment, there was no stratification of risk by treatment type or magnitude. The authors also further emphasised the low quality of the evidence, but suggested women should be advised that fertility is not compromised by treatment for CIN. The conclusions of this generally well-conducted review are likely to be reliable.

4.4.2.2 **Kyrgiou (2016)**

Kyrgiou (2016)(122) focused on studies reporting obstetric (>24 weeks gestation) and neonatal outcomes following local treatment for CIN or early cervical cancer. The review included studies reporting on obstetric outcomes (beyond 24 weeks of gestation), in women who had previously received local treatment for CIN or early invasive cervical cancer compared with women with no history of treatment. Any types of excisional and ablative treatments were included.

Outcomes pertaining to risk of overall pre-term birth were reported by 60 studies, with 25 reporting on 'severe' pre-term birth (<32-34 weeks), and 9 for 'extreme' prematurity (<28-30 weeks). Other outcomes included length of labour (precipitous or prolonged, use of analgesia (epidural, pethidine,

other), oxytocin use, cervical stenosis, and haemorrhage. Neonatal outcomes were low birth weight, admission to neonatal intensive care, stillbirth, APGAR scores, and perinatal mortality.

The review included 71 studies (6,338,982 participants, with 65,082 treated for CIN or early invasive cancer). Nearly all studies were retrospective cohort studies, and none were randomised trials. Most studies were considered high quality observational studies (Newcastle-Ottawa scores 8-10 in all but two studies). For all treatment types, risk of overall prematurity (<37 weeks gestation) was increased in the treated group versus the untreated group (RR 1.78, 95% CI 1.60 to 1.98, 60 studies), as was severe prematurity (<32-24 weeks gestation) (RR 2.40, 95% CI 1.92 to 2.99, 25 studies), and extreme prematurity (<28-30 weeks gestation) (RR 2.54, 95% CI 1.77 to 3.63, 9 studies). Compared with untreated women, all patients who were treated with LLETZ were at higher risk of giving birth prematurely (RR 1.56, 95% CI 1.36 to 1.79, 26 studies), severe prematurity (RR 2.13, 95% CI 1.66 to 2.75, 11 studies), and extreme prematurity (RR 2.57, 95% CI 1.97 to 3.35, 3 studies). The meta-analysis showed treatment for CIN increased the risk of preterm birth regardless of treatment method, with a higher magnitude of treatment effect associated with treatment techniques removing or ablating more tissue; deeper excisions were consistently associated with increased risk of preterm birth (≤10-12 mm; RR 1.54, 95% CI 1.09 to 2.18; ≥10-12 mm: RR 1.93, 95% CI 1.62 to 2.31; ≥15-17 mm: RR 2.77, 95% CI 1.95 to 3.93; ≥20 mm: RR 4.91, 95% CI 2.06 to 11.68). There was also an association between the number of procedures undergone and the risk of preterm birth; pregnancies in women who underwent more than one treatment were significantly more likely to be premature (RR 3.78, 95% CI 2.65 to 5.39).

The risk of other adverse outcomes such as spontaneous preterm birth, premature rupture of the membranes, chorioamnionitis, low birth weight, admission to neonatal intensive care, and perinatal mortality were also significantly increased after treatment. The authors concluded that any local treatment for preinvasive or early invasive disease will increase the risk of preterm birth in a subsequent pregnancy, and that the frequency and severity of adverse outcomes increases with greater cone depth and is higher for excision than for ablation. However, they noted that risks associated with small excisions are likely to be smaller than those related to untreated CIN during pregnancy, which is itself linked to preterm birth (RR 1.24, 95% CI 1.14 to 1.35) compared with the general population. The authors rightly noted the need to interpret the review results with caution, due to the lack of prospective and randomised evidence, a high risk of confounding in the included studies and significant heterogeneity. Given this, the conclusions of this generally well-conducted review are likely to be reliable. However, since most studies included in these reviews were not from recent UK cohort studies, the applicability of the conclusions of these reviews to the NHS context may be limited. (123-125)

4.5 Results: assessment of implementation

The review of implementation aimed to evaluate the following outcomes in studies of DYSIS and ZedScan: acceptability of the adjunctive technologies (clinicians and patients); patient satisfaction; successful database and record management; training requirements; capacity to perform colposcopies; and uptake and compliance.

As part of the wider database search for diagnostic accuracy studies and studies of clinical effectiveness five studies were identified which reported data on any of these implementation outcomes. These included four DYSIS studies(48, 61) (71, 126) and one ZedScan study.(105) All of these studies were linked to diagnostic accuracy studies included in the review of diagnostic accuracy (see Table 3).

4.5.1 Characteristics of included studies

Table 20 presents a summary of the characteristics of the five studies (48, 61) (71, 105, 126) included in the review of implementation. Three studies were conducted in the UK, (71, 105, 126) one was conducted in Spain(48) and one in the Netherlands.(61) Three studies reported data on patient satisfaction with adjunctive DYSIS. (61, 71, 126), one study reported on the acceptability of DYSIS to clinicians,(48) and one study reported views from both patients and colposcopists on DYSIS.(126) One study reported data on colposcopist training requirements associated with ZedScan.

Table 20 Characteristics of implementations studies

Study	Linked diagnostic accuracy study	Location	Study dates	Population and sample size	Study design	Adjunctive colposcopy technology	Outcomes
Budithi (2017) (126)	Budithi 2016 (42)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Coronado (2014)(48)	Coronado (2016)(47)	San Carlos Hospital, Madrid	NR	63 colposcopists	Survey questionnaires, retrospective case reviews	DYSIS	Acceptability of the adjunctive technologies to colposcopists
Louwers (2015)(61)	Louwers (2011)(57)	3 Dutch hospitals	July 2008 to September 2009	239 participants	Survey questionnaires	DYSIS	Patient satisfaction
Lowe (71)	Lowe (71)	4 NHS colposcopy clinics, UK	June 2015 to May 2016	763 patients	Survey questionnaires	DYSIS	Acceptability of the adjunctive technologies to patients
Palmer (2016)(105)	Tidy (forthcoming) (103)	Sheffield Teaching Hospitals	January 2014 to December 2015	5 colposcopists	Observational, single arm	ZedScanZedScan	Training requirements

4.5.2 Quality assessment of implementation studies

The quality of the studies that used a survey questionnaire was limited overall. The validity and reliability of the questionnaires was not established in any of the studies. Two studies included a sample that was considered likely to be representative of the population of interest (61, 126) . Only two studies (48, 61) accounted for relevant confounding factors (e.g. age, education, number of pregnancies, or colposcopist experience). The methods used to estimate training requirements in the ZedScan study were limited, making the validity of this study uncertain. Further results of the quality assessment of the survey questionnaires are reported in Appendix Tables 10.8.

4.5.3 Results of implementation studies

4.5.3.1 Acceptability to patients and patient satisfaction

Lowe (2016)

Lowe (2016)(71) conducted a survey in 763 patients referred to colposcopy clinics in four NHS hospitals to assess their experience with DYSIS colposcope with DYSISmap. Two questionnaires were designed: one for patients undergoing their first colposcopy examination, and one for with prior experience of colposcopy. The study was only reported as a conference abstract and the number of respondents for each questionnaire was not reported. Responses were given on a scale of 1 to 10 with higher scores indicating greater satisfaction/acceptability.

Participants both receiving their first colposcopy or with prior colposcopy experience found that their examination did not take longer than their previous smear test or colposcopy. Anxiety for all patients dropped during and after the examination with DYSIS colposcopy compared with the result of prior examination: from a median score 7 out of 10 before colposcopy to 4 during and 1 after the examination in patients undergoing their first colposcopy examination. Results were similar for patients with prior colposcopy experience (median 6 before, 3 during, and 1 after the examination).

All patients reported that they understood the DYSIS colour coded map and found the map reassuring. Finally all patients with previous colposcopy experience declared they preferred having their future colposcopies with DYSIS and would recommend DYSIS to family and friends requiring colposcopy.

The authors concluded that DYSIS with DYSISmap is very well received by patients and is not intimidating or requiring longer examination times. It also helps to improve patients experience and their understanding of their condition which in turn improve their overall experience and may reduce non-attendance rates.

Louwers (2015)

Louwers (2015)(61) was a sub-study of the trial by Louwers (2011)(57) and included 239 women who underwent colposcopy with DYSIS and DYSISmap. All participants were asked to complete a patient satisfaction questionnaire.

The results showed that 93.9% of the participants agreed or strongly agreed to have colposcopy with DSI if it assisted in locating cervical neoplasia, 29.5% agreed or strongly agreed that DYSIS was less comfortable than Pap smear, 16.5% reported that DYSIS made them feel nervous during the

examination colposcopy, and only 6.5% of participants thought that the DYSIS colposcope took too long.

When asked which test characteristics were considered most important, 88.3% of participants ranked test accuracy as the most important factors. Rapid testing was considered the second most important by 57.4%, and comfort the third most important by 40%. Quick turnaround on results was considered the second least important factor (56.1%) and cost (75.7%) was considered the least important.

A subset of 19 participants who had experienced colposcopy examination prior to the study showed similar results when compared with the participants who never had colposcopy before. However, all disagreed or strongly disagreed with the statement 'colposcopy with DSI takes too much time'.

The authors concluded that women are willing to accept discomfort (in the form of an additional or longer test) if the test has a clear clinical benefits.

Budithi (2017)

[redacted]

4.5.3.2 **Acceptability of the adjunctive technologies to clinicians**

Coronado (2014)

Coronado (2014)(48, 50) conducted a survey in 63 medical practitioners with different levels of colposcopy experience to gather their views on using DYSISmap images compared with

conventional colposcopy alone. The study also conducted a retrospective review of colposcopy and DYSISmap images to estimate the accuracy of conventional colposcopy and DYSIS when diagnosing cervical pathology based on different levels of practitioners experience.

Images from 50 participants with normal and abnormal cervix collected during colposcopy examinations and the corresponding DySIS maps were projected consecutively to the colposcopists. For each case, participants were asked to select one of the following four probable results for that case: normal, low-grade lesion, high-grade lesion or cancer.

The study population included 27 practitioners with low colposcopic experience (i.e. 1st to 3rd-year residents), 18 with medium experience (4th-year residents and gynaecologists with low experience) and 18 with high experience (experienced gynaecologists and accredited colposcopists). None of the participants had any previous experience with DYSIS.

Correct diagnosis was more frequent with DYSIS compared to conventional colposcopy in the low experience and medium experience group, but not in the high experience group (see Table 21).

Table 21 Results of diagnostic decisions in Coronado 2104

Group	Number in group	Mean number of correct diagnoses (95% CI)	
		DYSIS	Colposcopy
Low colposcopic experience	27	24.4 (22.7-26.2)	20.4 (18.8-21.9)
Medium experience	18	26.0 (25.0-27.0)	21.9 (20.4-23.4)
High experience	18	26.5 (24.4-28.7)	24.8 (22.8-26.9)

Table 22 presents the results of the survey. All experience groups agreed that DYSIS was generally better than colposcopy at guiding biopsy site selection, and tended to agree that DYSIS allows performing a colposcopy without experience.

Compared with the high experience group, low and medium experience groups were likelier to agree that: DYSIS interpretation is easier than conventional colposcopy; DYSIS is better at directing diagnosis; it provides more information than conventional colposcopy; and it is generally better than conventional colposcopy.

Table 22 Results of colposcopists' survey in Coronado 2014

Question	Colposcopic experience (mean,95% confidence interval)			
	Low(n=27)	**Medium(n=18)**	**High(n=18)**	**P value**
Is the DYSIS interpretation easier than CC?	4.0(3.6-4.4)	4.2(3.7-4.7)	2.8(2.2-3.5)	0.001
Did DYSIS orient better my diagnosis?	4.0(3.6-4.4)	3.9(3.4-4.4)	3.2(2.6-3.8)	0.028
Did DYSIS orient better my biopsy site?	4.3(4.0-4.5)	4.1(3.7-4.5)	3.7(3.2-4.3)	0.127
Do you believe that DYSIS offers more information than CC?	3.1(2.6-3.6)	3.5(3.0-4.0)	2.6(2.1-3.1)	0.074
Do you believe that DYSIS allows performing a colposcopy without experience?	3.4(2.9-3.9)	3.4(2.7-4.2)	3.7(3.2-3.8)	0.731
Do you believe that DYSIS is better than CC?	2.8(2.3-3.3)	2.9(2.2-3.5)	1.9(1.5-2.4)	0.030
Answers were grade as follows: 1(complete disagreement), 2(disagreement), 3(agreement), 4(good agreement) or 5(fully agree)				

The authors concluded that adjunctive DYSIS improves diagnostic accuracy compared with colposcopy alone, especially among less experienced colposcopists. The authors also stated that inclusion of the DYSIS map into colposcopy is an easy and intuitive way to improve conventional colposcope, particularly for clinicians with limited colposcopic experience.

Budithi (2017)

[redacted]

4.5.3.3 Training requirements

One study, conducted in a single centre in Sheffield which involved in-house colposcopists and linked to Tidy (2013)(94), reported the time needed to train the colposcopists using ZedScan for the first time.(105) The study reported that 5 -10 minutes additional time was needed for the initial training

period and the colposcopists were able to complete the initial 10-20 ZedScan measurements within 2-3 minutes after examining 10 to 20 patients. No further details were reported.

The authors concluded that ZedScan as an adjunct to colposcopy has added minimal time to each appointment and exerting negligible impact on clinical output.

4.5.3.4 **Other outcomes**

No evidence was found for the following outcomes: successful database and record management, capacity to perform colposcopies, uptake and compliance.

4.6 Clinical Effectiveness Summary and Conclusions

4.6.1 Diagnostic accuracy

Nine studies that evaluated adjunctive DYSIS (DYSISmap and DYSIS colposcope) were identified. Adjunctive DYSIS use was found to have higher sensitivity (81.25%, 95% CI 72.2 to 87.9) than standard colposcopy alone (57.91%, 95% CI 47.2 to 67.9) but lower specificity (70.40%, 95% CI 59.4 to 79.5) than colposcopy (87.41%, 95% CI 81.7 to 91.5). This difference appears to be primarily because adjunctive DYSIS leads to more positive test results (i.e. more women are judged to have possible high-grade CIN): in all studies the number of women with positive test results was higher with adjunctive DYSIS than with colposcopy alone. However, the summary positive predictive value for colposcopy alone was only 55.8% and so did not reach the recommended level for UK colposcopy of 65%. This may suggest that how colposcopy was used in the included studies may differ from UK practice. There was no evidence that DYSIS improved diagnostic accuracy (in terms of diagnostic odds ratios). There was insufficient evidence to assess whether adjunctive DYSIS improves cancer detection.

Only two included studies investigated ZedScan. Both were performed by the same researchers in Sheffield. [redacted] The other was a study of a pre-commercial ZedScan prototype. These issues limited our ability to assess the diagnostic accuracy of ZedScan as an adjunct to colposcopy. Results from the prototype study suggested that adjunctive ZedScan could improve diagnostic accuracy when compared to colposcopy alone (i.e. it could increase sensitivity at the same specificity as colposcopy or vice versa). [redacted]

Data on participant subgroups, including women with high-risk HPV or high-grade referrals were limited. The results suggested that colposcopy alone has poor sensitivity to detect high-grade CIN in women with low-grade referrals (e.g. mild dyskaryosis). Adjunctive DYSIS and ZedScan appeared to improve diagnosis in low-grade referral cases. There was some limited evidence that the diagnostic accuracy of adjunctive DYSIS may be greater in women with high-risk HPV infection.

Sensitivity analyses identified that the specificity of all methods was strongly dependent on what reference standard was used in women who were given a normal colposcopic evaluation result. Specificity was much higher where no biopsies were performed in those women, suggesting a possible verification bias due to under-diagnosis of high-grade CIN. This means that the actual specificity of colposcopy and adjunctive colposcopy is uncertain, as it depends on the use of the reference standard. Verification bias may not affect relative differences in diagnostic accuracy between index and comparator tests in such studies, assuming that it will affect the accuracy of both tests equally.

Test failure rates ranged from 2.9% to 16.7% in studies evaluating a commercial version of DYSIS. [redacted]

There was limited data on diagnostic biopsies and treatments conducted during or following examination with adjunctive colposcopy. Due to the lack of randomised evidence comparing adjunctive technology with colposcopy alone, evidence of the impact of adjunctive technology on the rates of diagnostic biopsies and treatment (including unnecessary treatments) is very limited.

4.6.2 Clinical effectiveness

Only three studies that reported data on our pre-specified clinical effectiveness outcomes were included. One study of ZedScan reported three adverse events, of which one was serious and two studies of DYSIS with DYSISmap reported that no adverse events occurred following colposcopy examination. No data were reported on mortality, morbidity and health-related quality of life in studies of DYSIS and ZedScan.

4.6.3 Implementation

There is reasonable evidence that DYSISmap as an adjunct to colposcopy is generally well received by patients referred for colposcopy and that patients are generally satisfied with the duration of examination (2 studies). There is evidence to suggest that DYSISmap was generally reassuring and that pre-examinations levels of anxiety decreased significantly during and after the examination (1 study), and that only a minority of patients (16.5%) felt nervous during the examination (1 study).

There is evidence from two surveys that adjunctive DYSIS was consistently perceived by clinicians to improve accuracy of colposcopy and confidence in their diagnostic decisions and biopsy site selection. There is evidence that adjunctive DYSIS was intuitive for clinicians with limited colposcopy experience and improved their evaluations (one study). There is evidence that additional time required to use ZedScan is minimal in experienced colposcopists. All included studies had significant limitations, therefore these findings need to be interpreted with caution.

No evidence was found for several of the pre-specified outcomes: successful database and record management, capacity to perform colposcopies, uptake and compliance. No evidence was found regarding training requirements for DYSIS. The limited evidence for ZedScan precludes conclusions for any of the implementation review pre-specified outcomes.

4.6.4 Conclusions

The review of diagnostic accuracy found that adjunctive DYSIS increased sensitivity, but decreased specificity when compared to colposcopy alone. This appears to be because the number of women classed as having possible high-grade CIN is increased, rather than any improvement in diagnostic accuracy per se. ZedScan I also appears to be associated with higher sensitivity and lower specificity than colposcopy alone when compared with the evidence from other included studies. However, the evidence for the accuracy of ZedScan I as an adjunct to colposcopy is limited as it is based on a single study at high risk of bias and due to a lack of direct comparative evidence with standard colposcopy. This precludes any definitive conclusions regarding the diagnostic accuracy of ZedScan I as an adjunct to colposcopy. There was insufficient evidence to directly compare DYSIS with ZedScan.

There was too little evidence to assess whether the technologies have any adverse effects. DYSIS appears to be well received by both patients and colposcopists.

Increased sensitivity should lead to more high-grade CIN cases being correctly diagnosed, but decreased specificity is also likely to lead to more unnecessary diagnostic biopsies and treatments in women without high-grade CIN. The clinical value of adjunctive colposcopy, whether with DYSIS or ZedScan, therefore depends on whether the value of diagnosing more CIN cases outweighs the disadvantages of more unnecessary biopsies and treatment.

5 Assessment of existing cost-effectiveness evidence

Relevant cost-effectiveness evidence of adjunctive colposcopy technologies (DYSIS with DYSISmap, and ZedScan I, hereafter referred to as "DYSIS" and "ZedScan") were systematically identified, appraised for quality and summarised. The objectives of the review were to identify key structural assumptions, highlight areas of uncertainty and assess the generalisability of the results of existing models to the current decision problem. The findings from the review also informed the development of a new decision analytic model reported in the following chapter.

5.1 Methods

Searches

The literature search previously reported in Section 4.1 was also used to identify studies relating to the cost-effectiveness of adjunctive colposcopy techniques.

Study selection

A broad range of studies were considered in the review including economic evaluations conducted alongside trials, modelling studies and analyses of administrative databases. Only full economic evaluations that compared two or more options and considered both costs and consequences (i.e. cost-minimisation, cost-effectiveness, cost-utility and cost-benefit analyses) were included in the review.

Relevant studies were then selected in two stages. Titles and abstracts identified by the search strategy were examined and screened for possible inclusion. Full texts of the potentially relevant studies were obtained. Two researchers (MP and PM) examined these independently for inclusion or exclusion and disagreements were resolved by discussion.

A quality appraisal was carried out using the checklist of Drummond and Jefferson (1996) (127) and is available in Appendix 10.9. This checklist evaluates the extent to which each review result provides detail on different aspects such as study design, data collected and its use in the economic evaluation, and analysis and interpretation of results.

5.2 Results of review of existing cost-effectiveness evidence

The initial search of economic databases identified a total of 182 references. After the initial screening of titles and abstracts, only 2 studies were considered to be potentially relevant and were ordered for full paper screening. Both studies met the selection criteria and were included in the review.

Of the 2 studies included, one was an independent assessment of the cost-effectiveness of DYSIS developed for the previous NICE DG4 assessment (Wade, 2013 (30)). The other study was a company funded assessment of a prototype version of ZedScan (Whyte, 2013 (128)). A summary and critique of these studies is reported in the following sections.

5.2.1 Review of Wade (2013)

5.2.1.1 Decision problem/objective

A decision-analytic model was developed to assess the cost-effectiveness of adjunctive colposcopy technologies for assessing suspected cervical abnormalities in women referred for colposcopy as part of the NHS cervical screening programme under the HPV triage screening protocol.

Three technologies were initially considered: DYSIS, LuViva Advanced Cervical Scan and Niris Imaging System. Due to the lack of reliable data, LuViva Advanced Cervical Scan and Niris Imaging System were subsequently excluded from the base case analysis.

The model evaluated costs from the perspective of the NHS and Personal Social Services, expressed in UK £ sterling at a 2011 price base. Outcomes in the model were expressed in terms of QALYs. The model employed a lifetime (50-year) horizon and costs and outcomes were discounted at a rate of 3.5% per annum.

5.2.1.2 Strategies/comparators

The base case economic evaluation compared the costs and health outcomes of DYSIS, alone and as a colposopic adjunct, with standard colposcopy. Base case results were presented by reason for referral (borderline and HPV+, mild and HPV+, moderate, severe, possible invasion, possible neoplasia, 3 times inadequate) and for the whole population based on a weighted average of the results of each reason for referral. A separate indicative analysis was undertaken to test the sensitivity needed for Niris and LuViva to be considered cost-effective given their reported costs and an assumed specificity.

5.2.1.3 Model structure

The model incorporated two elements: first, a decision tree to represent the initial diagnostic and treatment pathways for patients referred to colposcopy from the NHS Cervical Screening Programme (under the HPV triage screening protocol); and, second, a Markov model which simulates the natural history of patients and captures future cytological screening and referrals to capture the long-term costs and outcomes of the initial diagnostic and treatment pathways.

The decision tree was specifically developed for the appraisal informing NICE DG4, whereas the Markov model was based on a revised model previously used by Hadwin (2008) (129), and was referred to as the Sheffield model. The decision tree has three main components: (i) diagnostic outcome; (ii) treatment decision; and (iii) treatment outcome.

The diagnostic outcome depends on diagnostic accuracy given a patient's true underlying health state. Specifically, diagnostic accuracy is modelled as the probability of being diagnosed with health state *h'*, conditional on the true underlying health state *h*.

Treatment decisions depend on diagnostic outcome and the reason for referral. A patient may either not receive treatment or be referred for a diagnostic biopsy, a treatment biopsy (LLETZ) or a cancer treatment.

Treatment outcome impacts both the true underlying health state and subsequent screening. The impact on a patient's health state depends on the probability of being cured. If patients have not been treated they enter the natural history Markov model with their initial true underlying health state. For patients with pre-cancerous lesions who been treated with excision biopsy, there is a probability this is cured. If treatment has been successful, they enter the natural history model Markov in the `clear' state. If not, they enter the natural history model with their initial health state.

As previously stated, a state-transition (Markov) cohort model is used to capture the long-term costs and outcomes of the initial diagnostic and treatment pathways by simulating the natural history of patient and incorporating future cytological screening and referrals. Although the use of a cohort model was appropriate for the specific decision problem, the model itself subsequently required hundreds of separate states to be included in order to capture the complexity of screening pathways and the heterogeneity in treatment decisions and outcomes. This complexity arises because the screening pathways and treatment decisions depend on a patient's characteristics (e.g. age, health state), their previous history (e.g. screening results, treatment outcomes, follow-up) and these also impact the transitions between health states in the natural history model. With a cohort approach, the only way to account for individual heterogeneity and to build sufficient 'memory' to capture the complexities is to increase the number of states. Although the complexity could have potentially been more efficiently reflected by using a patient-level simulation, the final model structure appeared to rely heavily on the use of an existing natural history cohort model from Sheffield which may have constrained the authors in terms of their chosen modelling approach.

Treatment pathways incorporated in the model were based on NHSCSP Guidelines which describe good practice in treatment decisions and follow-up of pre-cancerous lesions and invasive cancer. However, the authors identified an important discrepancy between guidelines and clinical practice and chose to use evidence from the latter based on data from Gateshead to capture heterogeneity in treatment pathways. For instance, national guidelines state that a low-grade referral with normal colposcopy should be discharged without any treatment and returned to routine screening. Observational data from Gateshead clinic suggested that 73.5% of these patients would receive diagnostic biopsy and only 10.7% would be sent back to routine screening.

Adjunctive technologies to colposcopy were assumed to be used for the initial referral and for subsequent colposcopy appointments (treatment, follow-up). The model also assumed that there is no loss to follow-up and hence all women were assumed to attend subsequent appointments for colposcopy and cytology.

5.2.1.4 **Main sources of data**

The model incorporated three main sources of data input: (i) diagnostic accuracy; (ii) natural history of cervical cancer; and (iii) characteristics of the population referred for colposcopy.

Diagnostic accuracy

Diagnostic accuracy of colposcopy and DYSIS were based on specificity and sensitivity reported by Louwers (2011) (57). Louwers (2011) (57) report diagnostic accuracy based on a CIN2+ cut-off leading to a dichotomous classification of the performance of the diagnostic technologies. However, the economic model required the probability of the diagnoses of the different stages of disease, whether correct or incorrect, conditional on a patient's true underlying health state (e.g. clear, HPV, CIN1 etc). For example, a true 'clear' patient correctly classified below CIN2+ (and hence defined as a true-negative based on the dichotomous cut-off) could either have been correctly diagnosed as 'clear' or they could have been incorrectly diagnosed as 'CIN1'. Hence, additional assumptions were employed in Wade (2013) (30) to convert the diagnostic accuracy data into the probabilities required for the model.

The probabilities required for the model were calculated using main two steps. First, the probability of being diagnosed as a true positive, true negative, false positive or false negative was derived from Louwers (2011) (57). These probabilities depend on the devices' diagnostic accuracy. Second, the probability of being diagnosed with a specific stage of the disease, conditional on patients' true underlying state and on being true positive, true negative, false positive or false negative was derived from a study by Gallwas et al. (2012) (130), which reported the diagnostic accuracy of a different diagnostic device, the Niris Imaging System.

This approach relies on two strong assumptions: the results reported by Gallwas are reliable and can be generalised for other type of devices. The study by Gallwas (2012) (130) includes a 2x2 table with the outcome of colposcopy by patients' health state, confirmed by histology. However, biopsies were performed only when pre-cancerous lesions were suspected. The population targeted by the study therefore excludes false negatives. This was considered by Wade (2013) (30) as a significant bias and motivated the decision to exclude the Niris Imaging System from the main analysis. The second main assumption is that diagnostic accuracy of Niris Imaging System, conditional on being true positive, true negative, false positive or false negative is similar for colposcopy alone, DYSIS alone and DYSIS plus colposcopy.

Additionally, the model aimed to capture subsequent referrals for colposcopy when patients are followed-up or called for routine screening under the HPV triage scheme. Data on performance of the cytology and HPV tests were derived from Eggington (2006) (131). Sensitivity and specificity of HPV test given patient's age and cytology result were derived from the TOMBOLA study (Cotton, 2010 (132)).

Natural history of cervical cancer

The natural history model was based on the Sheffield model and simulated the progression of patients between nine mutually exclusive health states: clear, HPV, CIN1, CIN2/3, invasive cancer stages from 1 to 4 and death. Patients entered the natural history model in the health state based on screening and treatment outcomes. Patients were allowed to progress or regress between these states every 6 months. Age-related transition probabilities of progression and regression in the Sheffield model were derived from Myers (2000) (133).

The natural history model relies on three main structural assumptions: (i) the linear progression of patients between states; (ii) a single combined state for CIN2 and CIN3; and (iii) patients diagnosed with cancer who survive 5 years after treatment are cured and move to the `Clear' state. These assumptions are summarised below:

- First, patients are only allowed to progress stage by stage. They are initially infected by HPV, then develop CIN1, CIN2/3 and finally invasive cancer from stage 1 to 4. Cancer cannot regress without treatment. However, pre-cancerous lesions can regress without intervention to an earlier stage or directly to the clear state.
- Second, because the study by Myers (2000) (133) did not provide separate transition probabilities for CIN2 and CIN3 states, CIN2 and CIN3 were combined in the natural history model into a single combined health state. No additional mortality risk was assumed for pre-cancerous lesions and HPV, CIN1 and CIN2/3 and these states were also assumed to be asymptomatic. Patients cured of CIN were assumed to have the same risk of future CIN as the general population.
- Finally, the modelling of cervical cancer relies on a series of assumptions. The model uses different mortality rates for undiagnosed and treated cancer. Patients only progressed between cancer stages if they were not treated. Undetected cancer was assumed to be asymptomatic with a probability of developing symptoms during each 6 month cycle that increased by stage. It was assumed that a patient who develops symptomatic cancer would be systematically diagnosed and treated within the next 6 months. When a patient was diagnosed with asymptomatic cancer during a routine screening, it was assumed that she would be diagnosed with stage 1 cancer. After being diagnosed with cancer, patients faced a 5-year elevated mortality risk. Patients who survived 5-years were assumed to transition to the `Clear' state and at this point were assigned a QALY

decrement and cost associated with their previous cancer treatment. Patients who died from cancer immediately entered the death state but were assigned a QALY decrement and cost associated with their previous cancer treatment.

Characteristics of the population referred for colposcopy

Estimating the characteristics of patients referred for colposcopy is critical in the cost-effectiveness assessment of adjunctive colposcopy technologies. Women entered the model with a `true underlying health state' (e.g. clear, HPV, CIN1 etc) and a reason for referral (borderline changes, mild dyskaryosis, etc). The reason for referral impacts treatment pathways and outcomes and the initial true underlying health state impacts colposcopy results and disease progression. To be representative of the population referred for colposcopy, the estimated joint distribution has to capture the impact of both disease prevalence and the screening programme.

The joint distribution of reason for referral and true underlying health state in Wade (2013) (30) was based on three sources of data. The distribution of patients by reason for referral, under the HPV triage protocol, was based on data from the NHS Cervical Screening Programme, together with a study by Kelly (2011) (134). Kelly et al (134) reported the proportion of women with borderline or mild cytology results that tested HPV positive. Data from sentinel sites for HPV triage implementation (10% of the English cervical screening programme) were used to estimate the impact of HPV triage on the distribution of women referred to colposcopy. The weighted population used in the base case analysis was: 38.52% with borderline + HPV, 35.39% with mild dyskaryosis + HPV, 11.51% with moderate dyskaryosis, 13.06% with severe dyskaryosis, 0.51% with possible invasion and 1.01% with possible glandular neoplasia.

The proportion of women with a true underlying health state *h*, given reason for referral *r,* was based on a retrospective study conducted at the Northern Gynaecological Oncology Centre, Queen Elizabeth Hospital, Gateshead (hereafter referred to as the Gateshead data). The Gateshead data included 4533 patients who attended a colposcopy examination in 2008-2009. Patients' true health state was revealed by biopsy, where available. The Gateshead data has two potential limitations. First, data were collected from a single centre which may not be representative of the prevalence of the disease in the general population. Second, biopsies were not systematically performed. Where biopsy was not performed, the study only reported the colposcopy diagnostic. Since colposcopy is not 100% sensitive and specific, the colposcopy outcome may not reflect the true prevalence of the disease. Hence CIN1 and `Clear' health states, which do not need to be confirmed by histopathology, may be overrepresented. In an alternative scenario, the sample was restricted to diagnosis confirmed by histopathology. However, this approach tends to select more severe cases and therefore is likely to underestimate the prevalence of Normal, HPV and CIN1.

5.2.1.5 **Resource use and costs**

The resource use and costs estimates included the acquisition costs of the alternative technologies (including maintenance and use of disposables) and further treatments. The number of patients managed under a single colposcopy device was provided by clinical advisors and was used to calculate the average cost per procedure for each technology. To capture the additional costs of a colposcopy visit (e.g. diagnostic and treatment biopsy), treatment costs from the TOMBOLA study were used. Cancer costs by stage were derived from a UK-based study by Wolstenholme (1998) (135).

The cost per patient of colposcopy and adjunctive technologies has two main components: (i) a cost per patient, common to all devices, which includes costs related to the examination itself such as facilities and staff; and (ii) an additional cost that depends on the device and includes the cost of acquisition, maintenance and disposables. The UK-based TOMBOLA study (136) (trial of management of borderline and other low grade abnormal smears) was used to estimate the cost of colposcopy alone (including price of the device and maintenance) as well as per patient costs of biopsy and excision treatment (LLETZ). The examination with DYSIS was assumed to be equivalent to colposcopy alone in terms of staff resources, i.e. same length of consultation and negligible staff training. The additional cost includes the acquisition cost, annual maintenance costs and disposables, all provided by the manufacturer. It was assumed that clinics have the choice between investing in a binocular colposcope or the DYSIS device (colposcope plus digital map). Therefore the purchase price of a binocular colposcope was included in the cost of colposcopy alone but not for DYSIS. Another important assumption is the number of patients examined per year per colposcope. This is critical when estimating the cost per patient, especially if technologies differ in terms of the initial investment and throughput. An estimate of 1229 patients per year was assumed based on clinical advice. This was assumed to be exogeneous to the performance of the device.

Management costs of cervical cancer by stage at initial diagnosis were derived from Wolstenholme (1998) (135). The study was based on an audit of resources and costs over 5 years on 261 women in the Trent region of central England in 1990. Although these costs appear to be based on the best evidence available at the time, there exists uncertainty regarding how representative these estimates are given the historic nature of the study and the need to inflate costs over a significant time period.

5.2.1.6 **Quality of life/Utilities**

Within the model, colposcopy and DYSIS were assumed to impact health outcomes in two ways: through the disutility associated with the examination itself, subsequent treatment and tests; and through the disutility associated with the development of invasive cancer.

The direct disutility associated with colposcopy alone and DYSIS was not assumed to be different. However, because diagnostic accuracy impacts the number of subsequent treatments and follow-up, QALY decrements associated with colposcopy examination, cytology test and biopsy were important for the assessment of cost-effectiveness.

The disutility associated with cytology exam was assumed to be 0.02 (Insinga, 2007 (137)) over 1 month, i.e. -0.0016 per cytology exam. The disutility of colposcopy and biopsies were derived from a time trade-off analysis by Birch (2003) (138). The study reported HRQoL for three different scenarios: "three repeat Pap Smears" (0.958), "immediate colposcopy with no pathology" (0.927) and "cone biopsy after immediate colposcopy" (0.922). The difference of 0.031 between pap smears and immediate colposcopy was used as a QALY decrement applied for each colposcopy examination. The difference of 0.005 between colposcopy with no pathology and cone biopsy was used as a QALY decrement for diagnostic and treatment biopsies. As noted by the authors, this rather small decrement, similar for diagnostic and treatment biopsies, is a strong assumption and may underestimate the impact of biopsies on health. As noted in Section 4.4.2, recent evidence exists indicating that treatment biopsies may increase the risk of adverse obstetric outcomes and specifically pre-term delivery. However, evidence at the time the model was conducted was reported to be scarce and inconclusive. Given this uncertainty, the QALY decrement of a treatment biopsy on health outcomes was further explored in a separate scenario analysis. The HPV, CIN1 and CIN2/3 states were assumed to be asymptomatic and hence were assigned the same utility as the clear state, reported as 0.91.

Health utilities associated with the four stages of invasive cancer were derived from Chuck (2010) (139). It was assumed that invasive cancer would only be detected at an asymptomatic stage through routine screening. Patients who subsequently developed symptoms were assumed to be immediately referred for colposcopy and were appropriately diagnosed and treated. The model thus made an important distinction in the health utilities between undiagnosed and diagnosed cancer. Specifically the model incorporated much lower HRQoL scores for untreated (and therefore undiagnosed) cancer than for treated cancer. These estimates were reported to be based on estimates reported by Chuck (2010) (139).

In our review we identified some important uncertainties surrounding the source and subsequent application of the estimates within the model by Wade et al. The estimates reported by Chuck (2010) (139) are actually referenced to a separate study by Goldie (2004) (5). Goldie et al (5) distinguished `quality weights' for detected invasive cancer, by stage and quality weights after treatment for invasive cancer. The use of the estimates from Goldie et al (5) and their application in the model by Wade et al (30) raises several potential issues. First, it's unclear whether `detected invasive cancer' as

described by Goldie et al. can be interpreted as cancer `without treatment'. This appears inconsistent with the fact that undiagnosed cancer is assumed to be asymptomatic. Our interpretation of the estimates reported by Goldie et al (5) is that the lower weights of detected cancer might more appropriately indicate that disutility is higher at the time of diagnosis and initial treatment than `after treatment'. The `detected invasive cancer' stage might therefore be considered to capture the disutility associated with the initial period after diagnosis. This would appear more consistent with the initial treatment burden that patients treated for cervical cancer may face after being diagnosed but which may subsequently recover relatively quickly, particularly when cancer is detected at early stage. Second, the method to estimate these `quality weights' reported by Goldie et al (5) cannot be identified and hence it's unclear the extent to which these appropriately represent health utilities. Finally, there appears a reporting error in the Chuck study, and subsequently reproduced in the model by Wade et al (30): the score associated with stage 2 cancer `without treatment' is reported as 0.67 (higher than stage 1) in Chuck et al (139) and 0.56 in Goldie et al (5)

5.2.1.7 **Main results (including base case and key sensitivity analyses)**

The results of the economic evaluation compared DYSIS plus colposcopy to colposcopy alone, for each reason for referral and for the whole population. In most instances, colposcopy alone was found to be dominated by DYSIS plus colposcopy. That is, colposcopy alone had higher costs and lower health outcomes than DYSIS plus colposcopy (Table 23).

Table 23 Base case results for the whole population, Wade (2013)

Technology	Costs	QALYs	ICER
Colposcopy alone	1313.59	20.41339	
DYSIS + colposcopy	1254.00	20.42805	Dominant

A potentially counter-intuitive result identified was that an increase in a diagnostic device's specificity resulted in worse outcomes. In particular, it appeared better to falsely identify CIN1 patients as CIN2/3 than to find they are truly CIN1. According to the authors, this result suggested that the treatment of CIN1 is more cost-effective than watchful waiting because of the low cost and low QALY decrement associated with treatment biopsy. Further analyses subsequently determined the threshold of each input at which an increase in specificity would improve outcomes. The QALY decrement of treatment biopsy needed to be increased from 0.005 to 0.13 or its cost from £97 to £2758.

5.2.1.8 **Assessment of uncertainty**

Several scenario analyses were considered with the following variations in the base case assumptions: patients' age, duration of the HRQoL decrements as a result of cancer, cancer treatment costs, perfect

health for Clear and HPV states, QALY decrement associated with treatment biopsies and cytological screening, alternative costs of colposcope, alternative treatment probabilities and the assumption that patients who are tested negative by colposcopy or adjuncts would be diagnosed as clear. Overall, for all sensitivity analysis undertaken, colposcopy alone was dominated by DYSIS plus colposcopy.

A secondary analysis considered a higher cost and QALY decrement associated with treatment biopsy (-0.13 from 0.005 in the base case). At this value, higher specificity is expected to generate improved outcomes. The secondary analysis was also combined with sensitivity analyses previously described. Results suggested that colposcopy alone was still dominated by DYSIS plus colposcopy (Table 24).

A probabilistic sensitivity analysis (PSA) was not conducted and all results were based on deterministic estimates.

Table 24 Secondary analysis results with treatment biopsy QALY decrement of 0.13 for the whole population, Wade (2013)

Technology	Costs	QALYs	ICER
Colposcopy alone	1313.59	20.33799	
DYSIS + colposcopy	1254.00	20.34705	Dominant

5.2.2 Review of Whyte (2013)

5.2.2.1 Decision problem/objective

The aim of Whyte (2013) (128) was to assess the cost-effectiveness of a prototype version of ZedScan as an adjunct to colposcopy relative to standard colposcopy alone from an NHS perspective. The population included in the analysis were women referred to colposcopy from the NHS Cervical Screening Programme (under the HPV triage screening protocol.

The analysis focused on assessing the impact of ZedScan on initial colposcopy appointments and colposcopy follow-up appointments. Outcomes were predicted for three different types of colposcopy clinic: 'See and Treat', 'Treat later' and 'Triage' clinics, which allowed for the optimal screening pathway to be established, as well as the cost-effectiveness of ZedScan in each type of clinic. The different types of clinic were formally defined as:

- *Treat later Clinic:* No treatment at initial colposcopy appointment. Biopsy confirmation before treatment at a later colposcopy appointment.
- *See and Treat Clinic*: Women may receive treatment at initial colposcopy appointment if diagnosis suggests this is appropriate.
- *Triage Clinic*: HG referrals seen in a see and treat clinic so may receive 'diagnosis and treatment at same colposcopy appointment'. LG referrals seen in a treat later clinic.

The analysis used a diagnostic threshold for ZedScan which set the sensitivity at a similar level to that of standard colposcopy, resulting in the main difference between the two devices being their specificity rates. The analysis assessed the cost-effectiveness of ZedScan by assessing several outcomes which included: the number of colposcopy appointments, the number of biopsies conducted, costs related to colposcopy and adverse events, and overtreatment rates. In addition, the analysis also considered treatment rates of CIN and associated adverse event rates, as well as whether increased sensitivity with ZedScan might increase clinician confidence to offer more 'see and treat' appointments due to reductions in the numbers of unnecessary treatments and the associated cost-effectiveness of such changes.

The time horizon of the evaluation was 3 years and was justified on the basis that most patients would be returned to routine screening within this time period. Costs and outcomes were discounted at a rate of 3.5% and a price year was not stated.

5.2.2.2 Strategies/comparators

ZedScan adjunct with colposcopy was compared to colposcopy alone. No attempt was made to compare ZedScan with alternative diagnostic tools which can be used as an adjunct to colposcopy.

5.2.2.3 **Model structure**

The economic evaluation modelled the natural history of women at risk of developing cervical cancer and the colposcopy diagnostic pathway. A patient level model was constructed, allowing the model to track the underlying health state of patients and their location within the colposcopy pathway. After an initial colposcopy in the first cycle, patients are located in one of the following discrete locations within the colposcopy pathway: 'LG CIN1 follow-up', 'HG follow-up pathway', 'Test of Cure', 'Routine screening', 'Refer to colposcopy following fail at Test of cure', and 'Cancer'. Following the diagnostic pathway the model tracks patients natural history, with women able to progress or regress through the CIN stages. The discrete health states included in the analysis were: 'Clear', 'HPV', 'CIN1', 'CIN2', 'CIN3', and 'Cancer', with cancer divided into FIGO stages of severity from I-IV. A cycle length of six months was selected as this is the shortest time between repeat colposcopies.

The model estimated the number of colposcopy appointments and biopsies conducted at each of the clinic types, as well as the number who received treatment for CIN for each type of colposcopy. This allowed for the estimation of costs associated with each scenario, as well as the average utility decrements associated with colposcopy, biopsy and treatment. The model simulated 1,000,000 women for each diagnostic tool and each clinic type.

The distribution of the colposcopy population according to health state and cytology grade was estimated using data on the outcome of colposcopy given the referral cytology. After patients received their initial cytology examination then there were assumed to be seven possible outcomes. If the result was negative then patients are returned to routine screening, a mild or borderline outcome results in a HPV test being conducted, with a positive HPV test result leading to a low-grade referral to colposcopy, and a negative result leading to patients being returned to routine screening. If the cytology result was 'moderate', 'severe' or 'invasive cancer' then patients were sent to colposcopy as a high grade referral. If the outcome of cytology was inadequate then patients were sent for a repeat cytology test in 3 months' time, with three consecutive inadequate results leading to a low grade colposcopy referral. Patient's referral type was tracked as it was assumed that ZedScan would be used with a different threshold for low grade and high grade referrals, resulting in different sensitivities and specificities.

Whether patients received treatment and the timing of treatment was dependent on their referral grade, their colposcopy result and the clinic type. The three types of clinics that were considered in the analysis were 'see and treat', 'treat later', and 'triage'. At the 'see and treat' clinics women could receive treatment at their initial colposcopy appointment if the diagnosis is clear that it is appropriate. 'Treat later' clinics do not provide treatment at initial colposcopy appointment, instead patients receive a biopsy confirmation and are treated at a future appointment. 'Triage clinics' split patients by

their referral grade, with high grade referrals managed in a 'see and treat' clinic and low grade referrals managed in a 'treat later' clinic. Those treated for CIN are assumed to be treated with large loop excision of the transformation zone (LLETZ), although in reality a range of treatment options are available in practice.

After colposcopy, patients follow one of six pathways. Firstly, women with a low grade referral who are identified as clear are sent back to routine screening in three years' time. Secondly, patients who are identified with cancer are sent to oncology regardless of their referral grade. The third pathway results in women with a low grade referral identified as CIN1 receiving a further colposcopy in 12 months' time. If they are found to be CIN1 at the follow-up colposcopy they are sent to a further colposcopy a year later, but after a third CIN1 result they are treated. At the second or third colposcopy those who are identified as clear return to routine screening, women found to be CIN2+ are sent for treatment and those identified with cancer are referred to oncology. The fourth pathway involves women with a high grade referral who are identified as clear or CIN1 being referred to colposcopy in six months' time, with a subsequent result of CIN1+ resulting in treatment, and cancer leading to an oncology referral. Those who are identified as clear in the repeat colposcopy are sent back to a colposcopy in a further six months, with five consecutive clear colposcopy results resulting in patients being sent back to routine screening. The fifth pathway results in patients who are treated for CIN going on to receive test of cure which consists of a cytology test at six months, and a subsequent HPV test if the cytology result is negative. The final pathway involves referring patients who receive test of cure and have a positive cytology or a positive HPV test then patients to colposcopy.

Following completion of the screening phase, patients enter a natural history model. This model assumes that patients start with a high risk HPV infection, which can either clear or progress to CIN, with patients starting with mild changes (CIN1) and either progressing to mores severe stages (CIN2 and CIN3) or regressing back to clear. If patients progress to cancer then it is assumed that they can regress back to a non-cancer state with or without treatment. Progression and regression rates of CIN2/3 to Cancer were assumed to be similar to the rates from CIN1 to CIN2/3 and Clear.

Due to the analysis focussing on a time horizon of just three years the natural history model is unable to capture the long-term effects of failing to identify and treat CIN caused by ZedScan having a lower sensitivity than colposcopy for low grade referrals. In the short-term failing to treat those with CIN will reduce costs but, however, there will be longer-term treatment cost, health related quality of life and mortality impacts which are not captured within the time horizon.

5.2.2.4 **Main sources of data**

The methods used to identify appropriate parameter estimates were not transparently reported. The study makes reference to a review which was conducted in order to identify studies with information useful for understanding the natural history of HPV. However the details of the search were not reported. No review was explicitly reported for other parameters.

Natural history/baseline data

The review conducted to identify publications reporting data on the natural history of HPV and CIN found eight studies of relevance. Data taken from a French prospective study conducted by Sastre-Garau (2004) (140) was used in order to estimate the six month progression and regression rates between states in the natural history model. The study tracked 86 women with confirmed CIN1, and observed how many patients progressed and regressed over a median follow-up time of 24 months. The transition probabilities utilised in the model were highly uncertain due to the small sample size of the study. Additionally, strong assumptions were made that progression and regression rates from CIN2/3 to CIN1 and cancer were the same as those from CIN1 to clear/HPV and CIN2/3, with little justification provided for this assumption.

The proportions of the initial true underlying states of patients in the analysis and their reason for referral were estimated using data from a study published by Blanks and Kelly (2010) (141). This study examined cytology data from 102 laboratories and presented findings for patients who had received a received a follow-up colposcopy. The assumption is therefore made that the result patients received at colposcopy accurately determined their true underlying health status, which is a strong assumption as the sensitivity of colposcopy is below 100%. In order to address this limitation a sensitivity analysis was conducted in which the prevalence of CIN2+ was increased by 10%.

Treatment effects

The performance of ZedScan and standard colposcopy in terms of their respective sensitivity and specificity rates were measured using two methods: colposcopic impression (CI) and disease present (DP). Colposcopic impression measured performance by assessing whether a patient was correctly identified as either CIN2+ or normal/CIN1 by clinical impression only. Disease present on the other hand measured performance by looking at whether a patient was correctly identified or was scheduled to receive a biopsy, where biopsy was assumed to have 100% sensitivity and specificity. The CI method therefore results in a higher specificity value for the devices, whereas the DP method results in the devices having a higher sensitivity.

The data on the sensitivity and specificity of standard colposcopy and ZedScan were taken from the EpiCIN trial (Tidy, 2013 (94)). The study recruited 474 women referred to colposcopy with an abnormal cytology result and included two phases. The first phase involved using ZedScan to take

EIS readings from different points on the cervix before and after the application of acetic acid and assessing its performance against CI and DP. This allowed for a probability index and a threshold value for the detection of CIN to be calculated which indicated the sites for biopsy in the second phase. The second phase involved clinicians selecting biopsy sites before using ZedScan to identify additional sites based on whether the probability of high-grade CIN was greater than the selected threshold value. The sensitivity and specificity values for ZedScan and colposcopy used in the model were taken from phase 2 of the trial. Different sensitivity and specificity values were estimated for high grade and low grade referrals respectively.

A limitation of the analysis is that the sensitivity and specificity were assumed to be equal for clear/CIN1 and for CIN2/3, which is a simplification of reality. These sensitivity and specificity values will likely differ as patients with CIN1 will for example likely have a greater chance of being incorrectly identified as CIN2+ than those who are clear. This is an issue as the identification of CIN1 patients is important as they will experience a different follow-up treatment pathway to those diagnosed as clear.

Estimates of the frequency of biopsy at colposcopy were calculated from data found in phases 1 and 2 of the EpiCIN trial and using several assumptions. The data used was estimated rather than being observed which makes the data susceptible to error and the estimates do not come from a 'see and treat' clinic so its generalisability may be limited.

5.2.2.5 **Resource use and costs**

The costs of colposcopy, biopsy and treatment were estimated using data from Sheffield Teaching Hospital, and therefore it is unclear whether they are generalisable to the wider UK population. These costs were calculated using the price of components and staff time, with a fixed cost included for colposcopy.

The cost per use of the ZedScan device was assumed to be £31 which was stated to include the disposable tip, cost of device, training and maintenance. However, no calculations were reported to demonstrate how this cost had been derived. The ZedScan device was assumed to be used for all diagnostic colposcopies but not used for treatment colposcopies following biopsy confirmation of disease.

The costs of HPV testing and cytology were taken from the HPV sentinel sites. Adverse event costs were included for women experiencing severe bleeding or discharge (TOMBOLA, 2009 (142)).

5.2.2.6 **Quality of life/Utilities**

Quality of life decrements were included for bleeding, pain and discharge, with data on adverse event frequency and the duration of each event taken from the TOMBOLA trial, a large multi-centre UK

based study (TOMBOLA, 2009 (142)). Utility decrements were also included to capture patients' preferences for the follow-up they receive after an abnormal cytology result which were estimated for colposcopy, colposcopy with biopsy and colposcopy with LLETZ using the time trade-off method (Birch, 2003 (138)). The potential cost and quality of life impact of the increased risk of pre-term birth as a result of treatment or biopsy was not included in the model. This was justified based on conflicting results from studies identified.

5.2.2.7 **Main results (including base case and key sensitivity analyses)**

The base case results reported a lower frequency of biopsy, as well as lower total costs and a lower 'cost per woman with CIN2/3' treated for those diagnosed using ZedScan compared to standard colposcopy for each clinic type. ZedScan was also reported to lower the rates of over-treatment, with 12% of the level of overtreatment in 'see and treat' clinics, and 17% of the level for 'triage by cytology result' clinics compared to those who received standard colposcopy.

The lower costs reported for ZedScan were also reported to be due to a reduction in the number of follow-up appointments for CIN1. The authors concluded that using the DP method resulted in fewer biopsies being taken following ZedScan and more women being followed up with a cytology test rather than a repeat colposcopy appointment. Importantly, the lower sensitivity of ZedScan for low grade referrals also resulted in a lower number of CIN2+ treated with ZedScan as well as a minor reduction in the number of cancers identified at colposcopy across all clinic types. Hence, some of the reduction in total costs for ZedScan was as a result of under-treatment for CIN2+.

The base-results also found 'treat later' clinics to have the lowest cost per woman with CIN2/3 treated for both ZedScan and standard colposcopy. Based on their findings, the authors concluded that the results did not appear to support a move from a 'treat later' clinic to a 'see and treat clinic' using ZedScan. This was because the cost per woman with CIN2/3 treated was lower for a 'treat later' clinic using standard colposcopy than a 'see and treat' clinic using ZedScan.

The authors noted the limitations arising from restricting the scope of the model to initial colposcopy and follow-up for up to 3 years. Specifically, the long-term costs and consequences of failing to identify and treat CIN2+ or the impact of identifying and treating CIN or cancer at an earlier stage were not captured. The authors noted that care should thus be taken regarding the interpretation of the results as a reduction in treatment of CIN2+ or cancer will appear beneficial in the short time horizon of the model (reducing treatment costs) but would actually lead to higher costs and lower outcomes over a longer time horizon.

From a policy perspective these limitations mean that it is not possible to determine whether the short term benefits of ZedScan arising from a reduction in unnecessary treatments offset any potential

reduction in benefits over a longer time horizon and hence whether over a more appropriate horizon in which this could be reflected ZedScan would be cost-effective or not.

5.2.2.8 **Assessment of uncertainty**

A range of sensitivity analyses were conducted in order to assess the uncertainty around particular parameters. For underlying disease prevalence the proportion of CIN2+ patients was increased by 10% and for costs the values used in a previous DAR report (Wade, 2013 (30)) were used as an alternative (with the authors noting an important disparity in the cost of biopsy). Additionally, the threshold at which a biopsy was taken was lowered for ZedScan and colposcopy. Different values for the frequency of biopsy for patients who were diagnosed using ZedScan were also used, a low estimate which assumed that only one biopsy was required based on clinical guidance, and a high estimate where clinicians could take additional biopsies. An analysis was also conducted where ZedScan was assumed to have the same specificity as colposcopy, and therefore the only difference between the devices was their sensitivity.

Probabilistic sensitivity analysis (PSA) was also conducted to assess the joint uncertainty of the parameter inputs. Distributions were assigned to the test characteristic parameters, the initial distribution of health states, utility decrements and transition probabilities. However, it appears that an arbitrary estimate of uncertainty (+/-5% the base case value) was used to inform the distributions for both the natural history transition probabilities and the utility decrements. No details were reported in terms of the number of simulations undertaken within the PSA).

The results of the sensitivity analyses demonstrated that the findings appeared robust to a range of alternative assumptions. However, the findings were reported to be particularly sensitive to assumptions surrounding the costs of colposcopy. When estimates reported in Wade (2013) (30) were applied to the model, standard colposcopy appeared cheaper the ZedScan both in terms of total costs and cost per woman with CIN2/3 treated. The authors highlighted that the costs reported in Wade (2013) (30) for both cervical biopsy and LLETZ appeared markedly lower than those based on estimates derived from the Sheffield Teaching Hospital.

The sensitivity analysis also found that by setting the threshold in a way which resulted in the specificity of ZedScan being equal to that of colposcopy increased the sensitivity, and reduced the specificity of ZedScan. This resulted in an increase in the cost of using ZedScan and the number of patients treated, which reduced the benefits of the device in terms of cost per woman with CIN2/3 treated. However, ZedScan was still reported to be cheaper than using colposcopy alone.

Using the higher estimate of the number of biopsies taken when patients were diagnosed using ZedScan had a small impact on the cost per woman with CIN2/3 treated, but not enough to make

ZedScan the more expensive option. Adjusting the disease prevalence data and the length of colposcopy appointments had minimal impact on the results. The PSA results were reported to be comparable to the deterministic outcomes, demonstrating linearity in the parameter values.

5.3 Discussion of existing cost-effectiveness evidence and relevance to current decision problem

Our review identified 2 published studies which reported the cost-effectiveness of DYSIS and an earlier prototype version of ZedScan and which are partially relevant to the current decision problem. Although both studies evaluated the use of adjunctive colposcopy techniques for women referred for colposcopy only as part of the NHS cervical screening programme based on the current HPV triage screening protocol, only Whyte et al included test of cure. As a result, neither study fully informs the current decision problem which includes the current HPV triage protocol (including test of cure) and also the proposed HPV primary screening protocol.

Despite both studies considering a similar decision problem and referral population, there were important differences between the scope of the models and the analytic approaches employed. Only Wade et al (2013) (30) attempted to capture the longer term impacts of adjunctive colposcopy technologies in terms of lifetime costs and QALYs. In contrast, the evaluation of ZedScan was restricted to a much shorter time horizon (3-years). The shorter time horizon precluded an overall assessment of the cost-effectiveness of ZedScan since relevant longer terms costs and outcomes were not quantified. However, one potential strength of the ZedScan study was that it provided a more granular assessment of the impact on a variety of different outcomes (including rates of unnecessary treatment) as opposed to focusing on final outcomes expressed in terms of life-years gained and QALY outcomes by Wade et al (30). From a policy perspective the focus on final outcomes expressed in terms of LYG and QALYs is clearly not a limitation. However, the additional granularity in the reporting by Whyte (2013) (128) provided greater transparency concerning how cost and benefits manifest themselves with an adjunctive technology which may be particularly informative in understanding how the trade-off between sensitivity and specificity impact on the intermediate outcomes which then drive estimates of LYG and QALY differences.

Structurally and conceptually the models reflect similar pathways over the 3-year period which is common to both models. The main difference is that Whyte (2013) includes additional pathways for test of cure as part of the HPV triage screening protocol. Test of cure was not included by Wade (2013) as this was not formally part of the HPV triage screening protocol at the time the study was conducted.

Although both models share similar pathways over the initial 3-year period, there were important differences both in terms of the analytic approaches employed and in terms of how heterogeneity in

the subsequent management of patients was characterised. In terms of the analytic approaches, Wade (2013) (30) employed a cohort approach utilising several hundred mutually exclusive states. The patient-level approach by Whyte (2013) (128) resulted in a more efficient overall structure, albeit potentially at the computational expense of requiring 1,000,000 individual patients to be simulated to derive expected values for costs and outcomes. In terms of characterising the subsequent management of patients, the study by Wade (2013) (30) assigned probabilities to different management strategies based on clinical practice reported in the Gateshead study. The study by Whyte (2013) (128) characterised the different management strategies as a source of observable heterogeneity (as opposed to a source of uncertainty) and hence reported estimates to reflect 3 different types of clinical practice defined according to clinic type (i.e. see and treat, treat later/watchful waiting and triage clinics). The approach by Whyte et al may confer potential advantages compared to treating treatment practice as an uncertain variable (and hence assigning a probability to subsequent management strategies) as it provides a basis both for determining how the cost-effectiveness of the adjunctive technologies might vary according to different clinical practice as well as potentially informing the efficiency of these practices.

The studies also differed in terms of several key inputs. The most notable differences were in the source of transition probabilities for the natural history model which was derived from different studies and particularly the costs of biopsy and LLETZ. The impact of the different natural history transition probabilities is not possible to determine, although the rationale for using a dataset of only 84 patients was not clearly reported by Whyte et al (128). In contrast, the impact of different costs for biopsies and LLETZ were identified as an important factor by Whyte et al (128).

Both studies also share two important and common limitations. Firstly, both studies acknowledged a key assumption that followed from the use of diagnostic accuracy data based on a CIN2+ cut-off and the dichotomous classification of the performance of the diagnostic technologies. That is, the probability of a positive colposcopy result (CIN2+) is assumed to be identical within the clear, HPV and CIN 1 states and within the CIN2/3 and invasive cancer states. Secondly, both studies acknowledged that there may be additional risks of treatment (e.g. fertility and adverse obstetric outcomes) but neither study considered that these risks could be formally quantified given the sparcity and conflicting results from existing studies. To address the issues and uncertainties identified in the review and particularly to inform the cost-effectiveness of both adjunctive technologies under both HPV triage and HPV primary screening protocols, a new independent model was developed.

6 Independent economic assessment: York model

6.1 Overview

Section 5 identified a number of issues and uncertainties arising from previously published studies. A number of important limitations were also identified in relation to the current decision problem, specifically: (i) the lack of any previously published studies reporting on the cost-effectiveness of the commercial version of ZedScan (ZedScan I); (ii) the lack of any attempt to formally compare different adjunctive technologies and (iii) the absence of any studies evaluating cost-effectiveness of either DYSIS or ZedScan within an HPV primary screening protocol. For this reason, it has been necessary to develop a *de-novo* decision model (hereafter referred to as the 'York model').

The York model was developed to estimate the cost-effectiveness of adjunctive colposcopy technologies (DYSIS with DYSISmap and ZedScan I) for people who are referred for colposcopy through the NHS Cervical Screening Programme under either HPV triage (including test of cure) or the HPV primary screening protocol (including test of cure). The York model is implemented using a patient-level state-transition modelling approach.

The model provides a link between diagnostic test accuracy and final health outcomes expressed in terms of QALYs. This is necessary in order to provide decision makers with an indication of the health gain achieved by adjunctive colposcopy technologies, relative to their additional cost, in units which permit comparison with other uses of health service resources. This requires 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 also includes the impact of the technologies on unnecessary biopsies and excisions which may increase the risk of adverse obstetric outcomes.

The incremental cost-effectiveness of adjunctive colposcopy technologies (DYSIS with DYSISmap and ZedScan I, hereafter referred to as "DYSIS" and "ZedScan"), compared to conventional colposcopy alone, are determined based on an assessment of long-term NHS and Personal Social Service costs and QALYs. The time horizon of the model is a lifetime (60 years), costs and outcomes are discounted at 3.5% per annum and a 2015/2016 price year is used.

6.2 Contribution of the York model

Although the York model shares some of the assumptions and parameters from existing studies, it also provides a number of significant developments to existing cost-effectiveness analyses.

In the previous model used to inform DA4 (Wade, 2013 (30)), the model structure required the probability of the diagnoses of the different stages of the disease, whether correct or incorrect, conditional on a patient's true health state. Consequently, Wade et al used more granular data from

Gallwas (2012) (130) based on another technology (Niris Imaging System) with the assumptions that results from this study were reliable and generalizable to colposcopy alone and DYSIS. As previously highlighted in Section 5, the study by Gallwas (130) was subject to significant bias and the use of data from another technology to inform colposcopy and DYSIS diagnosis accuracy could be seen as an important limitation.

In the York model, treatment pathways only depend on the reason for referral (cytology result) and the dichotomous colposcopy result (CIN2+). This allows for the use of diagnostic accuracy estimates with a CIN2+ cut-off. For patients referred as LG with a negative colposcopy, the treatment pathway is identical whether they are diagnosed by the colposcopist as Clear, HPV or CIN1. For patients referred as HG and/or with a positive colposcopy, a biopsy will be systematically performed revealing patients true underlying health state.

The York model still relies on two key assumptions: (i) biopsy and histopathology test are 100% accurate; and (ii) the probability of a positive colposcopy result (CIN2+) is identical for Clear, HPV and CIN1 patients and for patients with CIN2/3 and invasive cancer. However, based on additional data provided by DYSIS manufacturer on the diagnostic accuracy of colposcopy alone and DYSIS, we are able to explore the impact of the second assumption on the cost-effectiveness results.

An important limitation of the two cost-effectiveness studies identified (Wade (2013) (30) and Whyte (2013) (128)) is that neither of the studies formally model the long term adverse consequences of treatment excision. Based on more recent evidence of the impact of treatment on obstetric outcomes (Kyrgiou, 2016 (122)), the York model includes the excess risk of pre-term delivery for women who received a LLETZ excision. We are therefore able to measure the consequences of an increase in treatments which arises from the higher sensitivity and lower specificity of adjunctive technologies compared to conventional colposcopy alone.

Finally, an important contribution of the York model is to inform the cost-effectiveness of adjunctive technologies under the HPV primary screening protocol. The implementation of HPV primary has two main consequences for the economic evaluation of adjunctive technologies: (i) the routine screening pathway is different; and (ii) the characteristics of the population referred for colposcopy are likely to be different. The impact of both of these issues is an important consideration regarding possible differences in the cost-effectiveness of adjunctive colposcopy technologies under the current and potential future screening programmes.

6.3 Model Structure

6.3.1 Choice of modelling approach

State-transition models can be used to conceptualise a decision problem in terms of the health states or conditions that individuals can be ("states"), how individuals more among these states ("transitions") and how likely such moves are ("transition probabilities") (Siebert, 2012 (143)). State values (sometimes called "rewards") are used to reflect the costs and health-related quality of life (HRQoL) implications of residing in, or transiting between, each health state. Estimates of expected costs and quality- adjusted life years (QALYs) are derived by assigning state values to the time spent by patients in each health state.

A state-transition model is appropriate for modelling events, such as routine screening tests, that occur at fixed points of time and for conditions that have health states that may change repeatedly over time. Disease progression can be characterised in a state-transition model as a set of transitions among the states for time periods, typically of fixed duration (e.g., months, years, etc.).

State-transition models can use either a patient-level or cohort-level (Markov) modelling approach to estimate the expected costs and outcomes across a particular population (Davis, 2014 (144)). In a patient-level simulation, the costs and outcomes for individual patients are modelled and the expected (mean) values are derived from an average taken across the entire sample of patients. In a cohort approach the expected cost and outcomes are estimated for an entire cohort and hence the costs and outcomes for individual patients are not explicitly modelled. The choice between using a patient-level simulation and a cohort approach requires careful consideration and appropriate justification (Davis, 2014 (144)).

The challenge for a cohort approach arises from the complexity that comes from interactions between the natural history model (Figure 1) and the screening and treatment pathways (Figure 2). The natural history of cervical cancer can be schematically represented as an eight state-transition model (see Section 6.3.2.1 for further details). Such a model could be implemented using either a patient-level simulation or cohort approach. The main consideration in determining the choice of modelling approach is whether the 'Markovian' assumption (i.e. that transition probabilities do not depend on past history or time in state), which underpins the cohort approach, is appropriate. Inevitably, transitions between the natural history states will depend both on patient characteristics and also on patient history through previous screening outcomes (e.g. being referred to CIN1 follow-up) or treatment outcomes (e.g. being cured from CIN2/3). Appropriately accounting for patient heterogeneity and history using a cohort approach would require a series of sub-cohorts which exponentially increases the required number of model states and would require hundreds of mutually exclusive states to be characterised. In this context, a cohort model becomes increasingly difficult to

implement and manage. In contrast, patient-level state-transition models are not limited by the Markovian assumption ensuring that transitions can appropriately reflect both individual patient characteristics and their history (using "tracker variables"). As a result, the complexities with the current decision problem can be more efficiently characterised using a patient-level simulation by significantly reducing the number of mutually exclusive states that are required.

6.3.1.1 **Patient-level Monte-Carlo simulation**

The model simulates individuals' experience with a Monte-Carlo simulation and can be formally defined as a *State transition - Patient Level - Monte-Carlo simulation.* A patient-level model estimates the mean costs and benefits for a group of patients by considering the costs and benefits of each individual within the group. Each individual has specific characteristics that both impact and depend on the occurrence of events and associated transitions. In the present model these characteristics are: age; health state (Clear, HPV, CIN1, CIN2/3, Cancer); reason for referral to colposcopy (high grade or low grade); next scheduled screening (routine call, 6 months cytology, 6 months colposcopy, test of cure, CIN1 follow-up); time elapsed since last screening; type of clinic visited by the patient (see and treat or watchful waiting).

The decision analytic model simulates for each patient the occurrence of uncertain events, such as disease progression, diagnostic results or treatments outcomes with a random walk, i.e. a series of uniform, pseudo-random numbers. A large number of simulations ensure that the proportion of patients in each state equals the individual probability. It is important to notice that a large number of simulations will appropriately characterise first-order uncertainty, i.e. the variability in the simulated experiences between patients, but not second-order uncertainty which is linked to uncertainty around parameter values.

6.3.1.2 **Implementation and schematics**

The model is implemented with the software TreeAge Pro 2016 (© 2016 TreeAge software, Inc) and was run to simulate 500,000 women referred for initial colposcopy appointment. The model has a decision tree structure, which represents events occurring sequentially as a pathway which are followed by individual patients. `Logic nodes' (circles with a L in the schematics) are used when the occurrence of the event is certain and only depends on a patient's characteristics. `Chance nodes' (empty circle in the schematics) are used when the occurrence of the event is uncertain and depends on a probability. `Clones' refer to subparts of the model common to different pathways (such as the Natural history subpart) and therefore do not appear on the schematics for the sake of clarity. A triangle marks the end of a cycle: if the patient is still alive at the end of the cycle, she enters the model again; if she dies, from cancer or other causes, she exits the model. The model structure is

identical for the three strategies (colposcopy alone, DYSIS and ZedScan), only the input parameters vary (diagnostic accuracy and costs).

Figure 16 Natural history of cervical cancer

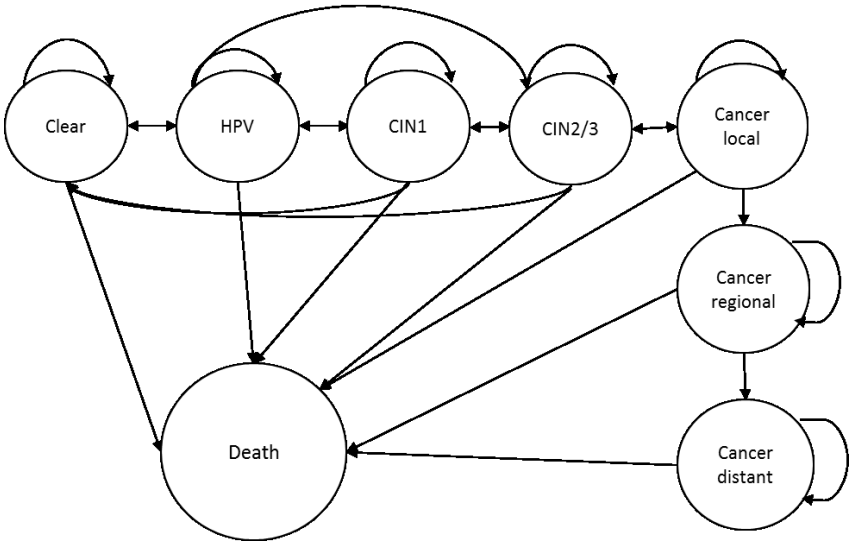
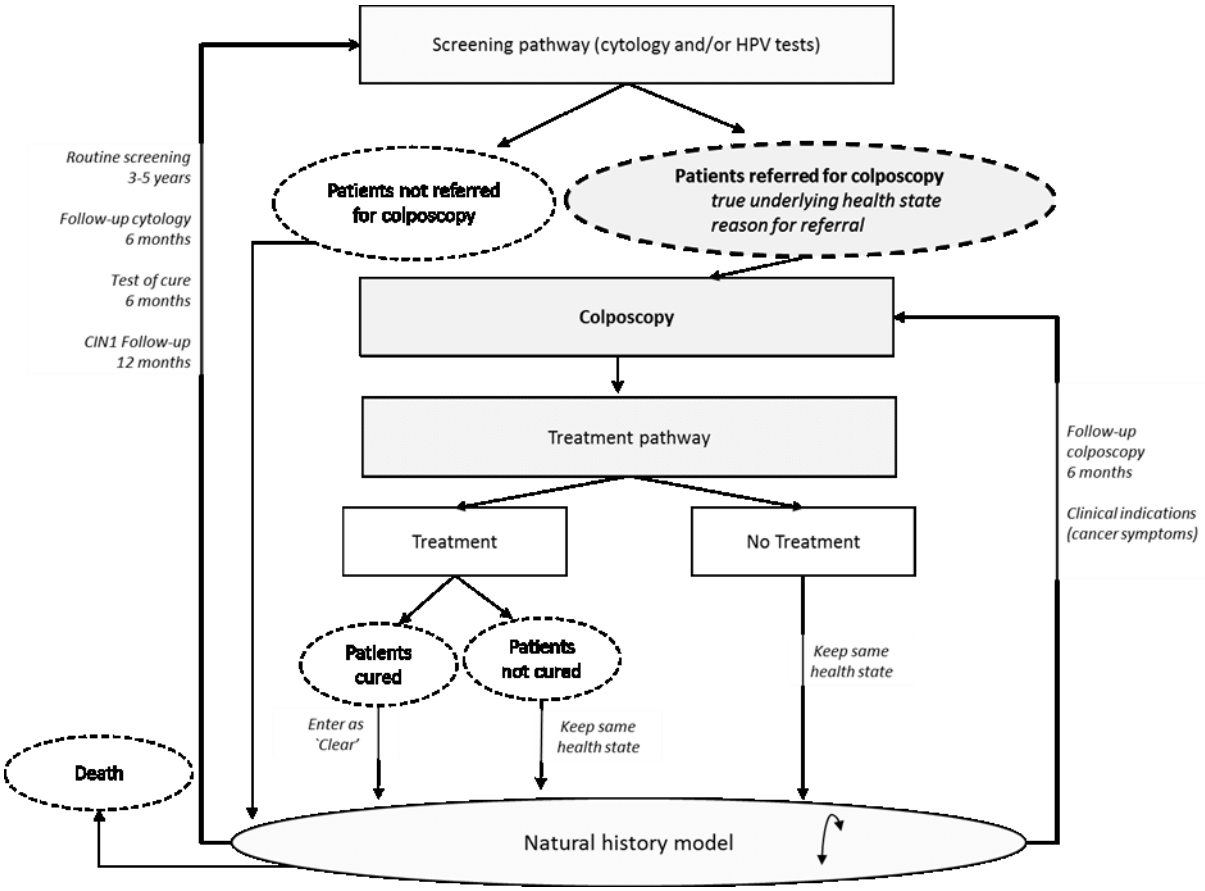


Figure 17 Links between screening, treatment pathways and natural history model



6.3.2 Main features of the model

The model can be separated into three main elements: (i) a natural history model; (ii) screening and treatment pathways; and (iii) adverse obstetric outcomes. Although time within each 6 month cycle is not explicitly modelled, screening events are assumed to occur before the natural history transitions because treatment outcomes may impact a patient's health state. The natural history model is derived from a widely used epidemiological model of cervical cancer and is discussed in more detail in Section 6.4.4. Screening and treatment pathways are modelled based on NHSCSP guidelines (15) and expert clinical opinion.

A patient enters the natural history model at each 6 month cycle. However she does not necessarily experience a screening episode every 6 months. Indeed, the occurrence of screening events depends on patient's characteristics (age, cancer symptoms) and history (previous exams and treatment). A patient who received treatment faces a risk of adverse obstetric outcomes every year.

6.3.2.1 Natural history model

The natural history model (Figure 18) captures the progression of cervical cancer from the 'Clear' state to stage 3 (distant) of invasive cancer. A patient enters the model with an initial health state and faces a 6 month transition probability to either stay in the same state, progress or regress. The probability will determine her subsequent health state at the beginning of the next cycle.

The natural history model incorporates eight health states: Clear, HPV infection without pre-cancerous lesion, CIN1, CIN2/3, invasive cancer (local, regional and distant) and death. The structure of the natural history model is derived from Kulasingam (2013) (145), an update of Myers (2000) (133), used for the previous cost-effectiveness model by Wade (2013) (30). Consequently, it relies on similar structural assumptions: HPV infection is a precondition to develop pre-cancerous lesions, CIN2 and CIN3 are modelled as a single combined health state and patients are assumed to be cured from cancer if they survive 5 years after treatment. The only update to the previous model is that HPV patients are allowed to develop CIN2/3 within 6 months.

The modelling of cancer progression relies on several assumptions; most of them are similar to the previous model by Wade et al (30). Cancer cannot be cured without treatment. A patient progresses across stages until she receives treatment, i.e. while cancer remains undetected. Whilst Wade et al (30) modelled cancer progression with four stages; our model considers only three stages (local, regional, distant). Indeed, progression and mortality rates have been updated based on a study by Campos (2014) (146) which relied on a three stages model. Consistently with Wade et al (30), a patient with undetected cancer faces a 6 months probability to develop symptoms; the model assumes that a patient with symptoms is immediately referred for colposcopy, identified and treated. Where asymptomatic cancer is detected by the NHS screening programme, it is assumed that the patient is a

stage 1 (local). A patient who survives 5 years after treatment is assumed to be cured and is back to the `Clear' health state.

6.3.2.2 Screening and treatment pathways

At the beginning of each cycle, the patient follows one of 4 main screening and treatment pathways (which all end with the natural history model):

a) No screening: the patient directly enters the natural history model;
b) Colposcopy pathway: the patient is directly referred for colposcopy (first cycle and cancer symptoms);
c) Routine screening: the patient is recalled to routine screening every 3 or 5 years after her last test, depending on her age.
d) Follow-up pathways: after treatment, diagnosis or inadequate result, the patient may be referred to follow-up such as test of cure (6 months after treatment), cytology and/or colposcopy (6 months after the initial test) or CIN1 follow-up (12 months after diagnosis).

During the first cycle, all patients have a colposcopy examination with different outcomes depending on their health state, reason for referral and diagnostic accuracy of colposcopy technologies. After the first cycle, subsequent examinations, follow-up or routine screening, depend on patient characteristics and history.

Colposcopy pathway

All patients are directed to the colposcopy pathway during the initial cycle. Patients can also be referred for colposcopy subsequently, after routine screening or follow-up tests or directly if they develop cancer symptoms. A patient who undertakes colposcopy is characterised by her health state, her reason for referral (low grade or high grade) and the type of clinic she visits (see and treat clinic or watchful waiting). These characteristics impact diagnostic and treatment outcomes (Figure 19).

Diagnostic outcome is modelled as the probability of being diagnosed after colposcopy as CIN2 or worse (`colposcopy positive'). This probability depends on patient's health state and diagnostic accuracy of colposcopy and adjunctive colposcopy technologies.

According to NHSCSP guidelines (15) and clinical experts, there are two possible types of management following a positive colposcopy. A patient with suspected CIN2 or worse can be immediately treated after colposcopy during the same appointment. An excision sample is then sent for histopathology to confirm initial diagnosis. The alternative is to perform a diagnostic biopsy, wait for histopathology to confirm CIN2 or worse and treat the patient during a second colposcopy appointment. To take into account heterogeneity in clinical practice and analyse the cost-effectiveness of colposcopy devices in different settings, the model considers two types of clinics: *`See and treat*

clinic' and *`Watchful waiting clinic'*. Modelling practice heterogeneity requires two further assumptions. First, the choice between see and treat and watchful waiting is assumed to be independent from diagnostic accuracy. Instead it is modelled as a patient characteristic: patients visit either a see and treat clinic or a watchful waiting clinic. Second, based on NHSCSP guidelines (15) and usual practice reported by clinical experts, immediate treatment after colposcopy is performed only where both cytology and colposcopy indicate CIN2 or worse, i.e. for patients with HG referral and positive colposcopy. In all other cases (LG with colposcopy positive, HG with colposcopy negative), a diagnostic biopsy is performed and the patient is called again for colposcopy and a treatment biopsy if necessary. LG referral patients with negative colposcopy do not receive any diagnostic biopsy or treatment.

Diagnostic outcome, reason for referral and a patient's health state (revealed by diagnostic biopsy) determine future screening tests. Patients with LG referral and normal colposcopy or histopathology results are discharged from the colposcopy clinic and sent back to routine screening. Patients with HG referral but normal histopathology results are not discharged and are sent to a 6 months colposcopy follow-up. Based on NHSCSP guidance (15), confirmed CIN1 lesions are not treated but patients are sent to CIN1 follow-up 12 months later. Confirmed CIN2/3 lesions are systematically treated and patients are sent to test of cure 6 months later. A patient who has been treated for CIN lesions faces a probability to be cured. If the treatment is successful she enters the natural history model in the `Clear' health state. If a patient has not received treatment or if the treatment has failed, she enters the natural history model with her initial health state. Patients diagnosed with cancer are assumed to be immediately treated and enter the natural history model with the `Cancer / treated' health state.

A key assumption is that diagnostic biopsy is assumed to be 100% specific and sensitive; it always reveals a patient's true underlying health state. Consequently, watchful waiting clinics never perform unnecessary treatments and patients referred for colposcopy with cancer symptoms, considered as HG referral, are always diagnosed and treated appropriately. The model does not consider conservative management for CIN2 lesions.

Routine screening

The NHS Cervical screening programme invites women aged 25 to 64 to have a cervical screening test. Women aged under 50 are invited 3 years after their last test, and women aged over 50 are invited 5 years after their last test. Women who have been treated for pre-cancerous lesions are invited 3 years after their last test, regardless of age. The model therefore keeps track of a patient's age as well as the number of cycles elapsed since her last screening.

Cervical cytology test results are graded depending on the degree of abnormality. To be consistent with data used for diagnostic accuracy of cytology, the model refers to the previous NHS system

terminology (BSCC 1986) and considers 6 possible cytology results: negative, inadequate, borderline change, mild dyskaryosis, moderate dyskaryosis, and severe dyskaryosis. The current NHS system terminology (ABC3) is used in a second step to characterise patients referred for colposcopy: borderline change and mild dyskaryosis are defined as low grade (LG) while moderate or severe are defined as high grade (HG).

The current management protocol is described in NHSCSP's colposcopy and programme management (15) and referred as `HPV triage' (Figure 20). An alternative protocol, known as `HPV primary', has been implemented in pilot sites across England and is to be rolled out in the future within the NHS cervical screening programme (Figure 21). The cost-effectiveness analysis considers these two protocols using separate models.

HPV triage

Under HPV triage, the patient is first tested with cytology. Diagnostic outcome is modelled as a probability of having a cytology result *r*, given underlying health state *h*. This probability depends on cytology test performance.

If cytology is negative, the patient is sent back to routine screening and will be invited again 3 or 5 years later. Where cytology shows moderate or severe dyskaryosis, the patients is referred for colposcopy as a HG. Where cytology shows borderline changes or mild dyskaryosis, the sample collected during the cervical screen is used for hr-HPV testing. The probability of being HPV positive depends on cytology result, a patient's health state and age. Where HPV is detected, the patient is referred for colposcopy as a LG. Otherwise, she is sent back to routine screening. Where cytology is inadequate, the patient is tested again 3 months later. Because the cycle length is 6 months in the model, the probability of having a first inadequate result is included in the probability of having a negative, borderline, mild, moderate or severe cytology result.

In case of two consecutive inadequate results, the patient is invited 3 months later for another cytology test, i.e. 6 months after her initial cytology test. The protocol is similar to routine screening (under HPV triage) except that a patient with a third inadequate cytology result is referred for colposcopy. Although a patient with three inadequate cytology results is not defined as low grade based on the ABC3 reporting terminology, clinical experts confirm that management after colposcopy is similar to LG patients, hence the LG referral used in the model.

HPV primary

Under HPV primary, the patient is first tested for Hr-HPV. Where HPV test is negative, the patient is sent back to routine screening. Where HPV test is positive, a cytology test is used as a triage to refer patients for colposcopy. A patient with borderline/mild or moderate/severe cytology result is immediately referred for colposcopy respectively as a LG or a HG. Similarly to the HPV triage, patients are tested again 3 months after a first inadequate cytology result. Consequently, in the model, the probability of having a first inadequate result is included in the probability of having a negative, borderline, mild, moderate or severe cytology result. Where cytology is twice inadequate or negative, the patient is rescreened 12 months later (`HPV primary rescreen 12 months in the model).

The 12 months follow-up protocol is similar to the initial routine test except that a patient with inadequate cytology is referred for colposcopy. Patients with a second consecutive HPV positive / cytology negative are rescreened 12 months later, i.e. 24 months after the initial test (`HPV primary rescreen 24 months' in the model). In this case, a positive HPV test is sufficient to be referred for colposcopy. A patient with negative HPV test is sent back to routine screening. Because HPV primary has not been implemented yet, there are uncertainties regarding the management post-colposcopy of patients with two consecutive negative cytology results. Indeed, under the HPV triage protocol, these patients were not referred to colposcopy clinics. According to clinical experts, it is likely that these patients would be managed in the same way as low grade referrals.

Follow-up: Test of cure

Based on NHSCSP guidelines (15), patients who receive treatment for CIN lesions are tested 6 months later (Figure 22). Since the model assumes that screening occurs at the beginning of a 6 months cycle, patients who have been treated during a specific cycle, will be sent to the test of cure pathway at the next cycle. First, the patient is tested with a cytology test. In case of inadequate, moderate or severe results, she is directly referred for colposcopy (with respectively a LG and HG referral). Where cytology results are negative, borderline or mild, the patient is tested for HPV and referred for colposcopy as LG if the HPV test is positive. She then enters the colposcopy pathway as described previously. Where HPV test is negative, the patient is sent back to routine screening and enters the natural history model.

Follow-up: Colposcopy 6 months

NHSCSP guidelines (15) do not explicitly define the `Colposcopy 6 months' pathway. However clinical experts suggest that a patient with HG referral and negative histopathology is usually not discharged from the colposcopy clinic. She will be tested again with cytology and colposcopy 6 months later (Figure 23). Given that high grade dyskaryosis has been previously identified, a HPV test is unlikely.

Follow-up: CIN1 follow-up

NHSCSP guidelines (15) recommend conservative management for confirmed CIN1 lesions. Instead of receiving treatment biopsy, the patient is tested 12 months after the first diagnosis. If CIN1 is still present, she is tested again 12 months later. According to clinical experts, there is heterogeneity in the management of CIN1 follow-up. Most likely, the patient is sent back to the community and follows a similar pathway to routine screening (Figure 24). The model assumes that in case of positive colposcopy and/or HG referral, a diagnostic biopsy is systematically performed (no see and treat). Based on NHSCSP guidelines (15), confirmed CIN1 is treated only if lesions are persistent after 24 months. Where CIN2/3 lesions or cancer are detected at any stage, the patient receives appropriate treatment.

6.3.2.3 Adverse obstetric outcomes

The adverse obstetric outcomes model (Figure 25) captures the impact of treatment for CIN on adverse obstetric outcomes. The findings from two recent systematic reviews were previously summarised and discussed in Section 4.4.2. The 2 reviews reported results across a range of adverse fertility, pregnancy and obstetric outcomes. In the absence of robust evidence indicating an adverse treatment impact on fertility and early pregnancy outcomes (<24 weeks), the adverse obstetric outcome model was limited to capturing the impact of an increased risk of preterm birth reported by Kyrgiou (2016) (122).

Following treatment for CIN, the adverse obstetric outcomes model captures the excess risk of treatment on preterm birth rates (< 37 weeks gestation) and applies a payoff to capture associated costs and QALY decrements. Since the model only attempts to characterise the excess treatment risk, only women who receive treatment for CIN enter the adverse obstetric outcome model. Within the model a tracker variable is assigned to an individual patient following treatment with CIN. For each 12 month period following treatment (and up until the age of 45), the model captures the excess risk of preterm birth (<37 weeks) based on age-specific conception rates (adjusted for legal abortion), the risk of preterm birth for untreated women and the higher relative risk reported with treatment. The cost and QALY decrements capture the additional initial management costs associated with preterm birth and the increased probability of neonatal mortality as well as QALY decrements associated with higher risks of disability among survivors.

Figure 18 Natural history model

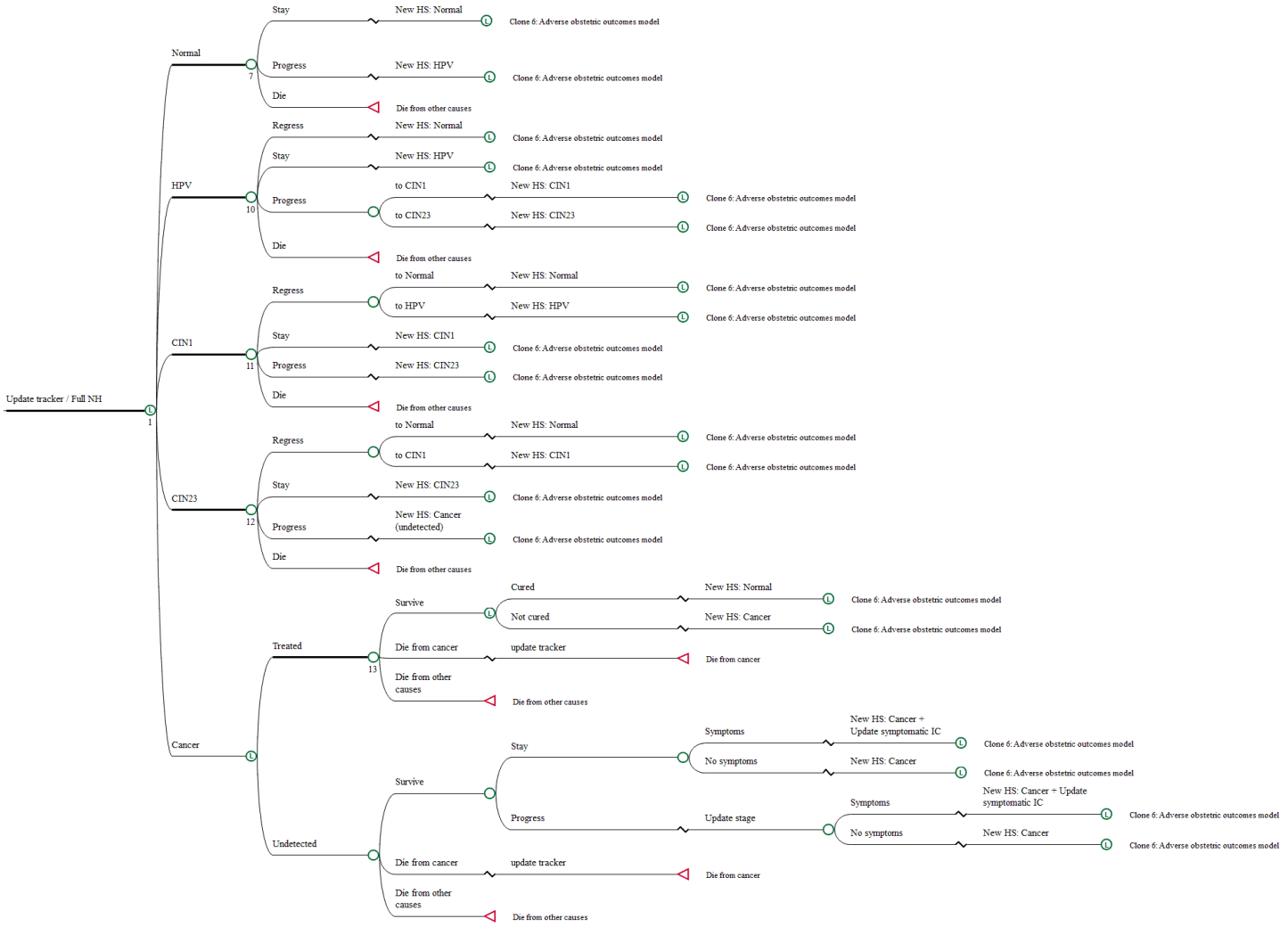


Figure 19 Treatment pathway after colposcopy

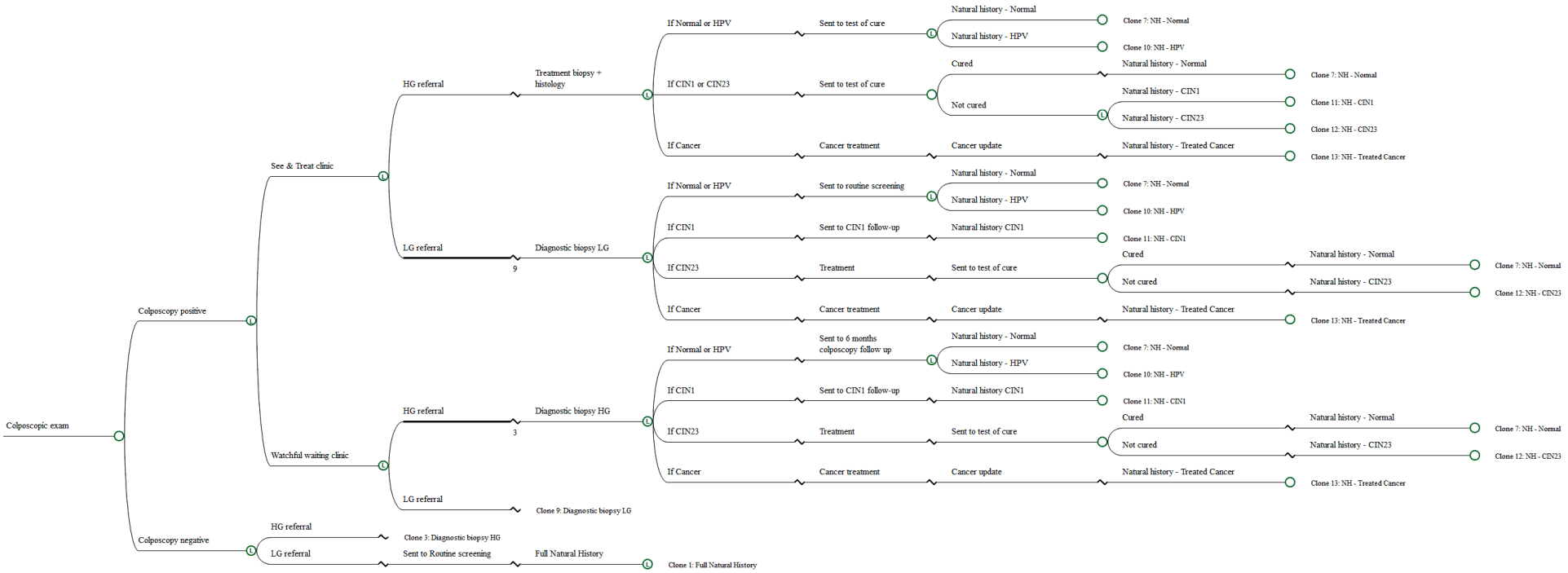


Figure 20 HPV triage - routine screening and follow-up

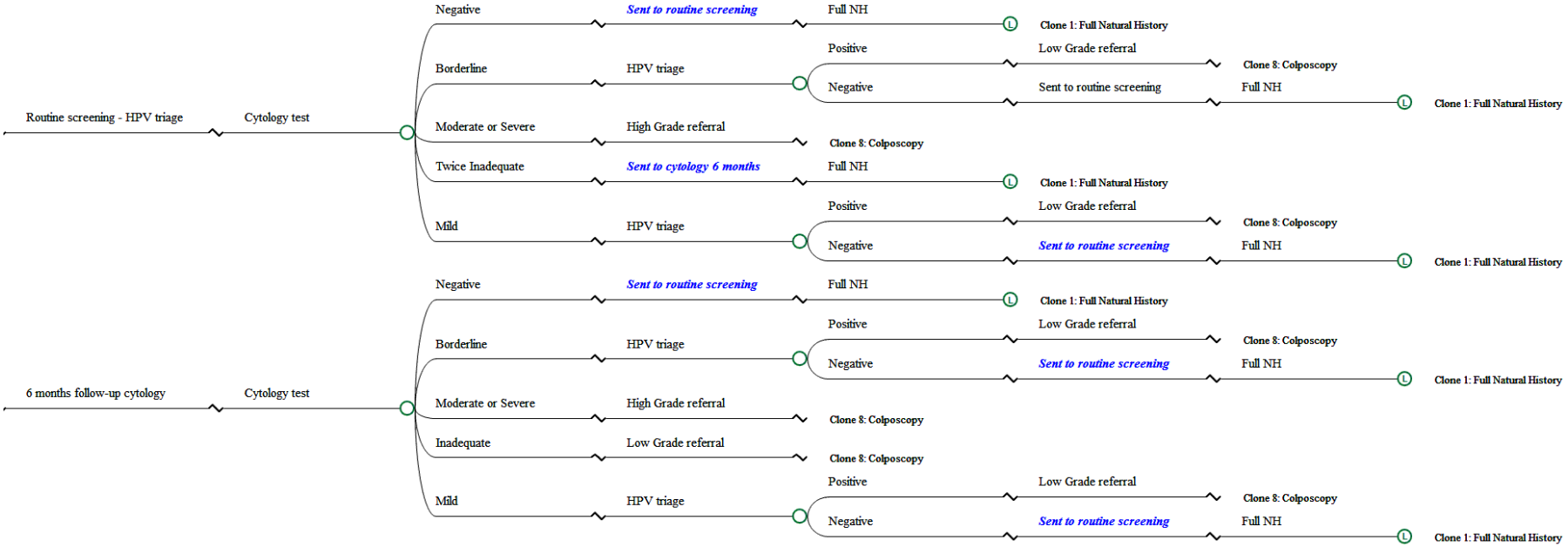


Figure 21 HPV primary - routine screening and follow-up

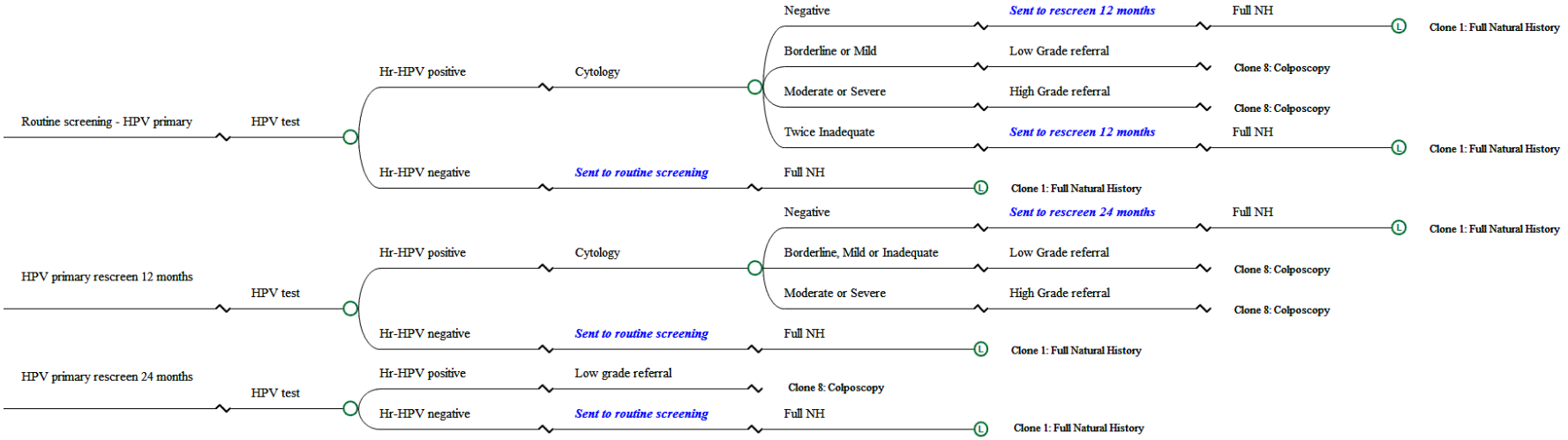


Figure 22 Test of cure

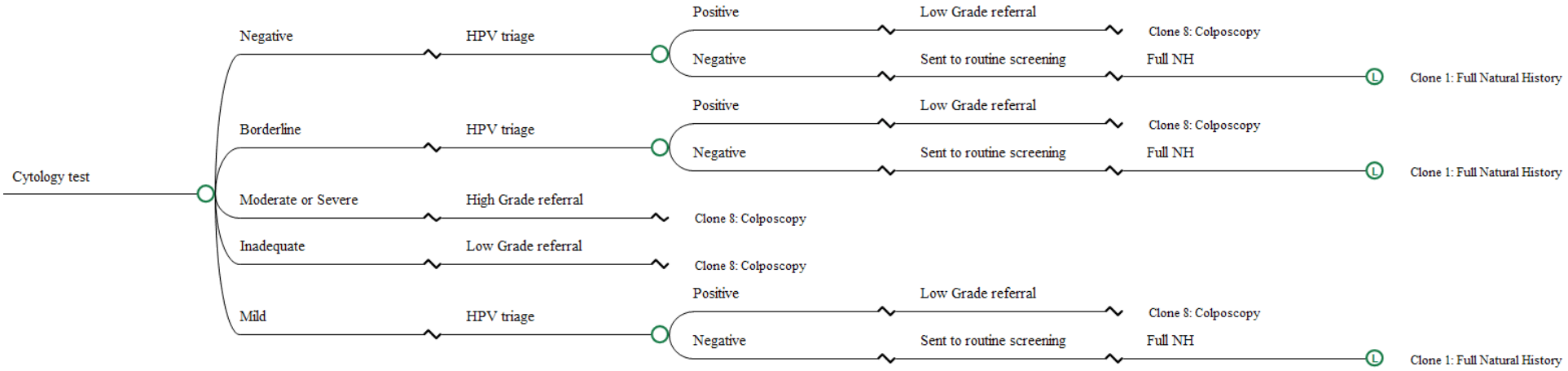


Figure 23 Colposcopy 6 months

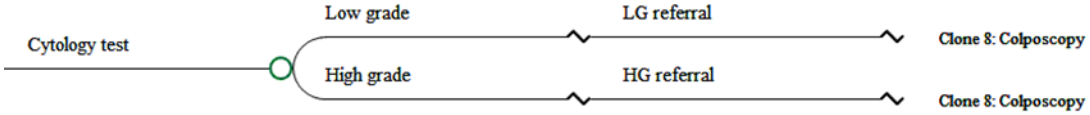


Figure 24 CIN1 follow-up

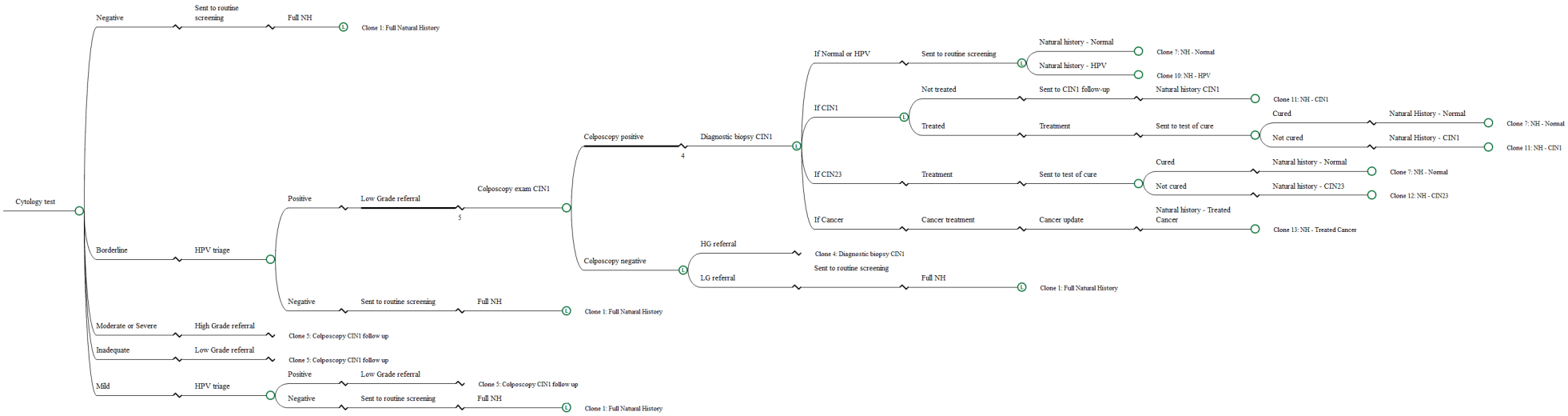
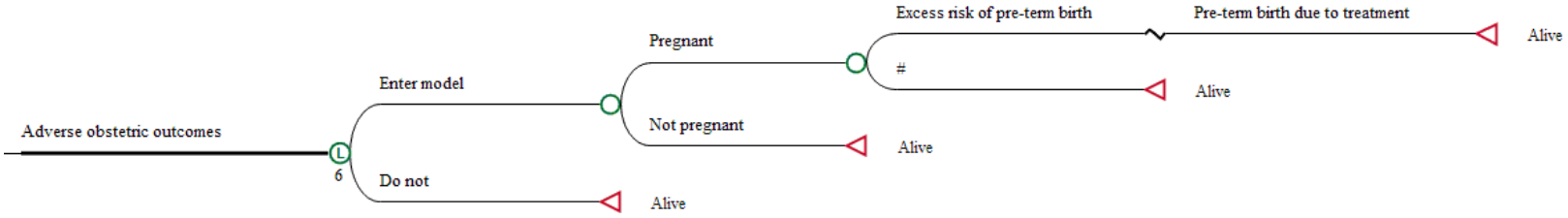


Figure 25 Adverse obstetric outcomes



6.4 Model input parameters

6.4.1 Diagnostic accuracy

6.4.1.1 Colposcopy and adjunctive technologies

The sensitivity and specificity of colposcopy alone and adjunctive use of DYSIS and ZedScan are based on the best-evidence estimates of diagnostic accuracy reported in Section 4.3.4.6. An assumption is made that the binocular and video colposcopes have the same diagnostic performance and hence the diagnostic accuracy of colposcopy is based on the evidence reported in the DYSIS studies. From the estimates of diagnostic accuracy, we derive the probability a positive colposcopy result, i.e. CIN2 or greater, given a patient's true underlying health state. A key assumption is that the probability of a positive colposcopy result is similar for Clear or CIN1 and for CIN2/3 or invasive cancer. A consequence of the CIN2 threshold is that detecting CIN1 during the colposcopy examination is not considered as a positive colposcopy result. However, if the patient is referred as HG, a diagnostic biopsy will systematically reveal CIN1 and the patient will be managed appropriately.

Based on the limitations identified in the clinical effectiveness review section and particularly the lack of data on the diagnostic accuracy of colposcopy alone for the current version of ZedScan, separate pairwise analyses are presented comparing adjunctive DYSIS with colposcopy alone; ZedScan with colposcopy alone and ZedScan with DYSIS. Table 25 details the sensitivities and specificities used in the base case analyses.

Table 25 Sensitivities and specificities used in the base case – CIN2+ cut-off

Technology	Sensitivity (95% CI)	Specificity (95% CI)	Source
Colposcopy alone	57.91% (47.2 to 67.9)	87.41% (81.7 to 91.5)	Regression model
DYSIS	81.25% (72.2 to 87.9)	70.40% (59.4 to 79.5)	Regression model
ZedScan	[redacted]	[redacted]	Tidy (forthcoming) (103)

6.4.1.2 Cytology and HPV tests

Performance of cytology and HPV tests is also required for the model when patients are recalled for routine screening or follow-up (cytology 6 months, test of cure, CIN1 follow-up).

Performance of cytology test is modelled as the probability of having a certain cytology result (negative, borderline changes, mild dyskaryosis, moderate dyskaryosis, severe dyskaryosis), given a patient's true underlying health state (Table 26). Diagnostic accuracy of cytology was derived from a published UK-based study on cervical screening programme cost-effectiveness (Hadwin, 2008 (129)) (probabilities were displayed in an unpublished document by Eggington (2006) (131)). The probability of an inadequate cytology result was estimated to be 2.7%, based on NHS cervical

screening programme (2015-2016) (18). The probability of having an inadequate cytology result is assumed to be independent of a patient's underlying health state and previous cytology results. These data were used for both HPV triage and HPV primary protocol.

Performance of HPV test is modelled as the probability of having a positive HPV test result given patient's true underlying health state, cytology result and age. Diagnostic accuracy of HPV test under the HPV triage protocol (i.e. after a borderline or mild cytology result) was based on Cotton (2010) (132) using data from the TOMBOLA trial. The TOMBOLA trial aimed to compare different method of management for women with low-grade cervical abnormalities under the NHS cervical screening programme in the UK. The study included 4439 women between 1999 and 2002, aged 20-59 years, with a cytology test showing borderline nuclear abnormalities or mild dyskaryosis. A cross-sectional analysis of trial data provided sensitivity and specificity of a single HPV test in detecting CIN2 or worse by cytology result and age (Table 27). Under the HPV primary protocol, probabilities of a positive HPV test result by health state were derived from the ARTISTIC study which based these estimates on extensive data in the literature on High-Risk HPV testing (Kitchener, 2014) (147) (Table 28).

Table 26 Probability of cytology results, given true underlying health state (HPV triage and HPV primary protocols)

Probability of cytology result by Health state	Clear	HPV	CIN1	CIN2/3	Cancer	Source
Inadequate	0.027	0.027	0.027	0.027	0.027	NHS Cervical screening programme 2015-2016 (18)
Borderline	0.002	0.266	0.262	0.086	0.082*	Hadwin (2008) (129)
Mild	0.003	0.077	0.213	0.126	0.134*	
Moderate	0.001	0.065	0.148	0.187	0.153*	
Severe	0.000	0.025	0.056	0.228	0.604*	

*Adjusted for higher inadequate results

Table 27 HPV triage protocol - Sensitivity and specificity (detecting CIN2+) of HPV test by previous cytology result and age group

	Sensitivity of HPV test		Specificity of HPV test		Source
Age group	Borderline cytology	Mild cytology	Borderline cytology	Mild cytology	
20-24	79.7%	80.8%	46.3%	32.5%	Cotton (2010) (132)
25-29	74.3%	76%	63%	43.2%	
30-39	66.7%	70.5%	73.4%	52.2%	
40-59	31.3%	64.7%	86.5%	63.6%	

Table 28 HPV primary protocol - Probabilities of a positive HPV test, by health state

Health state	Probability of a positive HPV test	Source
Clear	0.014	Kitchener (2014) (147)
HPV	0.821	
CIN1	0.8415	
CIN2/3	0.955	
Cancer	0.957	

6.4.2 Underlying health state and reason for referral

Women referred for colposcopy from the NHS Cervical Screening Programme enter the model with two initial characteristics: a true underlying health state (Clear, HPV, CIN1, CIN2/3 or Cancer) and a reason for referral (low grade or high grade). The joint distribution of health state and reason for referral is linked to disease prevalence as well as routine screening diagnostic accuracy. For instance, the distribution under HPV triage is likely to be different from the distribution under HPV primary. For example, HPV primary screening is expected to be more sensitive, i.e. more CIN2+ cases are likely to be referred for colposcopy, but also less specific leading to more low-grade referrals. Consequently, different estimates are used for the HPV triage and HPV primary protocols.

HPV triage

Table 29 reports the joint distribution of health state and reason for referral in a HPV triage protocol. Because, the HPV triage protocol is currently implemented in the NHS cervical screening programme in England, the joint distribution of health state and reason for referral was based on outcomes of colposcopy referrals published in the NHS cervical screening programme 2015-2016 (18). From April 2015 to June 2015, all 55 operating laboratories in England collected outcomes of colposcopy referrals and linked these results to the reason for referral. Consistently with the model structure, women referred after non-negative samples showing either borderline or mild dyskaryosis with positive HPV test or persistent inadequate results were considered as low-grade. Women referred after a potentially significant abnormality, including high-grade dyskaryosis (moderate or severe) high grade, invasive squamous carcinoma or glandular neoplasia of endocervical type were considered as high grade. In total, 31,114 samples were collected. We excluded 570 cases for which results were unknown or showed non cervical cancer. On the remaining 30,544 cases, 68.6% were low grade and 31.4% were high grade. Outcomes of colposcopy referral (cervical cancer, CIN3, CIN2, CIN1, HPV only, no CIN/no HPV) were confirmed by biopsy where colposcopy revealed abnormality. Where no abnormalities were detected at colposcopy examination, patients are considered as `Clear'. However, because colposcopy is not 100% sensitive, an unknown proportion of patients with no abnormality

detected might have been misdiagnosed. Consequently, the distribution may underestimate the proportion of CIN2 and worse in the population.

Table 29 Initial characteristics of women referred for colposcopy under HPV triage protocol

Health state and reason for referral	%	Source
Clear LG	27.59	NHS Cervical screening programme 2015-2016 (18)
Clear HG	1.20	
HPV LG	10.32	
HPV HG	0.89	
CIN1 LG	19.44	
CIN1 HG	2.53	
CIN2/3 LG	11.16	
CIN2/3 HG	25.97	
Cancer LG	0.07	
Cancer HG	0.82	

HPV primary

Table 30 reports the joint distribution of health state and reason for referral in a HPV primary protocol. Data came from unpublished preliminary results collected in HPV primary pilot sites and included in total [redacted] women referred for colposcopy. [redacted] women were referred after the first round of routine screening (HPV+ and cytology result borderline or worse); [redacted] after the second round (12 months repeat); and [redacted] after the third round (24 months repeat). As expected, the proportion of low grade referral under the HPV primary protocol is slightly higher than under the HPV triage protocol [redacted]

However, these preliminary results must be interpreted with caution. First, data collection is still incomplete especially for women referred at the third round. Second, about 70% of the data on HPV primary [redacted] come from laboratories which are implementing the HPV genotyping triage. During the second round, women detected with HPV 16/18 were immediately referred for colposcopy, even if their cytology test was negative. The impact of genotyping on the characteristics of the population referred for colposcopy is hard to predict with potentially more low grade referrals (women with HPV+ and cytology negative are referred sooner) but also more severe cases due to the presence of HPV 16/18. Finally, because pilot sites were not randomly selected we can expect selection issues and especially variability in the prevalence of HPV and CIN lesions compared to the general population, regardless of the impact of a change in the routine screening protocol. For the analysis under HPV primary protocol, we use data reported by all pilot sites (with and without genotyping) as a base case (Table 30) and provide sensitivity analyses around the characteristics of

the initial population using data from pilot sites who are and are not implementing genotyping (see section 6.4.2).

Table 30 Initial characteristics of women referred for colposcopy under HPV primary protocol

Health state and reason for referral	%	Source
Clear LG	[redacted]	HPV primary pilot sites
Clear HG	[redacted]	
HPV LG	[redacted]	
HPV HG	[redacted]	
CIN1 LG	[redacted]	
CIN1 HG	[redacted]	
CIN2/3 LG	[redacted]	
CIN2/3 HG	[redacted]	
Cancer LG	[redacted]	
Cancer HG	[redacted]	

6.4.3 Treatment probabilities

6.4.3.1 See and treat and Watchful waiting clinic

Treatment decisions after a positive colposcopy result, i.e. diagnostic biopsy or immediate treatment, vary considerably across England. Currently, for women referred with high-grade abnormalities, the most common treatment at first attendance is excision (53.2%), followed by diagnostic biopsy (35%). The use of excision at first attendance for high grade referral ranges from 11.6% in London to 65.4% in the North West (NHS cervical screening programme 2015-2016 (18)).

Heterogeneity in treatment decisions after a positive colposcopy is modelled as two different types of clinic a patient may visit and is independent of health state or diagnostic accuracy. A patient may either visit a `See and treat' clinic or a `Watchful waiting' clinic. Because NHSCSP advice that positive predictive value for CIN2 or worse should be at least 90% to undergo `see and treat', the model assumes that the use of excision at first attendance is only possible for HG referral with positive colposcopy result. Where patients are LG referral, CIN2 or worse must be confirmed by the diagnostic biopsy result before being treated. This assumption has been validated by clinical experts.

Since the cost-effectiveness of adjunctive colposcopy devices is likely to be driven by treatment practice, results are presented separately for the two types of clinics. Indeed, a low specificity of colposcopy leads to over treatment in a `See and treat clinic'. In contrast, because biopsy is assumed to be 100% sensitive and specific, watchful waiting clinics are assumed to never over-treat patients. Furthermore, watchful waiting requires two colposcopy examinations: a first one where a diagnostic

biopsy is performed, a second one where CIN2 lesions or worse are treated. Whereas `See and Treat' clinics only require one colposcopy.

6.4.3.2 Probability of cure from treatment biopsy

The probability of cure after treatment biopsy was derived from a study by Ghaem-Maghami (2011) (148) that reported failure rates for 2455 women treated for CIN for the first time between 1989 and 2004. 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 or worse. 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). We calculated the weighted excision failure rate of CIN2/3 as 10.1% (Table 31).

Table 31 Probability of treatment failure with excision

Diagnosis	Failures	n	Probability of failure	Source
CIN1	28	570	4.9%	Ghaem-Maghami (2011)(148)
CIN2	87	886	9.8%	
CIN3	103	999	10.3%	
CIN2/3	190	1885	10.1%	Calculated from Ghaem-Maghami (2011) (148)

6.4.3.3 Probabilities of adverse obstetric outcomes

For each 12 month period following treatment, the model captures the excess risk of preterm birth (<37 weeks) based on age-specific conception rates (adjusted for legal abortion), the risk of preterm birth for untreated women and the higher relative risk reported with treatment.

Age-specific conception rates were derived from national conception statistics reported by the Office of National Statistics (ONS) (149). The ONS statistics bring together records of birth registrations (including live births or stillbirths) and abortion notifications. Hence, the conception input data applied in the model does not include conceptions resulting in miscarriages or illegal abortions. The annual probability of conception (adjusted for legal abortion) applied in the model was derived from age-specific conception and legal abortion rates reported per 1000 women (England and Wales) (Table 32).

The excess risk of preterm birth was then estimated based on applying a relative risk representing the additional risk following treatment for CIN to the probability of preterm birth without treatment. The increase in relative risk (RR) following treatment (LLETZ) was assumed to be 1.56. This was based on the results reported by Kyrgiou (2016) (122) for all treatments in all preterm births (<37 weeks) where the external comparison includes the overall population.

The RR of preterm birth was then applied to the probability of preterm birth for untreated women. The probability of preterm birth for untreated women was assumed to be 7.3% based on data reported in NICE NG25 (Preterm labour and birth). Consequently, the excess risk of pre-term delivery for women treated with LLETZ was estimated to be 4.09% (0.073*(1.56-1)).

Table 32 Annual probability of conception, by age group

Age group	Conception rate per 1,000 women in age-group	Percentage of conceptions leading to abortion	Annual probability of conception	Source
25-29	127.2	18.2	0.1040[a]	ONS 2015 England and Wales (149)
30-34	125.5	13.6	0.1084	
35-39	68.9	16.7	0.0574	
40+	15.4	15.4	0.0111	

a. 127.2/1000 * (1 – 18.2/100) = 0.1040

Table 33 Excess risk of pre-term delivery

Parameter	Value	Source
Risk of pre-term delivery for untreated women	0.073	NICE NG25
Increase in relative risk following treatment	1.56	Kyrgiou *et al.* (2016) (122)
Excess risk of pre-term delivery	0.0409	Calculated

6.4.4 Natural history model

6.4.4.1 Pre-cancerous lesions

Transition probabilities from the `Clear' state to CIN2/3 were based on transition probabilities reported by Kulasingam (2013) (145), an update of Myers (2000) (133) used in Wade (2013) (30). Kulasingam (2013) (145) took into account recent evidence that for young women (aged under 30 years), high-grade CIN may occur early in the course of a high-risk HPV infection. Recent studies also suggested that CIN may be more frequent in young women but that progression to cancer from high-grade CIN is low. Compared to Myers (2000) (133), HPV and CIN incidence and regression estimates were higher but progression rates between CIN states and from CIN2/3 to Cancer were also lower. Transition probabilities were reported by the authors as annual probabilities and converted as 6 months probabilities in our model (Table 34).

Table 34 Transition probabilities in the natural history model (Clear to Cancer)

Parameters	Age	Annual probability	6 months probability	Source
Clear to HPV	24-29	0.05	0.0253	Kulasingam (2013) (145)
	30-49	0.01	0.0050	
	50 and over	0.005	0.0025	
HPV to Clear	15-24	0.7	0.2081	
	25-29	0.5	0.1535	
	30-39	0.25	0.0800	
	40-49	0.15	0.0488	
	50 and over	0.05	0.0165	
HPV to CIN1	--	0.9*0.06	0.9*0.0305	
HPV to CIN2/3	--	0.1*0.06	0.1*0.0305	
CIN1 to Clear	15-34	0.9*0.1	0.9*0.0513	
	35 and over	0.9*0.06	0.9*0.0305	
CIN1 to HPV	15-34	0.1*0.1	0.1*0.0513	
	35 and over	0.1*0.06	0.1*0.0305	
CIN1 to CIN2/3	15-34	0.02	0.0101	
	35 and over	0.06	0.0305	
CIN2/3 to Clear	--	0.5*0.06	0.5*0.0305	
CIN2/3 to CIN1	--	0.5*0.06	0.5*0.0305	
CIN2/3 to Cancer	15-29	0.01	0.0050	
	30 and over	0.04	0.0202	

6.4.4.2 Invasive Cancer

Table 35 reports the parameters used to estimate the likelihood of symptoms of cervical cancer, progression across stages and cancer-related mortality. Women with undetected cancer may progress to a more severe stage (from Local to Regional to Distant), with an increasing probability of developing symptoms. Once cancer is detected, the model assumes that patients will receive stage-specific treatment and face an excess risk of mortality due to cervical cancer. Cancer-specific mortality depends on stage and decreases by time since diagnosis. After 5 years, excess mortality due to cancer is assumed to be zero and patients are assumed to be cured. We assume that women with undetected cancer continually face the year 1 probability of cancer mortality until diagnosis.

Our estimates were based on Campos (2014) (146), that reported monthly probability of symptoms, progression and mortality by stage (Local, Regional, Distant). Cancer-specific mortality in Campos (2014) (146), was derived from the Surveillance, Epidemiology, and End Results (SEER) Programme registry data from 2000 to 2009.

Table 35 Symptoms, progression and mortality of invasive cancer

Parameters		Cancer stage	Reported value	6 months probability	Source
Probability of symptoms - undetected cancer		Local	0.0174 / 1 month	0.1000	Campos (2014) (146)
		Regional	0.0735 / 1 month	0.3675	
		Distant	0.1746 / 1 month	0.6838	
Progression - undetected cancer		Local to Regional	0.02 / 1 month	0.1142	
		Regional to Distant	0.025 / 1 month	0.1409	
Mortality – undetected cancer		Local	0.0016 / 1 month	0.0096	
		Regional	0.0095 / 1 month	0.0557	
		Distant	0.0293 / 1 month	0.1634	
Mortality - detected cancer	1 year post-diagnosis	Local	0.0016 / 1 month	0.0096	
		Regional	0.0095 / 1 month	0.0557	
		Distant	0.0293 / 1 month	0.1634	
	2-3 years post-diagnosis	Local	0.0014 / 1 month	0.0084	
		Regional	0.0078 / 1 month	0.0459	
		Distant	0.0195/ 1 month	0.1114	
	4-5 years post-diagnosis	Local	0.0009 / 1 month	0.0054	
		Regional	0.0036 / 1 month	0.0214	
		Distant	0.0076 / 1 month	0.0447	

6.4.4.3 All-cause mortality

Mortality rates from causes other than cervical cancer were calculated using data from the Office for National Statistics (ONS) in England and Wales in 2015 (150). Deaths due to cervical cancer were subtracted from the total number of deaths for each age group. 2015 ONS data on the population for each age group were then used to calculate an annual mortality rate, converted as a 6 month probability in the model (Table 36).

Table 36 All-cause mortality excluding cervical cancer (6 months probability)

	Total number of deaths	Death due to cervical cancer	Deaths excluding cervical cancer	Population size	Annual mortality rate	6 months probability of death	Source
15-24	678	2	676	3,516,313	0.00019	0.00010	ONS 2015 (150)
25-34	1,368	54	1,314	3,927,723	0.00033	0.00017	
35-44	3,265	92	3,173	3,754,387	0.00085	0.00042	
45-54	8,438	119	8,319	4,116,650	0.00202	0.00101	
55-64	16,389	108	16,281	3,334,140	0.00488	0.00244	
65-74	35,752	137	35,615	2,917,683	0.01221	0.00612	
75-84	72,044	135	71,909	1,837,553	0.03913	0.01976	
85 +	132,917	73	132,844	894,520	0.14851	0.07724	

6.4.5 Resource utilisation and cost data

6.4.5.1 Devices costs

The cost-effectiveness analysis requires an estimate on the average cost per procedure of each of the technologies being assessed. A colposcopy examination with DYSIS or ZedScan is assumed to be equivalent to colposcopy alone in terms of staff resources and length of consultation. The average cost of a procedure includes a set-up cost, annual recurring costs and per patient costs. Information provided by the manufacturers has been used to estimate the costs of DYSIS and ZedScan. For the purchase price and maintenance costs of colposcopy we used estimates provided by clinical advisors for the previous DAR (Wade, 2013 (30)) and inflated to 2016 prices.

The set-up cost consists of the capital cost of the machine. The purchase price of each technology was annuitised over the expected lifetime of the technology. Consistent with Wade (2013) (30), the lifetime of a colposcopy was estimated to be 15 years. The lifetime of DYSIS and ZedScan were estimated to be 5 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 was estimated to be 10% of the purchase price and disposables to be equivalent to cost of a speculum (£2.15). The annual maintenance costs and disposable costs of the adjunct technologies were provided by the manufacturers. For DYSIS annual maintenance costs included the DYSIS viewer licence registration and renewal as well as a 5 year service and maintenance plan. The price of DYSIS disposable speculum (£3.50) was added to the per-patient cost. ZedScan manufacturer claimed no routine maintenance costs. However a single-use EIS sensor (£30.00) is required for each patient examined. To estimate the total cost per patient, it is necessary to estimate the number of patients expected to be treated each year. We assumed that this

number was independent of the type of devices and used the previous estimate of 1229 patients per device per year (Table 37). Sensitivity analyses were undertaken to test this particular assumption (see section 6.4.2). As ZedScan uses binocular colposcope to guide the probe or to confirm diagnosis, the cost of a colposcope was also added to its total cost. DYSIS devices already include a colposcope and therefore do not require this additional cost.

Additional to the cost related to the device itself, the costs of a colposcopy visit, diagnostic biopsy and treatment (LLETZ) were estimated from NHS reference costs (151). NHS reference costs reported the cost (2016 prices) of a "diagnostic colposcopy", a "diagnostic colposcopy with biopsy" and a "therapeutic colposcopy" (Table 38). The uncertainty surrounding whether NHS reference costs accurately reflect resource use and in particular include histology/pathology costs is explored in a sensitivity analysis (see section 6.4.2).

In the base case, we estimated the cost of a colposcopy visit to be £175 with a binocular colposcope, £180.49 with DYSIS and £205.52 with ZedScan. Additional costs of a diagnostic biopsy and a treatment were estimated to be respectively £47 and £63. The costs of a cytology test and a HPV test were derived from the TOMBOLA study (136), inflated to 2016 prices, and were estimated to be respectively £37.19 and £29.66 (Table 39).

Table 37 Base case costs of colposcopy alone, DYSIS and ZedScan

Cost component	Colposcopy alone	DYSIS	ZedScan	Source
Assumed useful life of equipment (years)	15	5	5	Clinical advisors
Purchase price (£)	10,734	30,500	3000	Manufacturers
Equivalent annual cost (£)[a]	900	6527	642	
Annual maintenance cost (£)	1073	530	0	
Disposables (per patient, £)	2.15	3.5	30	
Total cost per patient (£)[b]	3.75	9.24	30.52	

Table 38 Treatment costs

Treatment	Unit cost, 2016 prices (£)	Source
Colposcopy examination only	175	NHS reference costs (151)
Colposcopy with biopsy	222	
Colposcopy with LLETZ	238	

Table 39 Costs per treatment, by device, used in the model

Treatment	Device	Cost per treatment (£)
Colposcopy examination only	Colposcopy alone	175
	DYSIS	180.49 (175 – 3.75 + 9.24)
	ZedScan	205.52 (175 + 30.52)
Diagnostic biopsy		47 (222 - 175)
LLETZ		63 (238 – 175)
Cytology test		37.19
HPV test		29.66

6.4.5.2 Cancer costs

Cancer costs by stage were taken from a UK-based study by Martin-Hirsch (2007) (152) which estimated costs associated with the management of women with abnormal cervical cytology. Unit costs for cancer treatment (including chemotherapy, radiotherapy and inpatient care) were obtained by the authors from the National Reference Costs, British National Formulary and from personal communications with purchasing department of clinics included in the study (6 centres in England and Wales). Average costs per cancer treatment were reported in £ at 2006 price, by cancer stages using the FIGO grading (stages I to IV). We assume that the average cost of Stage I and Stage II refer to `Local' stage, Stage III to `Regional' stage and `Stage IV' to `Distant' stage. In the model, all costs were inflated to 2016 prices.

Table 40 Total treatment cost per cancer stage

Cancer treatment, by stage	Cost per event (£, 2006)	Cost per event (£, 2016)	Source
Stage I	2785	3434	Martin-Hirsch (2007) (152)
Stage II	4448	5484	
Stage III	12,562	15,487	
Stage IV	12,777	15,752	
Local	--	4459	Calculated from Martin-Hirsch (2007) (152)
Regional	--	15,487	
Distant	--	15,752	

6.4.5.3 Costs associated with adverse obstetric outcomes

The additional costs associated with preterm birth were derived from the same source as the QALY decrements. The study by Lomas (2016) (153) reported an expected incremental (discounted) lifetime cost of £24,071 per birth (inflated to £24,610 in 2016 prices). This estimate incorporates an estimate

of the initial inpatient neonatal care and ongoing costs over the following 18-years of live in survivors associated with higher rates of disability.

6.4.6 Health outcomes

Health utility values refers to patient's health measured on an interval scale, where 0 represents death and 1 represents perfect health. QALY estimates combine both the utility value 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 health utility over a set time period converted into lost QALYs.

6.4.6.1 Screening disutility

Disutility associated with screening and treatment were based on a recent study, especially designed to estimate utility values for HPV testing and cytology based screening states among women targeted for cervical screening (Simonella and Canfell, 2014 (154)). 43 women (mean aged 49 years), living in Sydney, Australia, participated to the study. Participants were asked to state their preferences (rank and utility scores) for hypothetical states relating to cytology and HPV screening and pre-cancerous lesions. Utility values were estimated via a two-stage standard gamble. The model uses utility values reported by Simonella and Canfell (2014) (154) for four types of screening episodes: (i) a routine screening episode with normal cytology result; (ii) a false positive referral to colposcopy; (iii) a colposcopy referral that leads to confirmed but not treated CIN1; and (iv) a colposcopy referral that leads to the treatment of CIN lesions. Each scenario was described in a narrative format in Simonella and Canfell (2014) (154) to characterise the screening process and possible adverse outcomes associated with examination and treatment. Consequently, this set of values captures the disutility associated with the screening process, from the experience of being screened (even if the test result is negative) to the possible short-term adverse outcomes of colposcopy and treatment.

Simonella and Canfell (2014) (154) reported the mean standard gamble utility values over a 12 months period. In the model we converted these scores into QALY decrements (1- mean utility value) of undergoing a screening episode (initial referral for colposcopy, follow-ups or routine screening). A screening episode with cytology and/or HPV test which did not result in a referral for colposcopy induced a QALY decrement of 0.0062. The QALY decrement associated with false positive referral for colposcopy (cytology and/or HPV test are positive but colposcopy or histopathology are negative) or a confirmed but not treated CIN1 lesion was estimated to be 0.0276. Finally, a positive diagnosis followed by excision treatment of CIN lesion induced a QALY decrement of 0.0296 (Table 41).

Table 41 Disutility associated with screening, diagnosis and treatment of CIN

Screening episode	QALY decrement	Source
Negative cytology and/or HPV	0.0062	Simonella and Canfell (2014) (154)).
False positive referral for colposcopy	0.0276	
Diagnosed CIN1	0.0276	
Treatment of CIN	0.0296	

6.4.6.2 Health-related quality of life of underlying true health states

As HPV, CIN1, CIN2/3 and undetected cancer are considered to be asymptomatic, we apply age and gender specific utilities from the Measurement and Valuation of Health survey, a nationally representative interview survey of 3395 men and women living in the UK conducted in 1993 (Kind, 1999 (155)) (Table 42). The possible disutility that patients can experience once CIN lesions are identified is subsequently captured by screening disutility as outlined previously.

QALY decrements associated with invasive cancer were obtained from a published study (Goldie, 2004 (5)). The authors reported HRQoL for detected invasive cancer' and HRQoL `after treatment for invasive cancer', by stage (local, regional and distant). We considered the first set of HRQoL as a utility score associated with the first year post-diagnosis, during which patients undergo treatment. We used the second set for the remaining 4 years during which patients are not yet considered to be cured from cancer but do not receive further treatments (Table 43).

Table 42 Health-related quality of life (utilities) for women, by age group

Age group - Women	Utility	Source
25-34	0.93	Kind (1999) (155)
35-44	0.91	
45-54	0.85	
55-64	0.81	
65-74	0.78	
75+	0.71	

Table 43 QALY decrements associated with detected invasive cancer

Invasive cancer	Stage	QALY decrement	Source
Year 1 post-diagnosis	Local	0.35	Goldie (2004) (5)
	Regional	0.44	
	Distant	0.52	
Years 2,3,4 and 5 post-diagnosis	Local	0.03	
	Regional	0.1	
	Distant	0.38	

6.4.6.4 QALY decrement associated with adverse obstetric outcomes

A QALY decrement was applied to capture the HRQoL and mortality consequences of the increased risk of preterm birth following treatment for CIN. We did not attempt to identify evidence for this parameter systemically. Instead we restricted our search to the evidence reported in NICE NG25 (Preterm labour and birth) (156). Although NICE NG25 reports utility and QALY estimates, none of these directly provided the required estimates for our model (i.e. the QALY decrement associated with preterm birth < 37 weeks). Instead, we sourced estimates based on discussions with colleagues and identified a recent study by Lomas (2016) (153) which reported cost and QALY decrements which matched the requirements of the model. The QALY decrement reported in Lomas (2016) was 1.3 QALYs and was derived from calculations based on the QALY loss associated with neonatal mortality and the discounted QALY loss associated with increased disability rates reported among survivors.

6.5 Analytic methods

A decision model was developed to estimate the cost-effectiveness of adjunctive colposcopy technologies (DYSIS and ZedScan I) for women referred for colposcopy through the NHS Cervical Screening Programme under either HPV triage (including test of cure) or the HPV primary screening protocol (including test of cure).

The decision model is implemented using a patient-level state-transition modelling approach. The time horizon of the evaluation is 60 years and costs and outcomes are discounted at a rate of 3.5% and a 2015/2016 price year is used.

The model captures the long term impact of standard colposcopy and adjunctive colposcopy technologies in terms of average cost and average QALYs per patient. The analysis compares colposcopy alone to DYSIS, colposcopy alone to ZedScan and DYSIS to ZedScan based on incremental costs and QALYs and the incremental cost-effectiveness ratio (ICER). In addition, the model predicts several outcomes which include, for 1000 women referred for colposcopy: the number of CIN2+ cases missed, the number of women who developed cancer, the number of women who died from cancer, the number of women who received treatment (LLETZ), the number of unnecessary treatments and diagnostic biopsies, and the number of women who experienced adverse obstetric outcomes (pre-term delivery).

The model was run to simulate 500,000 women referred for colposcopy. This large number of iterations was necessary to ensure that the proportion of patients in each state equals the individual probability. In the base case and in scenario analysis, simulations were run separately for each routine screening model (HPV triage protocol and HPV primary protocol), each type of clinic (See and treat, Watchful waiting) and for each reason for referral (all referrals, low grade (LG) and high grade (HG)). In order to obtain reproducible results and to limit statistical variation from one simulation to the next, the same number (or "seed") was used to initialise the sequence of pseudo-random number.

Structural assumptions are identical for the three strategies (colposcopy alone, DYSIS, ZedScan) only the diagnostic accuracy and the cost of the devices vary. The differences between HPV triage and HPV primary models are: characteristics of the population referred for colposcopy; routine screening pathways; and diagnostic accuracy of HPV test. We assume that women who visit a *See and treat* clinic are treated at initial appointments only if colposcopy is positive (CIN2+) and cytology result is moderate or severe (HG referral). Women who visit *Watchful waiting* clinics are never treated at their initial appointment. A diagnostic biopsy is assumed to be systematically performed to confirm the diagnostic results. Since we assume 100% specificity and sensitivity for diagnostic biopsy, patients never receive unnecessary treatment in a simulation with Watchful waiting clinics.

6.5.1 Base case analysis

The characteristics of the base case are summarised in Table 44 and Table 45. Details on structural assumptions and input parameters are provided in sections 6.2 and 6.3.

Table 44 Characteristics of the base case analyses (1/2)

Parameters	Value / Source	Comment
Number of cycles	120 (60 years)	
Discount rate	3.5%	
STRUCTURE		
Adverse obstetric outcomes	YES	Excess risk of pre-term delivery
See and treat for HG only	YES	
Use of ZedScan	Diagnostic colposcopy only	
Treatment pathways	NHSCSP guidelines and clinical experts	
Attendance rate	100%	No patients were lost to follow-up
INPUT PARAMETERS		
Diagnostic accuracy		
Colposcopy	Regression	Cut-off CIN2+
DYSIS	Regression	Cut-off CIN2+
ZedScan	Tidy (forthcoming) (103)	Cut-off CIN2+
Cytology	Eggington (2006) (131)).	
HPV test (HPV triage)	Cotton (2010) (132)	
HPV test (HPV primary)	Kitchener (2014) (147)	
Initial population		
Age at start	36	Average age under NHS cervical screening programme
HPV triage	NHS Cervical screening programme (18)	
HPV primary	Pilot sites	No genotyping HPV 16/18
Treatment probabilities		
Cured after LLETZ	Ghaem-Maghami (2011) (148)	
Adverse obstetric outcomes	Kyrgiou (2016) (122)	
Natural history		
CIN	Kulasingam (2013) (145)	
Cancer	Campos (2014) (146)	
All-cause mortality	ONS data (150)	

Table 45 Characteristics of the base case analyses (2/2)

Costs		
Colposcopy alone	NHS reference cost (151)	

DYSIS	Manufacturer	
ZedScan	Manufacturer	
Number of patients treated per colposcope per year	1229	
LLETZ and biopsy	NHS reference cost (151)	
Cytology and HPV tests	TOMBOLA study (136)	
Cancer costs	Martin-Hirsch (2007) (152)	
Adverse obstetric outcomes	Lomas (2016) (153)	
Health outcomes		
Screening disutility	Simonella (2014) (154)	Screening episodes
Baseline	Kind (1999) (155)	Age and gender specific
Cancer	Goldie (2004) (5)	5 years decrement
Pre-term births	Lomas (2013) (153)	

6.5.2 Sensitivity and scenario analyses

To investigate the impact of parameter uncertainty on the results, several sensitivity analyses were undertaken focusing on diagnostic accuracy, costs of technologies, costs of treatment and biopsies and the initial characteristics of the population referred for colposcopy under the HPV primary protocol. In addition, three scenario analyses were undertaken to explore alternative structural assumptions: (i) restricting the analysis to a three year period to evaluate costs and outcomes within a single screening interval; (ii) excluding adverse obstetric outcomes; and (iii) assuming that ZedScan is used alongside colposcopy at all appointments. Sensitivity analyses and scenarios used the same assumptions and parameter values as the base case unless stated.

6.5.2.1 Uncertainty around diagnostic accuracy

- **SA1** - Colposcopy alone and DYSIS: Louwers (2011) (66).

In the first sensitivity analysis (SA1), diagnostic accuracy for colposcopy alone and DYSIS were based on a single study, Louwers (2011) (66). Louwers (2011) (66) was selected as it is the only study considered as low risk of bias (see section 4.3.2). It also provides a positive predictive value of colposcopy alone above the NHS standard of 65% (PPV=70.37, see section 4.3.4.1). Compared to the base case, the Louwers study (66) reported slightly lower sensitivity and specificity for both colposcopy alone and DYSIS (Table 46). Since similar data were not available for ZedScan, SA1 only compares DYSIS to colposcopy alone.

Table 46 Sensitivity analysis: diagnostic accuracy of colposcopy alone and DYSIS based on Louwers (2011)

Technology	Sensitivity (95% CI)	Specificity (95% CI)	Source
Colposcopy alone	51.35% (42.05 to 60.65)	82.09% (75.60 to 88.58)	Louwers (2011) (66)
DYSIS	78.38% (70.72 to 86.04)	63.43% (55.285 to 71.59)	

- **SA2** – Impact of a CIN2+ cut-off (colposcopy alone and DYSIS)

SA2 explores the implications of using a CIN2+ cut-off, i.e. the assumption that specificity is independent of being Clear, HPV or CIN1, and sensitivity is independent of being CIN2/3 or Cancer. Unpublished data provided by DYSIS manufacturer from the Louwers study (66) were used to estimate the probability of a positive colposcopy (i.e. detecting CIN2 or worse) by health state for colposcopy alone and DYSIS (Table 47). Since similar data were not available for ZedScan, SA2 only compares DYSIS to colposcopy alone.

Table 47 Sensitivity analysis: probabilities of a positive colposcopy result (CIN2+) by health state for colposcopy alone and DYSIS

Health state	Colposcopy alone	DYSIS	Source
Clear or HPV	[redacted]	[redacted]	Louwers (2011) (66)
CIN1	[redacted]	[redacted]	
CIN2/3	[redacted]	[redacted]	
Cancer	[redacted]	[redacted]	

- **SA3** – Diagnostic accuracy of colposcopy alone from Tidy (2013)

SA3 compared ZedScan to colposcopy alone using diagnostic accuracy from Tidy (2013) (102) for colposcopy alone and Tidy (forthcoming) (103) for ZedScan. Tidy (2013) (102) was a study of a ZedScan prototype, conducted in a similar context to Tidy (forthcoming) (103) and therefore provides an alternative estimate for colposcopy alone to inform the direct comparison between ZedScan and colposcopy (see section 4.3.4.6). Tidy (2013) (102) reported significantly higher sensitivity and specificity for colposcopy alone than the meta-analysis results (Table 48).

Table 48 Sensitivity analysis: diagnostic accuracy of colposcopy alone based on Tidy (2013)

Technology	Sensitivity (95% CI)	Specificity (95% CI)	Source
Colposcopy alone	73.56% (64.3 to 82.8)	83.49% (76.5 to 90.5)	Tidy (2013) (102)
ZedScan	97.85% (96.5 to 99.2)	58.63% (55.1 to 62.1)	Tidy (forthcoming) (103)

- **SA4.1 and 4.2** –Lower and upper bound of specificity and correlated sensitivity of DYSIS

SA 4.1 and 4.2 characterise the uncertainty around the estimates of specificity and sensitivity of DYSIS compared to colposcopy alone (Table 49). SA 4.1 used the lower bound of specificity from the 95% CI of the regression model estimates and the correlated sensitivity from the ROC curve (see section 4.3.4.1). SA 4.2 used the upper bound of specificity from the 95% CI of the regression model

estimates and the correlated sensitivity from the ROC curve. In both analyses, we used the base case values for colposcopy alone (average point estimates of the regression model).

Table 49 Sensitivity analysis DYSIS: lower and upper bound specificity and correlated sensitivity

Technology	Sensitivity	Specificity	Source
Colposcopy alone	57.91%	87.41%	Regression model (average point estimates)
SA4.1: lower bound (2.5%) specificity			
DYSIS	83.6%	59.4%	Regression model
SA4.2: upper bound (97.5%) specificity			
DYSIS	78.5%	79.5%	Regression model

- **SA4.3 and 4.4** –Lower and upper bound of specificity and sensitivity of ZedScan

SA 4.3 and 4.4 characterise the uncertainty around the estimates of specificity and sensitivity of ZedScan compared to colposcopy alone (Table 50). Since there was only one study available (Tidy, forthcoming) (103), we were not able to estimate the correlated sensitivity for extreme values of specificity. Instead, in order to reflect the negative correlation between specificity and sensitivity, SA 4.3 used the upper bound of specificity from the 95% CI reported in Tidy (forthcoming) (103) and the lower bound of sensitivity (from the 95% CI); SA 4.4 used the lower bound of specificity and the upper bound of sensitivity. In both analyses, we used the base case values for colposcopy alone.

Table 50 Sensitivity analysis ZedScan: lower and upper bounds (95% CI) of sensitivity and specificity

Technology	Sensitivity	Specificity	Source
Colposcopy alone	57.91%	87.41%	Regression model (average point estimates)
SA4.3: 97.5% sensitivity – 2.5% specificity			
ZedScan	99.2%	55.1%	Tidy (forthcoming) (103)
SA4.4: 2.5% sensitivity – 97.5% specificity			
ZedScan	96.5%	62.1%	Tidy (forthcoming) (103)

6.5.2.2 Uncertainty around costs

- **SA5.1 and 5.2** – Impact of throughput on the cost of devices

SA5.1 and 5.2 explore the impact of throughput on the cost of devices by assuming alternative estimates of the number of patients examined per colposcope per year. This parameter is used to estimate the cost per patient of DYSIS and ZedScan. SA5.1 simulated a 50% decrease in the number of patients per colposcope per year (614 instead of 1229), which drives up the cost of DYSIS and ZedScan. SA5.2 simulated a 50% increase in the number of patients per colposcope per year (1844 instead of 1229). Because the cost of a colposcopy examination with a binocular colposcope is based on NHS reference cost, the cost of colposcopy alone remains unchanged. Given its higher purchase price, the cost of DYSIS is more sensitive to a variation in the number of patients than ZedScan (Table 51).

Table 51 Sensitivity analysis: number of patients examined per colposcope per year (+/- 50%)

Cost of colposcopy examination (£), by device	Lower bound 614 patients per colposcope per year	Upper bound 1844 patients per colposcope per year
Colposcopy alone	175	175
DYSIS	184.63	179.11
ZedScan	206.05	205.35

- **SA6** - Costs of diagnostic biopsy and LLETZ

We noted an important discrepancy in the estimates of the cost of a colposcopy with treatment (LLETZ) between the NHS reference cost (£238) and the cost reported by Whyte (2013) (128) (£590). The costs for LLETZ reported by Whyte (2013) (128) included an estimate pathology cost of £407. NHS reference costs should theoretically include all associated costs of LLETZ (including associated histology/pathology costs). However, there is some uncertainty surrounding whether the reference costs accurately reflect actual resource use and particularly histology/pathology costs.

Consequently, in SA6, the cost estimates of histology/pathology for a diagnostic biopsy and a LLETZ reported in Whyte (2013) (128) (respectively £53 and £407 in 2011/2012 prices) were added to the NHS reference costs (Table 52).

Table 52 Sensitivity analysis: costs of biopsies and LLETZ

	Cost per treatment (£)	Source
NHS reference cost		
Diagnostic biopsy	47	NHS Reference costs
LLETZ	63	
Histology/pathology costs		
Diagnostic biopsy	55.72*	Whyte (2013) (128)
LLETZ	427.89*	
Total cost (NHS ref cost + histology/pathology cost)		
Diagnostic biopsy	102.72	
LLETZ	490.89	

*inflated to 2015/2016 prices assuming Whyte (2013) reported 2011/2012 prices

6.5.2.3 Population referred for colposcopy under HPV primary protocol

- **SA7.1 and 7.2**: alternative distributions of health state and reason for referral from HPV pilot sites

To address the uncertainty around the characteristics of the population referred for colposcopy under HPV primary protocol (see section 6.3.2), SA 7.1 and 7.2 respectively used data from pilots sites without HPV16/18 genotyping and pilots sites with genotyping. Although the proportion of LG and HG appear very similar between the two types of pilot sites, the prevalence of HPV is higher in pilot sites which are not implementing genotyping (Table 53). It is important to note that this sensitivity analysis is not intended to explore the impact of alternative HPV primary screening protocols but rather to use the variation observed between different sites as a means of exploring the potential impact of uncertainty around the characteristics of the population referred.

Table 53 Characteristics of women referred for colposcopy under HPV primary, by types of pilot sites

Health state and reason for referral (%)	Pilot sites – No genotyping	Pilot sites - Genotyping
Clear LG	[redacted]	[redacted]
Clear HG	[redacted]	[redacted]
HPV LG	[redacted]	[redacted]
HPV HG	[redacted]	[redacted]
CIN1 LG	[redacted]	[redacted]
CIN1 HG	[redacted]	[redacted]
CIN2/3 LG	[redacted]	[redacted]
CIN2/3 HG	[redacted]	[redacted]
Cancer LG	[redacted]	[redacted]
Cancer HG	[redacted]	[redacted]

6.5.2.4 Scenario analyses

Scenario analyses were undertaken to consider the impact of three key structural assumptions.

- **Sc1**: time horizon of three years

In Sc1, the model was run for only three years to evaluate the cost-effectiveness of adjunctive technologies with a short-term perspective. Indeed, a three years window captures costs and health outcomes of the initial colposcopy appointment and immediate follow-ups (including test of cure or CIN1 follow-up) but does not capture potential long term consequences such as future screenings, disease progression and adverse obstetrics outcomes.

- **Sc2:** adverse obstetric outcomes were excluded

Sc2 simulated the cost-effectiveness results of adjunctive technology without taking into account potential adverse obstetrics outcomes of treatment excision.

- **Sc3**: ZedScan was used alongside colposcopy at all appointments

Whilst the base case assumed that ZedScan was only alongside colposcopy only during the initial appointment (before histology results), Sc3 was run assuming that ZedScan would be used at all appointments, including therapeutic colposcopies after confirmation by histology results. Note that, as it is the case for DYSIS, no additional benefit is associated with the use of adjunctive technologies during therapeutic colposcopies.

6.5.3 Model validation

The face validity of the model structure and key assumptions were evaluated by our clinical advisors. A series of steps were undertaken to ensure the internal validity of the model, including: (i) double checking model input estimates with the original sources; (ii) repeated testing of individual elements of the model; and (iii) extensive logical tests and sensitivity analysis to ensure the model behaved as would be expected. The results of the model were cross-validated by comparing results to the previous published studies to ensure that any possible differences were identified and could be explained.

6.6 Results of the independent economic assessment

The economic evaluation compares DYSIS to colposcopy alone, ZedScan to colposcopy alone and ZedScan to DYSIS. Table 54 to Table 61 display the average cost and QALYs per patient, the incremental cost and QALYs per patient and the incremental cost-effectiveness ratio (ICER) as well as secondary outcomes for the base case. Figure 26 to Figure 37 graphically summarise the base case results, sensitivity and scenario analyses using a cost-effectiveness plane to plot the incremental cost and incremental QALYs. Detailed results for the sensitivity and scenario analyses are displayed in Appendix 10.10.

6.6.1 Base case results

The base case results are presented separately for the HPV triage and HPV primary screening protocols. The results are presented based on clinical practice (See and treat, Watchful waiting) and according to the reason for referral (all referrals, high grade and low grade referrals).

6.6.1.1 HPV triage protocol – Base case results

Results for the base case analysis under HPV triage protocol are summarised in Figure 26 and presented in more detail in Table 54 to Table 56 (costs and QALYs) and in Table 57 (secondary outcomes).

In Figure 26, the incremental costs and QALYs of DYSIS vs. colposcopy alone, ZedScan vs. colposcopy alone and ZedScan vs. DYSIS are represented visually using onseparate cost-effectiveness planes. The horizontal axis divides the plane according to the incremental cost (positive above and negative below) and the vertical axis divides the plane according to the incremental QALYs (positive to the right and negative to the left). The cost-effectiveness plane is thus divided into four quadrants with different implications for decision making. If an intervention falls in the SE quadrant then it dominates the comparator technology (i.e. less costly and more effective). Similarly, the intervention would be dominated by the comparator in the NW quadrant. When non-dominance exists (NE and SW quadrants), the resulting ICER can be compared against the conventional cost-effectiveness threshold (£20,000-£30,000 per QALY) to determine whether the intervention is cost-effective or not. In Figure 1, a £20,000 threshold is represented by the straight line which further divides the NE and SW quadrants. Points above and below the line indicate respectively that the ICER of the intervention is higher or lower than the threshold. Results by type of clinics and reason for referral are represented in each plane by distinct markers.

The main results of the base case analysis under HPV triage protocol can be summarised as follows:

- DYSIS routinely dominated colposcopy alone, regardless of the type of clinics or the reason for referral (Table 54). The only exception was for HG referrals in Watchful waiting clinic

setting, where DYSIS was more costly and more effective with an associated ICER of £675 per QALY.

- ZedScan also dominated colposcopy alone in See and treat clinics (Table 55). However, in Watchful waiting clinics, ZedScan was always more effective than colposcopy alone but also more costly. The ICER for ZedScan in Watchful waiting clinics ranged from £272 (LG referrals) to £4070 per QALY (HG referrals).

- The higher sensitivity of DYSIS and Zedscan resulted in increased QALYs compared to conventional colposcopy alone in all sets of results. In addition, the incremental gain in QALYs always appeared higher for LG referrals. The higher incremental gain for LG referrals is due to the assumption that a diagnostic biopsy will not be performed if colposcopy is negative. Hence, false negatives for LG referrals will therefore potentially be missed making higher sensitivity a more critical consideration for LG referrals.

- The impact on total cost appears to depend on the technology and clinic practice. Both adjunctive technologies generally decrease the average cost per patient in See and treat clinics. In Watchful waiting clinics however, the average cost generally decreases to a smaller extent with DYSIS and appears to increase with ZedScan compared to colposcopy alone.

- The indirect comparison between ZedScan and DYSIS showed that ZedScan routinely appeared more effective but also more costly than DYSIS (Table 56). The ICER for ZedScan ranged from £109 per QALY for HG referrals in See and treat clinics to £9918 per QALY for HG referrals in Watchful waiting clinics.

- Secondary outcomes from the simulations show that a higher specificity (colposcopy alone) limits the number of unnecessary treatments and biopsies and consequently reduces the number of adverse obstetric outcomes (Table 57). In contrast, a higher sensitivity (adjunctive technologies) reduces the number of undetected CIN2+, the number of new cancer cases and the number of death due to cancer;

Figure 26 Base case, cost-effectiveness results – HPV triage

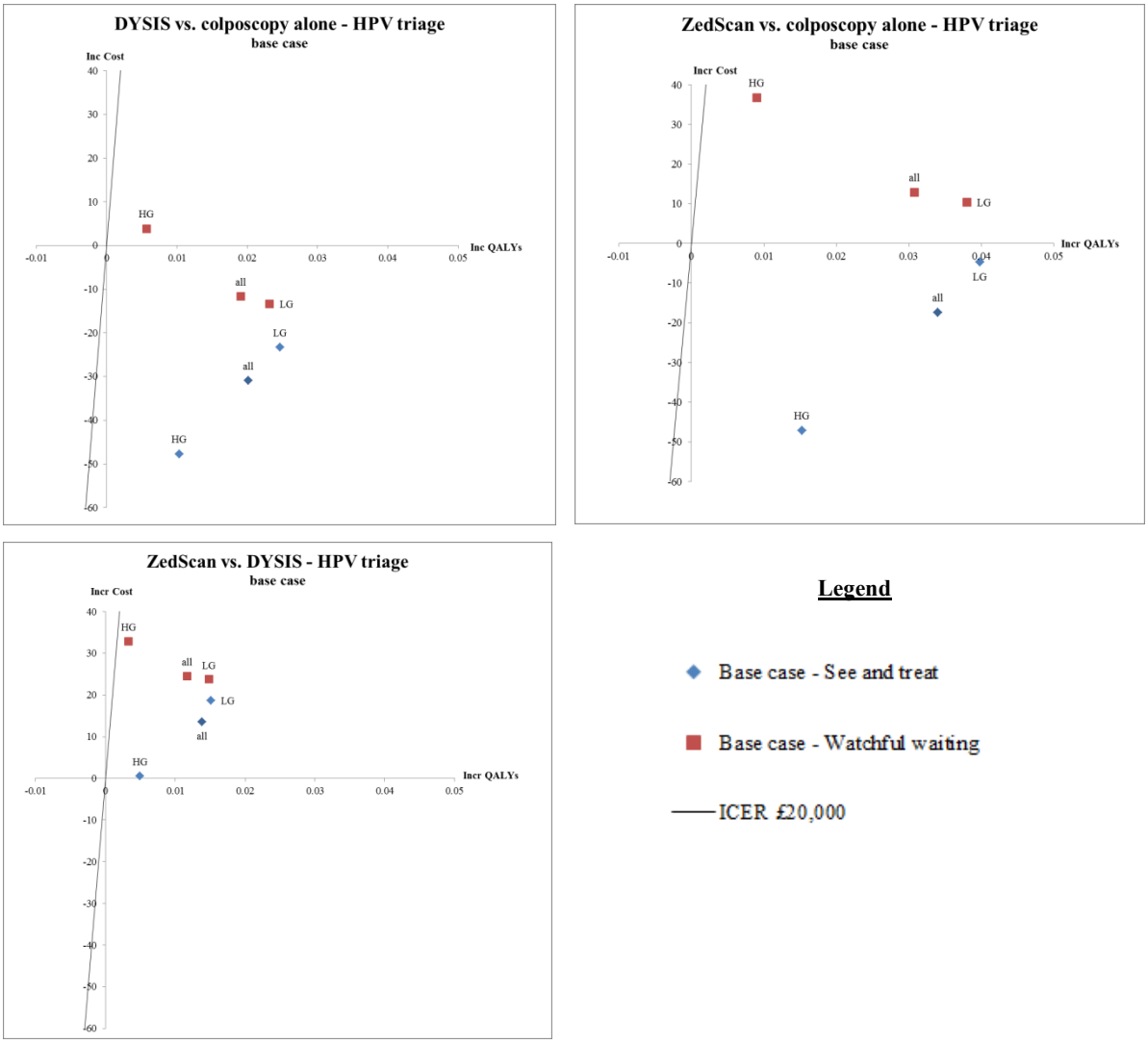


Table 54 Base case results, HPV triage - DYSIS vs. colposcopy alone

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	Colposcopy alone	903.28	19.16500			
	DYSIS	872.34	19.18516	-30.94	0.02016	Dominant
LG referrals	Colposcopy alone	793.97	19.16330			
	DYSIS	770.65	19.18794	-23.33	0.02464	Dominant
HG referrals	Colposcopy alone	1139.13	19.16122			
	DYSIS	1091.43	19.17156	-47.70	0.01034	Dominant
Watchful Waiting clinics						
All referrals	Colposcopy alone	953.02	19.16286			
	DYSIS	941.33	19.18194	-11.69	0.01908	Dominant
LG referrals	Colposcopy alone	812.85	19.16283			
	DYSIS	799.47	19.18601	-13.38	0.02318	Dominant
HG referrals	Colposcopy alone	1252.07	19.16008			
	DYSIS	1255.93	19.16580	3.85	0.00571	675

Table 55 Base case results, HPV triage - ZedScan vs. colposcopy alone

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	Colposcopy alone	903.28	19.16500			
	ZedScan	885.91	19.19901	-17.37	0.03401	Dominant
LG referrals	Colposcopy alone	793.97	19.16330			
	ZedScan	789.30	19.20307	-4.68	0.03978	Dominant
HG referrals	Colposcopy alone	1139.13	19.16122			
	ZedScan	1091.97	19.17651	-47.16	0.01529	Dominant
Watchful waiting clinics						
All referrals	Colposcopy alone	953.02	19.16286			
	ZedScan	965.87	19.19363	12.85	0.03078	418
LG referrals	Colposcopy alone	812.85	19.16283			
	ZedScan	823.19	19.20082	10.34	0.03799	272
HG referrals	Colposcopy alone	1252.07	19.16008			
	ZedScan	1288.82	19.16911	36.75	0.00903	4070

Table 56 Base case results, HPV triage - ZedScan vs. DYSIS

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	DYSIS	872.34	19.18516			
	ZedScan	885.91	19.19901	13.57	0.01385	980
LG referrals	DYSIS	770.65	19.18794			
	ZedScan	789.30	19.20307	18.65	0.01514	1232
HG referrals	DYSIS	1091.43	19.17156			
	ZedScan	1091.97	19.17651	0.54	0.00495	109
Watchful waiting clinics						
All referrals	DYSIS	941.33	19.18194			
	ZedScan	965.87	19.19363	24.54	0.01170	2098
LG referrals	DYSIS	799.47	19.18601			
	ZedScan	823.19	19.20082	23.72	0.01481	1601
HG referrals	DYSIS	1255.93	19.16580			
	ZedScan	1288.82	19.16911	32.89	0.00332	9918

Table 57 Base case, HPV triage - secondary outcomes (per 1,000 women referred)

	Strategy	Missed CIN2+	Develop Cancer	Die from cancer	LLETZ	Unnecessary treatment (Clear, HPV)	Unnecessary treatment (CIN1)	Unnecessary diagnostic biopsy	Pre-term delivery
See and Treat clinics									
All referrals	Colposcopy alone	69	43	9	466	9	18	139	4.0
	DYSIS	30	34	7	501	22	39	229	4.4
	ZedScan	3	29	6	524	30	52	291	4.8
LG referrals	Colposcopy alone	91	51	10	276	6	18	131	1.4
	DYSIS	39	40	8	318	15	39	245	1.8
	ZedScan	4	33	6	343	22	51	323	2.1
HG referrals	Colposcopy alone	22	26	7	879	14	16	149	10.0
	DYSIS	9	22	6	902	34	36	192	10.3
	ZedScan	1	20	6	916	49	50	220	10.5
Watchful Waiting clinics									
All referrals	Colposcopy alone	69	44	9	449	0	0	147	3.9
	DYSIS	30	37	8	465	0	0	252	4.1
	ZedScan	3	32	7	477	0	0	325	4.2
LG referrals	Colposcopy alone	92	52	10	259	0	0	137	1.3
	DYSIS	39	43	8	283	0	0	260	1.7
	ZedScan	4	37	7	299	0	0	347	2.0
HG referrals	Colposcopy alone	22	27	7	862	0	0	164	9.5
	DYSIS	10	24	7	864	0	0	230	9.4
	ZedScan	1	23	6	866	0	0	276	9.5

6.6.1.2 HPV primary protocol – Base case results

Results for the base case analysis under HPV primary protocol are summarised in Figure 27 and presented in more details in Table 58 to Table 60 (costs and QALYs) and in Table 61 (secondary outcomes). The interpretation of cost-effectiveness plans in Figure 27 is the same than for Figure 26.

As regards the cost-effectiveness of adjunct technologies, conclusions are quite similar under HPV primary and HPV triage protocols:

- In most instances, DYSIS dominated colposcopy alone except for HG referral in Watchful waiting clinics where the ICER was estimated to be £1095 per QALY (Table 58).

- Results for ZedScan were more varied. ZedScan only dominated colposcopy alone for HG referral in a See and treat clinic. In all other cases, ZedScan was more effective but also more costly than colposcopy alone. The ICER ranged from £417 per QALY for LG referrals in See and treat clinics to £4922 per QALY for HG referrals in Watchful waiting clinics (Table 59).

- ZedScan was always more effective but also more costly than DYSIS. The ICER ranged from £426 per QALY for HG referrals in See and treat clinics to £8190 per QALY for HG referrals in Watchful waiting clinics (Table 60).

- Consistent with findings reported in the ARTISTIC study (Kitchener, 2014 (147)), simulations under the HPV primary protocol predicted higher health outcomes and a lower average cost per patient than under HPV triage. As regards the cost-effectiveness of adjunctive technologies, the most significant impact of the HPV primary protocol was to reduce the incremental effect of the adjunctive technologies on health outcomes. Because HPV primary routine screening presents a higher sensitivity overall, CIN2+ cases which were missed at the initial colposcopy appointment have a higher probability to be diagnosed three years later during routine screening avoiding subsequent development of cancer. The lower sensitivity of colposcopy alone compared to adjunctive technologies therefore appears less critical in this context.

Figure 27 Base case, cost-effectiveness results – HPV primary

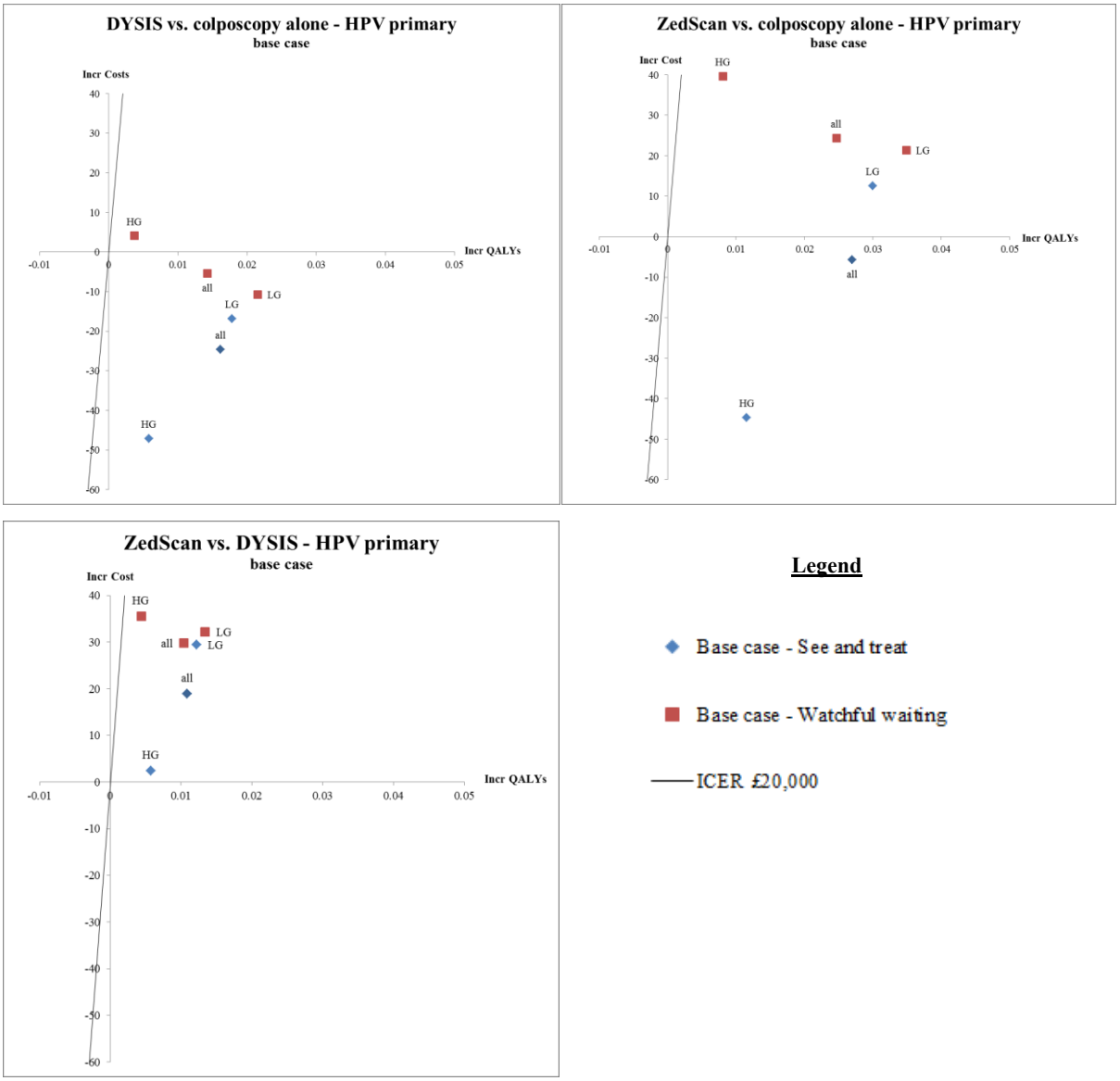


Table 58 Base case results, HPV primary – DYSIS vs. colposcopy alone

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	Colposcopy alone	850.08	19.17506			
	DYSIS	825.46	19.19120	-24.62	0.01614	Dominant
LG referrals	Colposcopy alone	732.33	19.19008			
	DYSIS	715.46	19.20787	-16.87	0.01779	Dominant
HG referrals	Colposcopy alone	1126.93	19.16192			
	DYSIS	1079.83	19.16774	-47.11	0.00581	Dominant
Watchful waiting clinics						
All referrals	Colposcopy alone	894.41	19.17511			
	DYSIS	889.04	19.18937	-5.37	0.01426	Dominant
LG referrals	Colposcopy alone	748.86	19.18496			
	DYSIS	738.10	19.20646	-10.77	0.02150	Dominant
HG referrals	Colposcopy alone	1236.94	19.15863			
	DYSIS	1240.99	19.16234	4.06	0.00371	1095

Table 59 Base case results, HPV primary – ZedScan vs. colposcopy alone

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	Colposcopy alone	850.08	19.17506			
	ZedScan	844.41	19.20206	-5.67	0.02700	Dominant
LG referrals	Colposcopy alone	732.33	19.19008			
	ZedScan	744.85	19.22007	12.52	0.03000	417
HG referrals	Colposcopy alone	1126.93	19.16192			
	ZedScan	1082.27	19.17347	-44.66	0.01155	Dominant
Watchful Waiting clinics						
All referrals	Colposcopy alone	894.41	19.17511			
	ZedScan	918.78	19.19977	24.37	0.02466	988
LG referrals	Colposcopy alone	748.86	19.18496			
	ZedScan	770.26	19.21984	21.40	0.03487	614
HG referrals	Colposcopy alone	1236.94	19.15863			
	ZedScan	1276.58	19.16668	39.64	0.00805	4922

Table 60 Base case results, HPV primary protocol – ZedScan vs. DYSIS

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	DYSIS	825.46	19.19120			
	ZedScan	844.41	19.20206	18.95	0.01085	1746
LG referrals	DYSIS	715.46	19.20787			
	ZedScan	744.85	19.22007	29.39	0.01220	2408
HG referrals	DYSIS	1079.83	19.16774			
	ZedScan	1082.27	19.17347	2.45	0.00574	426
Watchful Waiting clinics						
All referrals	DYSIS	889.04	19.18937			
	ZedScan	918.78	19.19977	29.74	0.01040	2860
LG referrals	DYSIS	738.10	19.20646			
	ZedScan	770.26	19.21984	32.16	0.01338	2404
HG referrals	DYSIS	1240.99	19.16234			
	ZedScan	1276.58	19.16668	35.58	0.00434	8190

Table 61 HPV primary protocol - Secondary outcomes, base case (per 1,000 women referred)

	Strategy	Missed CIN2+	Develop Cancer	Die from cancer	LLETZ	Unnecessary treatment (Clear, HPV)	Unnecessary treatment (CIN1)	Unnecessary diagnostic biopsy	Pre-term delivery
See and Treat clinics									
All referrals	Colposcopy alone	82	33	7	446	8	14	164	3.9
	DYSIS	34	25	5	478	20	30	296	4.2
	ZedScan	4	20	4	498	28	40	386	4.5
LG referrals	Colposcopy alone	103	38	7	263	6	14	164	1.3
	DYSIS	42	28	5	300	15	30	323	1.6
	ZedScan	5	22	4	322	21	40	433	2.0
HG referrals	Colposcopy alone	30	21	6	883	14	14	162	10.0
	DYSIS	12	18	5	904	33	31	231	10.2
	ZedScan	1	16	5	917	46	42	276	10.4
Watchful Waiting clinics									
All referrals	Colposcopy alone	82	34	7	432	0	0	172	3.8
	DYSIS	34	27	6	450	0	0	316	4.0
	ZedScan	4	22	5	460	0	0	417	4.1
LG referrals	Colposcopy alone	104	39	7	251	0	0	170	1.2
	DYSIS	43	30	6	273	0	0	337	1.6
	ZedScan	5	24	5	288	0	0	454	1.9
HG referrals	Colposcopy alone	30	22	6	869	0	0	177	9.6
	DYSIS	12	20	6	871	0	0	267	9.5
	ZedScan	1	18	5	873	0	0	330	9.5

6.6.2 Sensitivity analyses results

To investigate the impact of parameter uncertainty on the results, several sensitivity analyses were undertaken focusing on diagnostic accuracy, costs and the initial characteristics of the population referred for colposcopy under the HPV primary protocol.

6.6.2.1 Uncertainty around diagnostic accuracy

Uncertainty around diagnostic accuracy of colposcopy alone, DYSIS and Zedscan was assessed with sensitivity analyses SA1 to SA4.4 (see section 6.4.2.1 for a detailed description). Because sensitivity analyses are different for DYSIS and ZedScan, results are presented separately in Figure 28 and Figure 29. Detailed results on average and incremental cost and QALYs are presented in Appendix 10.10 (Table 76 to Table 89) for each sensitivity analysis, under HPV triage and HPV primary protocols.

For DYSIS compared to colposcopy alone, results were globally unchanged compared to the base case analysis:

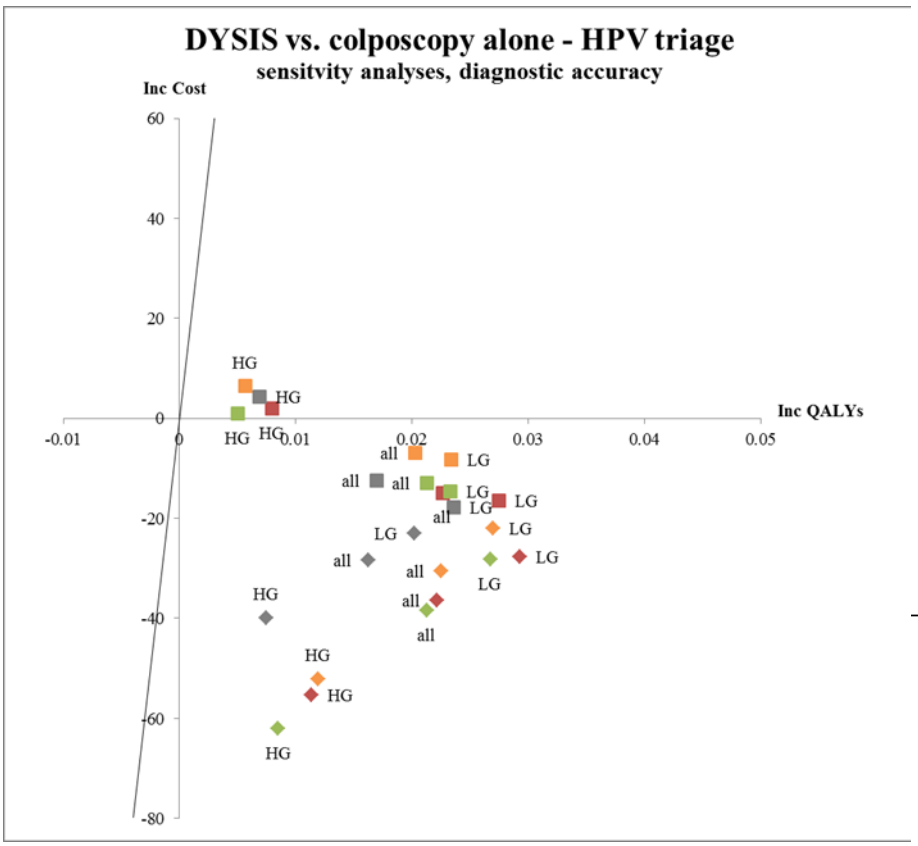
- DYSIS dominated colposcopy alone in most instances except for HG referrals in Watchful waiting context where the ICER ranged from £188 (SA2 under HPV triage, Table 78) to £1633 (SA2 under HPV primary, Table 79).

Sensitivity analyses results comparing ZedScan to colposcopy alone were more varied:

- The lower and upper bounds of ZedScan specificity and sensitivity (SA4.3 and SA4.4) had little impact on results. ZedScan still dominated colposcopy alone in See and treat clinics and was more effective but also more costly than colposcopy alone in Watchful waiting clinics, both under HPV triage and HPV primary.

- When ZedScan was compared to colposcopy alone based on diagnostic accuracy data which stemmed from a similar setting (SA3), the incremental cost increased and the incremental QALYs decreased. Overall, ZedScan no longer dominated colposcopy alone in See and treat clinics with an ICER ranging from £590 under HPV triage to £1457 under HPV primary. In Watchful waiting clinics the ICER increased, from £418 in the base case to £1910 in SA3 under HPV triage and from £988 to £4023 under HPV primary. Under HPV primary, the ICER exceeded £20,000 per QALY for HG referral in Watchful waiting clinics (Table 80 and Table 81).

Figure 28 Uncertainty around diagnostic accuracy - DYSIS vs. colposcopy alone



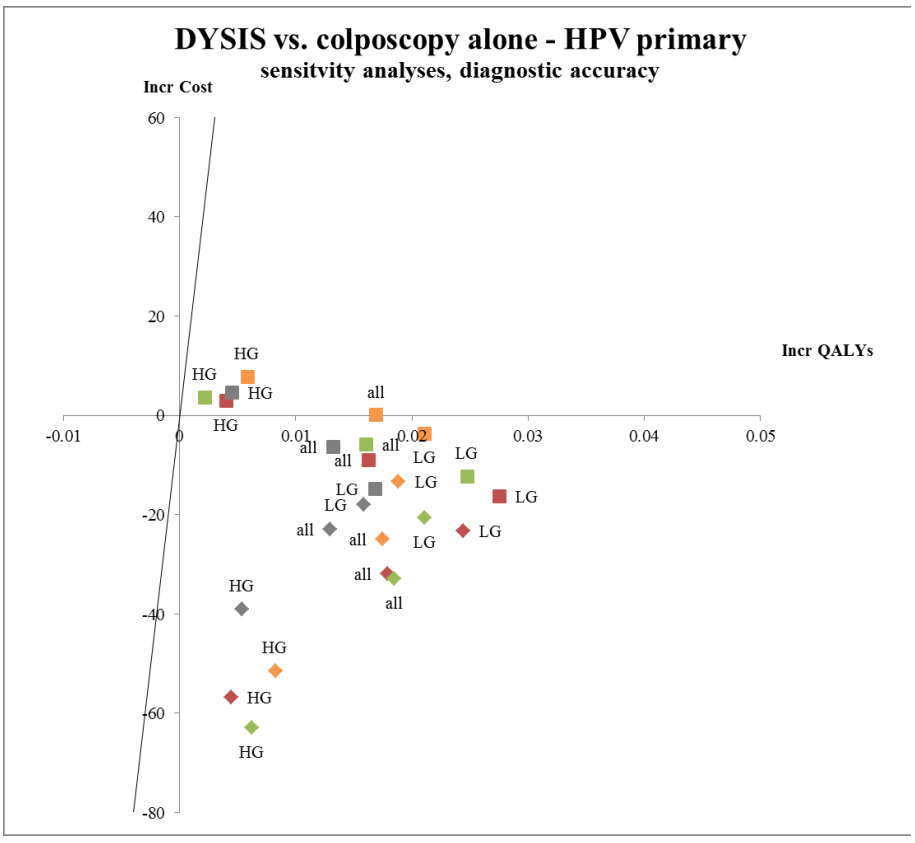
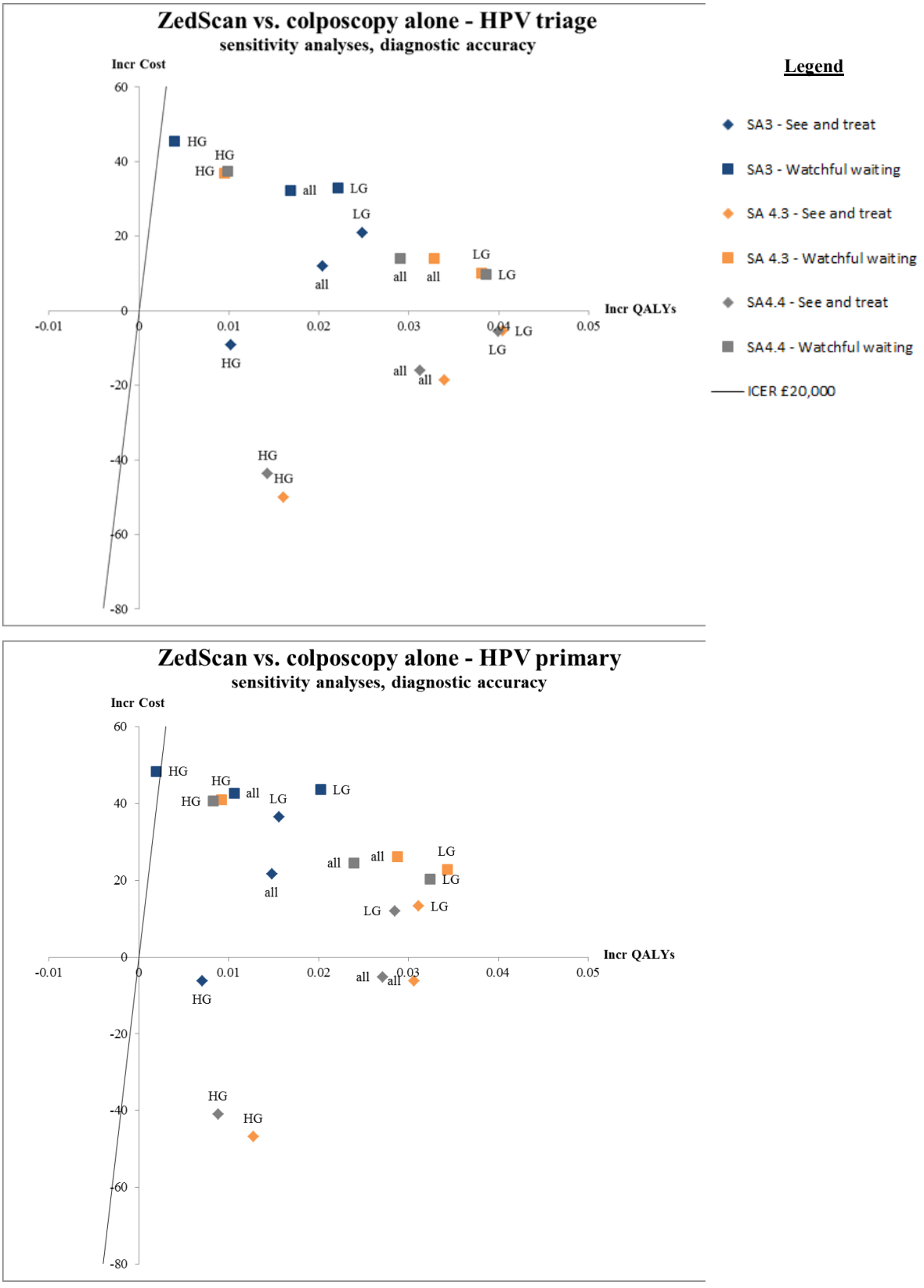


Figure 29 Uncertainty around diagnostic accuracy - ZedScan vs. colposcopy alone



6.6.2.2 Uncertainty around costs

Sensitivity analyses results as regards the uncertainty around costs of devices (SA5.1 and SA5.2) and costs of diagnostic biopsy and LLETZ (SA6) are summarised in Figure 30 for the HPV triage screening protocol and Figure 31 for the HPV primary protocol. Since only the cost parameters were varied, incremental QALYs are identical between the sensitivity analyses and the base case for each type of simulation. Note that in Figures 5 and 6, the scale of the vertical axis of the cost-effectiveness plans has been altered in order to represent higher incremental costs. Detailed results are presented in Appendix 10.10 (Table 90 to Table 101).

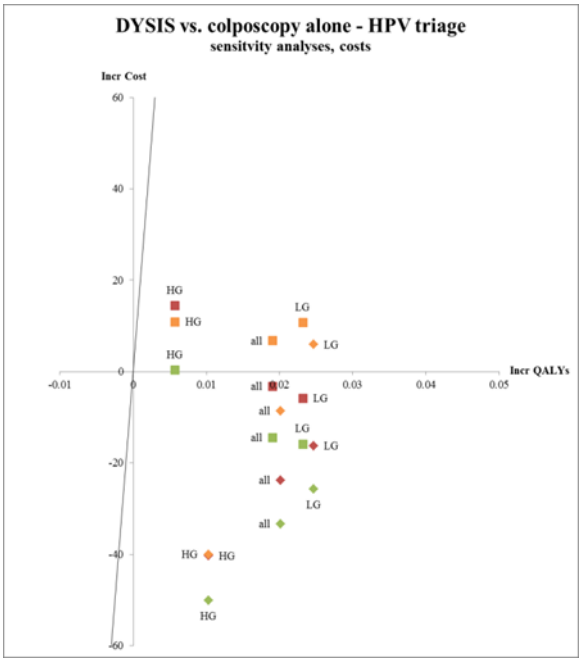
Logically, SA5.1 and SA6 increased the incremental cost up for both technologies but did not appear to alter the base case conclusions:

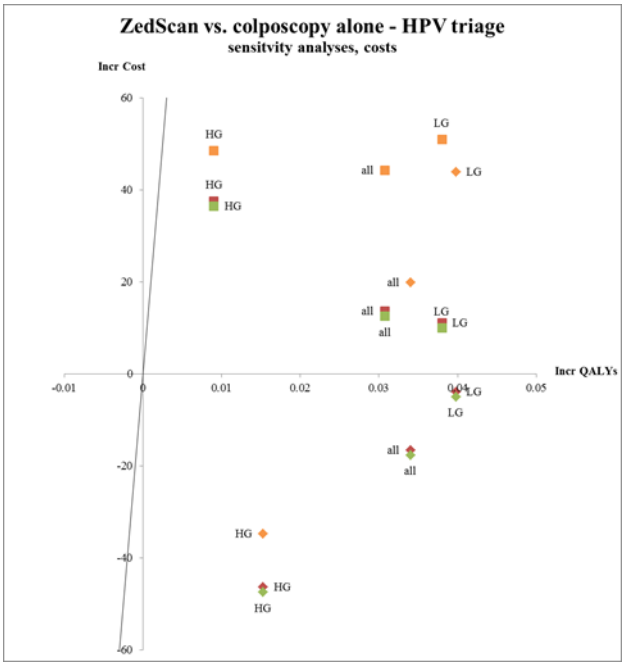
- Due to the higher purchase price, the results for DYSIS appeared more sensitive to a decrease in the number of patients per colposcope per year (SA5.1). DYSIS no longer dominated colposcopy alone in Watchful waiting clinics under HPV primary with an ICER of £270 for all referrals (Table 93).

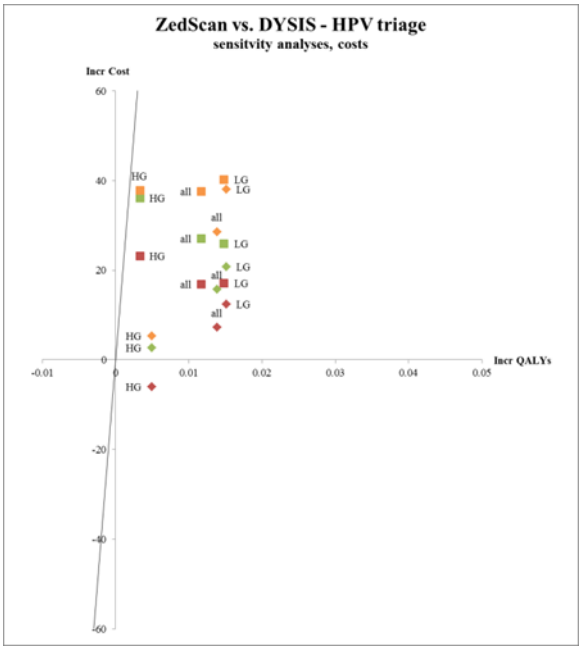
- Due to the lower purchase price of ZedScan the results did not appear sensitive to the assumed variation in throughput (SA5.1 and SA5.2). However, because of its high sensitivity and low specificity, the higher cost estimates for diagnostic biopsies and LLETZ (SA6) impacted the results of ZedScan more significantly than DYSIS, especially for LG referrals in Watchful waiting clinics. ZedScan no longer dominated colposcopy alone, regardless of the type of clinics or the routine screening protocol. The ICER increased to £6709 for HG in Watchful waiting clinics under HPV primary (Table 106).

- Results on the indirect comparison between ZedScan and DYSIS were unchanged.

Figure 30 Uncertainty around costs - HPV triage



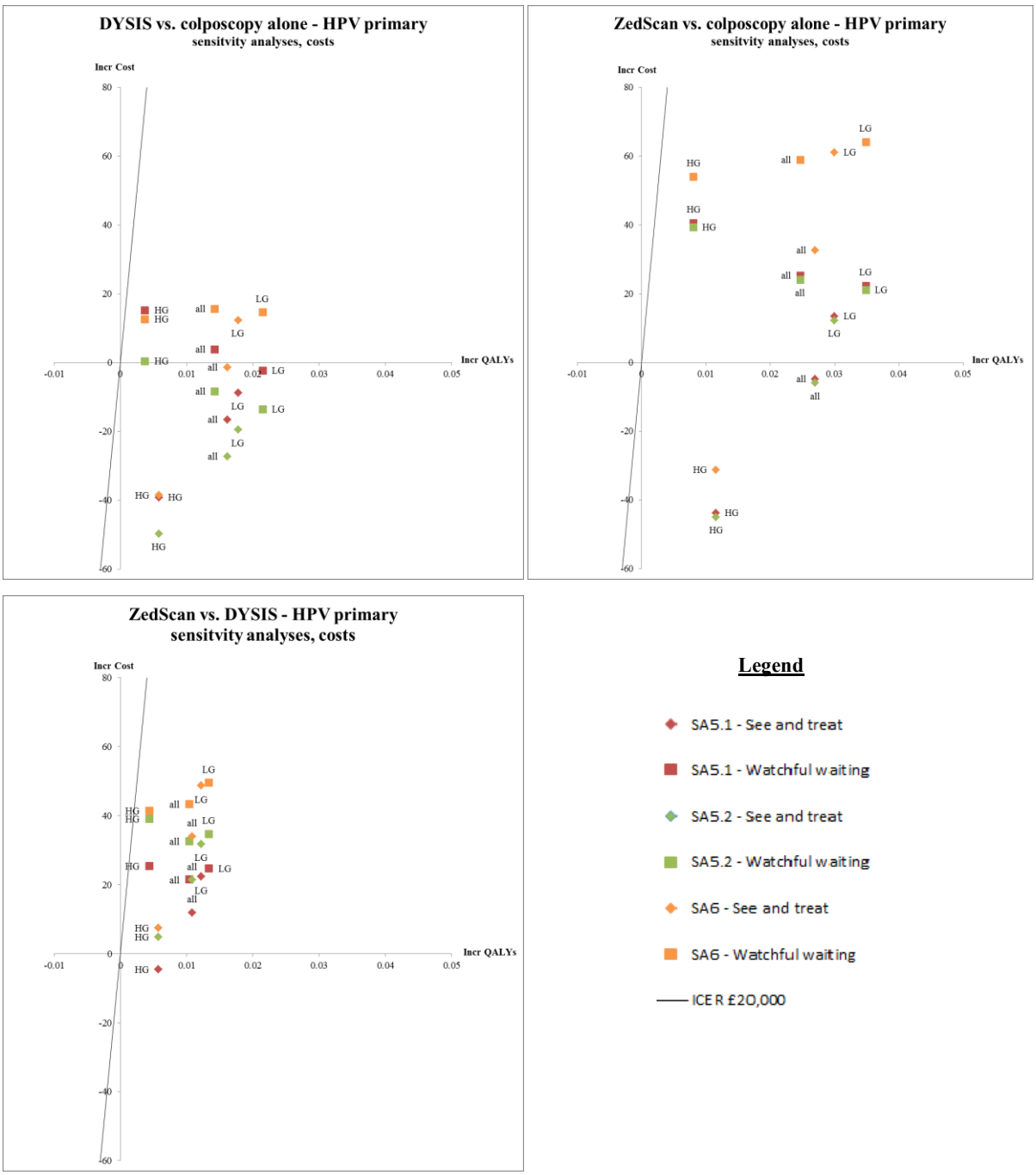




Legend

- SA5.1 - See and treat
- SA5.1 - Watchful waiting
- SA5.2 - See and treat
- SA5.2 - Watchful waiting
- SA6 - See and treat
- SA6 - Watchful waiting
- ICER £20,000

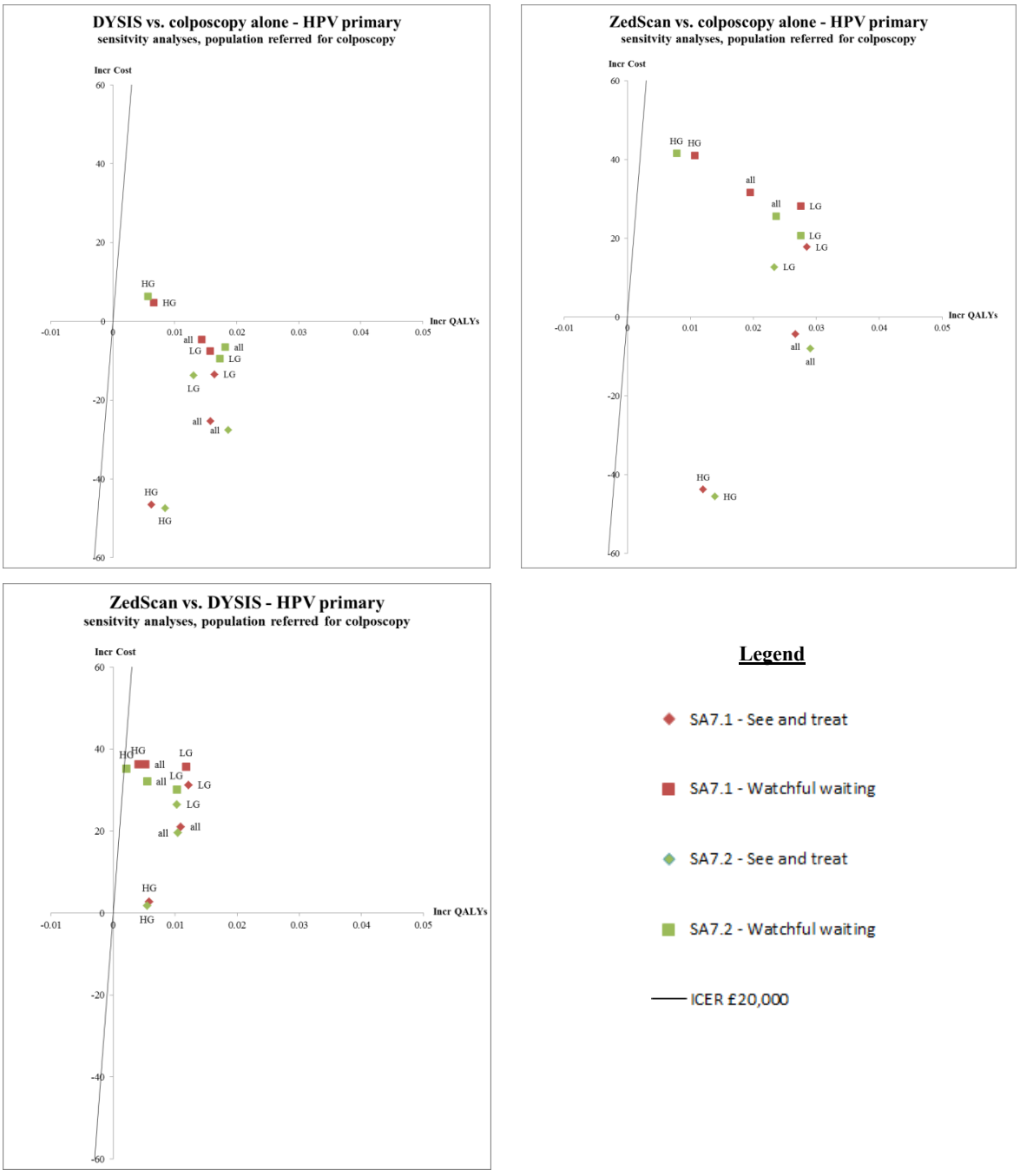
Figure 31 Uncertainty around costs - HPV primary



6.6.2.3 Population referred for colposcopy under HPV primary protocol

SA 7.1 and 7.2 used the variation observed between pilot sites, respectively without and with HPV 16/18 genotyping, to explore the potential impact of uncertainty around the characteristics of the population referred for colposcopy under HPV primary protocol. Results are summarised in Figure 32 and presented in more detail in the Appendix 10.10 (Table 108 to Table 113). Overall, results are unchanged compared to the base case and the impact of a variation in population characteristics appears to be relatively small.

Figure 32 Population referred for colposcopy under HPV primary protocol



6.6.3 Scenarios

Three scenario analyses were undertaken to explore alternative structural assumptions: restricting the analysis to a three year period; excluding adverse obstetric outcomes; and assuming that ZedScan was used alongside colposcopy at all appointments.

6.6.3.1 Scenario 1: time horizon of three years

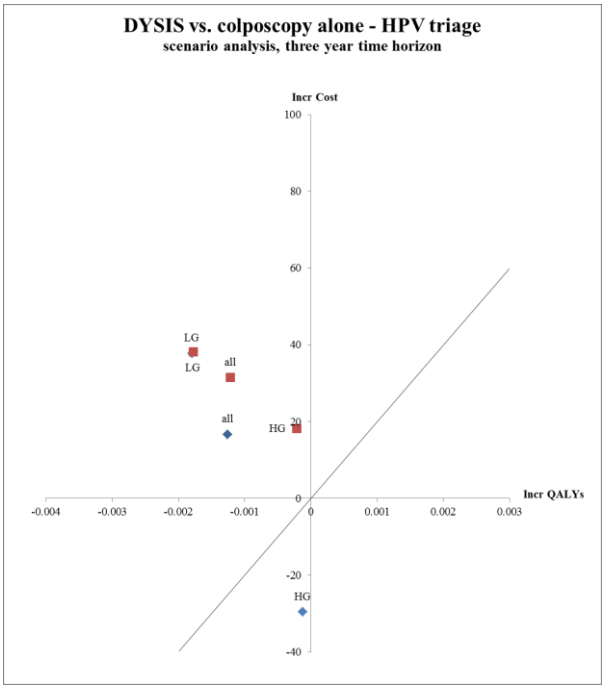
The model was run for only three years to capture the cost and health outcomes of colposcopy and adjunctive technologies in the short term. Figure 33 and Figure 34 summarise the results under HPV triage and HPV primary protocols. Average and incremental costs and QALYs as well as secondary outcomes are displayed in Appendix 10.10 (Table 114 to Table 121).

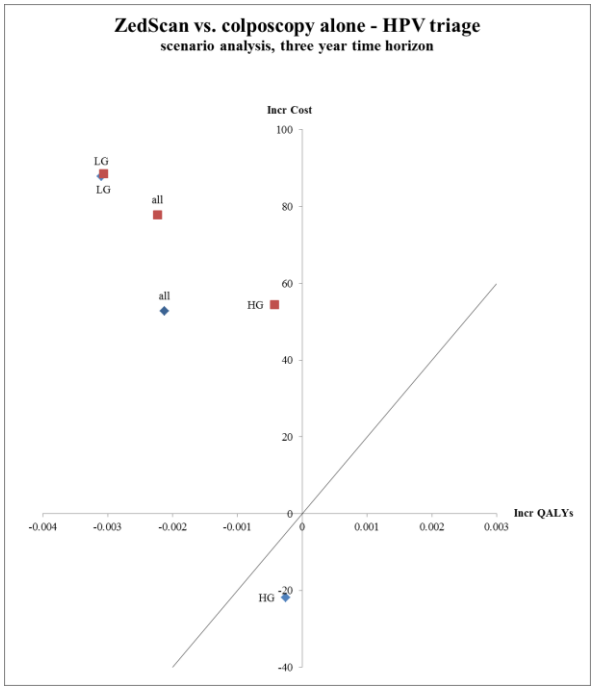
Results were dramatically different when long-term costs and health outcomes were not taken into account in the evaluation:

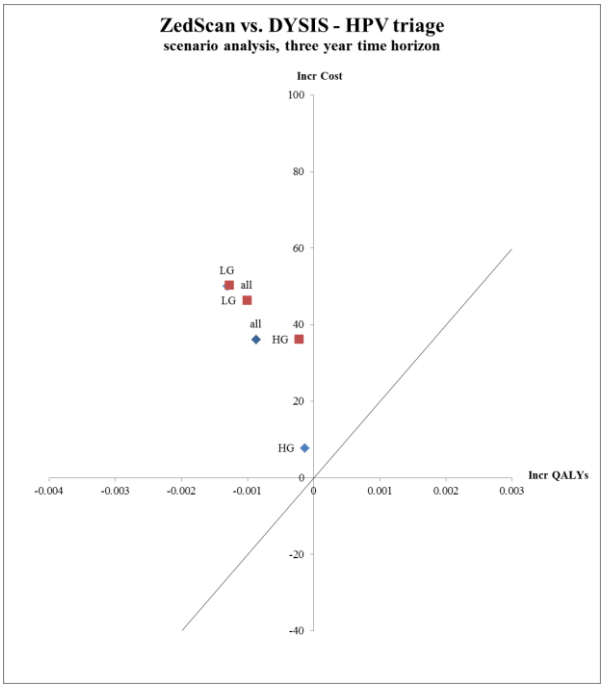
- In the short term, colposcopy alone routinely dominated DYSIS and ZedScan, i.e. was less costly and more effective. The higher specificity of colposcopy alone limited the number of treatments and therefore reduced the average cost compared to DYSIS or ZedScan. Meanwhile, the lower specificity of colposcopy alone was less penalised since most individuals with untreated CIN2+ would have not developed cancer or died from cancer three years after their initial examination (Table 120 and Table 121).

- Only for HG referrals in See and treat clinics, both DYSIS and ZedScan were less costly, but also less effective, than colposcopy alone. For DYSIS and ZedScan against colposcopy alone, the ICERs were respectively £236,692 and £85,045 per QALY under HPV triage (Table 114 and Table 115); £250,587 and £110,371 per QALY under HPV primary (Table 117 and Table 118).

Figure 33 Scenario analysis, 3 year time horizon - HPV triage







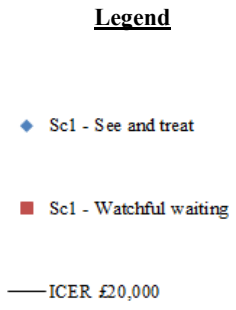
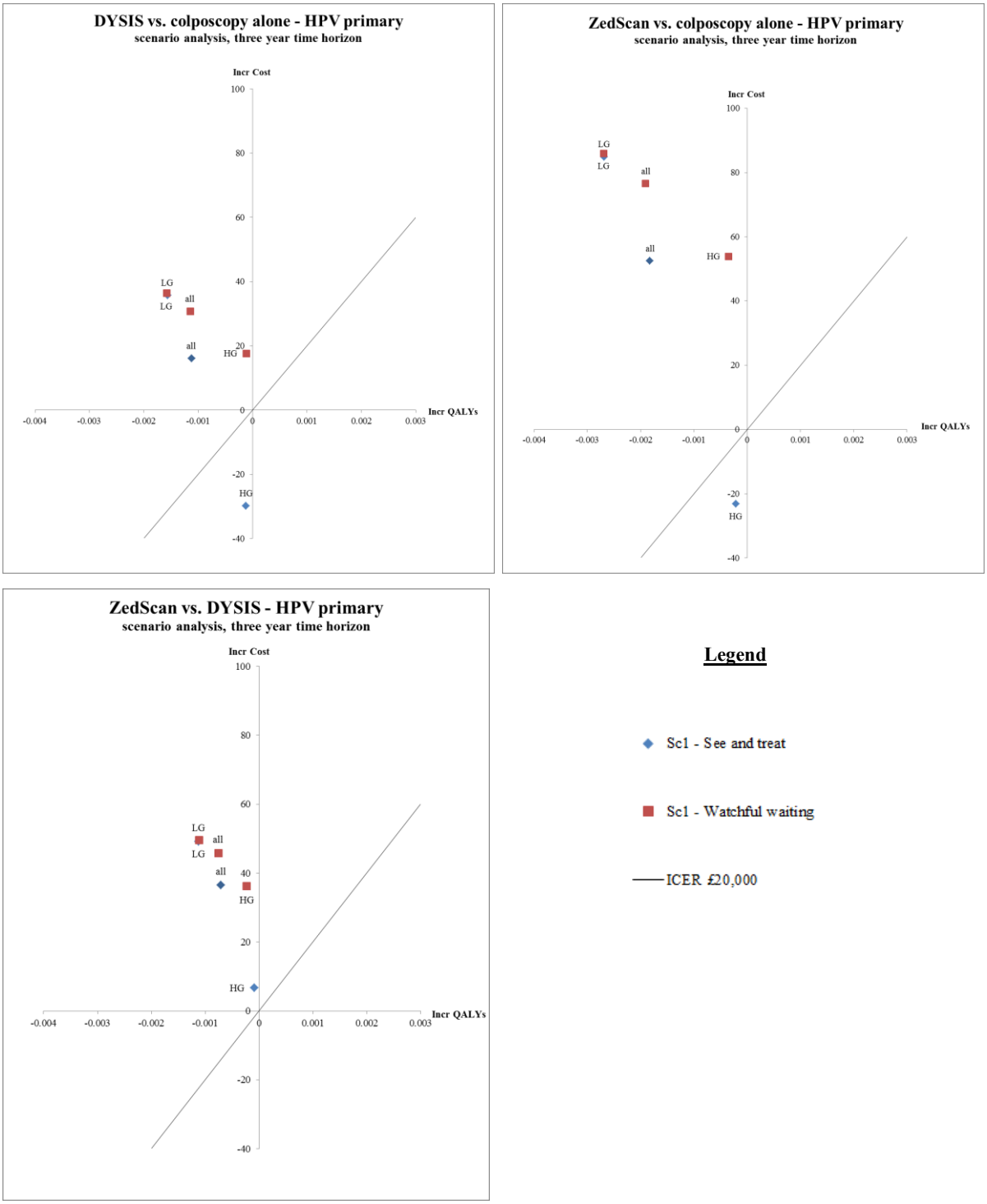


Figure 34 Scenario analysis, 3 year time horizon - HPV primary



6.6.3.2 Scenario 2: adverse obstetric outcomes were excluded

Scenario 2 excluded from the analysis the adverse consequences of CIN treatment on obstetric outcomes. Results are summarised in Figure 35 and Figure 36 and presented in more detail in Appendix 10.10 (Table 122 to Table 127).

Where adverse obstetric outcomes were excluded, all technologies were found to be less costly than in the base case scenario.

Cost-effectiveness results for DYSIS and ZedScan compared to colposcopy alone are unchanged, both under HPV triage and HPV primary protocols:

- DYSIS routinely dominated colposcopy alone, regardless of the type of clinics, the reason for referral or the routine screening protocol.
- ZedScan also dominated colposcopy alone in See and treat clinics. However, ZedScan was more effective but also routinely more costly than colposcopy alone in Watchful waiting clinics.

Similarly to the base case, ZedScan was routinely more effective and more costly than DYSIS:

- Because ZedScan presents a lower specificity than DYSIS, the ICER was lower when adverse obstetric outcomes were excluded compared to the base case scenario: £427 per QALY vs. £980 per QALY for See and treat clinics under HPV triage (all referrals); £1476 per QALY vs. £1746 per QALY under HPV primary (all referrals).

Figure 35 Scenario analysis, no adverse obstetric outcomes - HPV triage

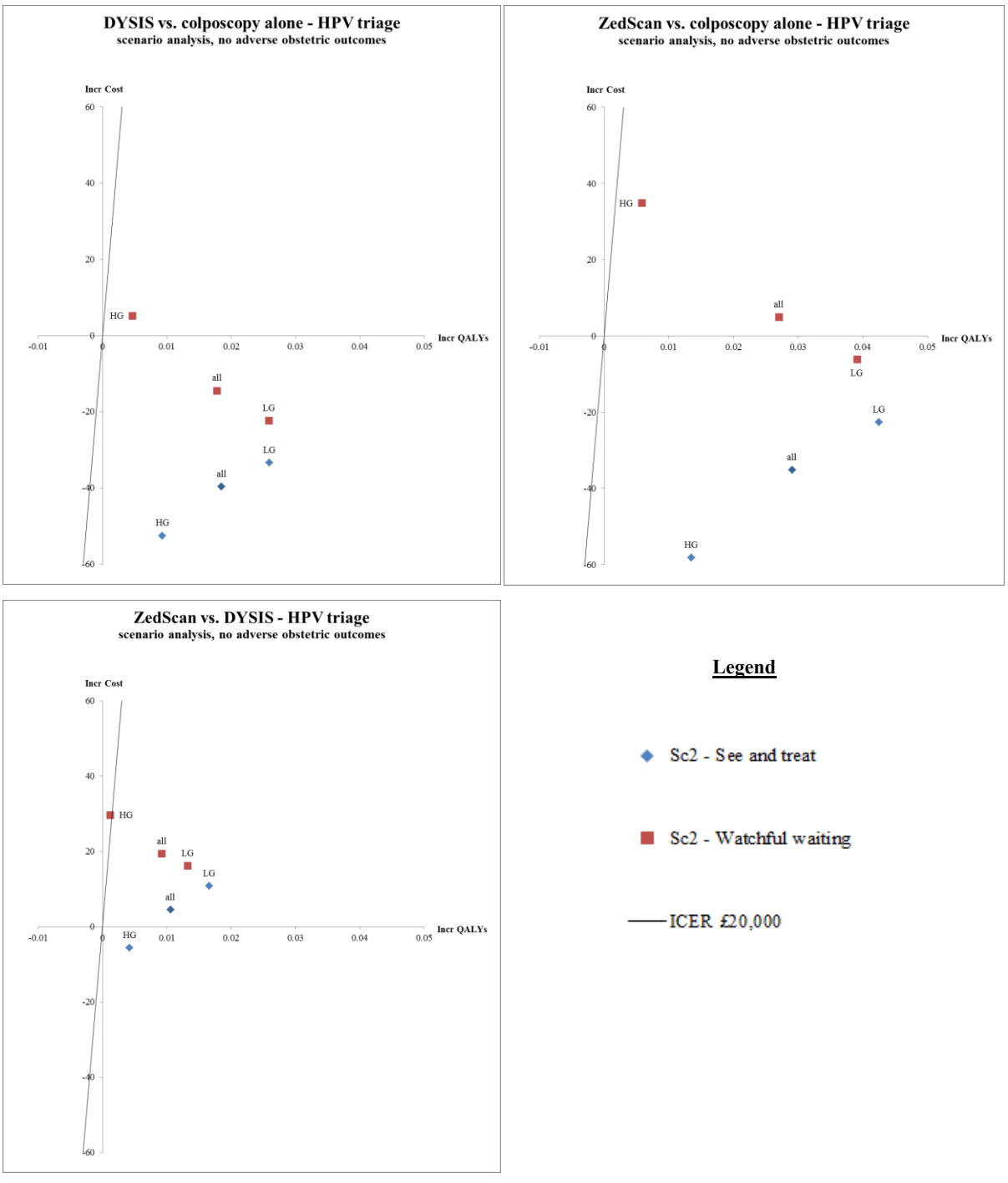
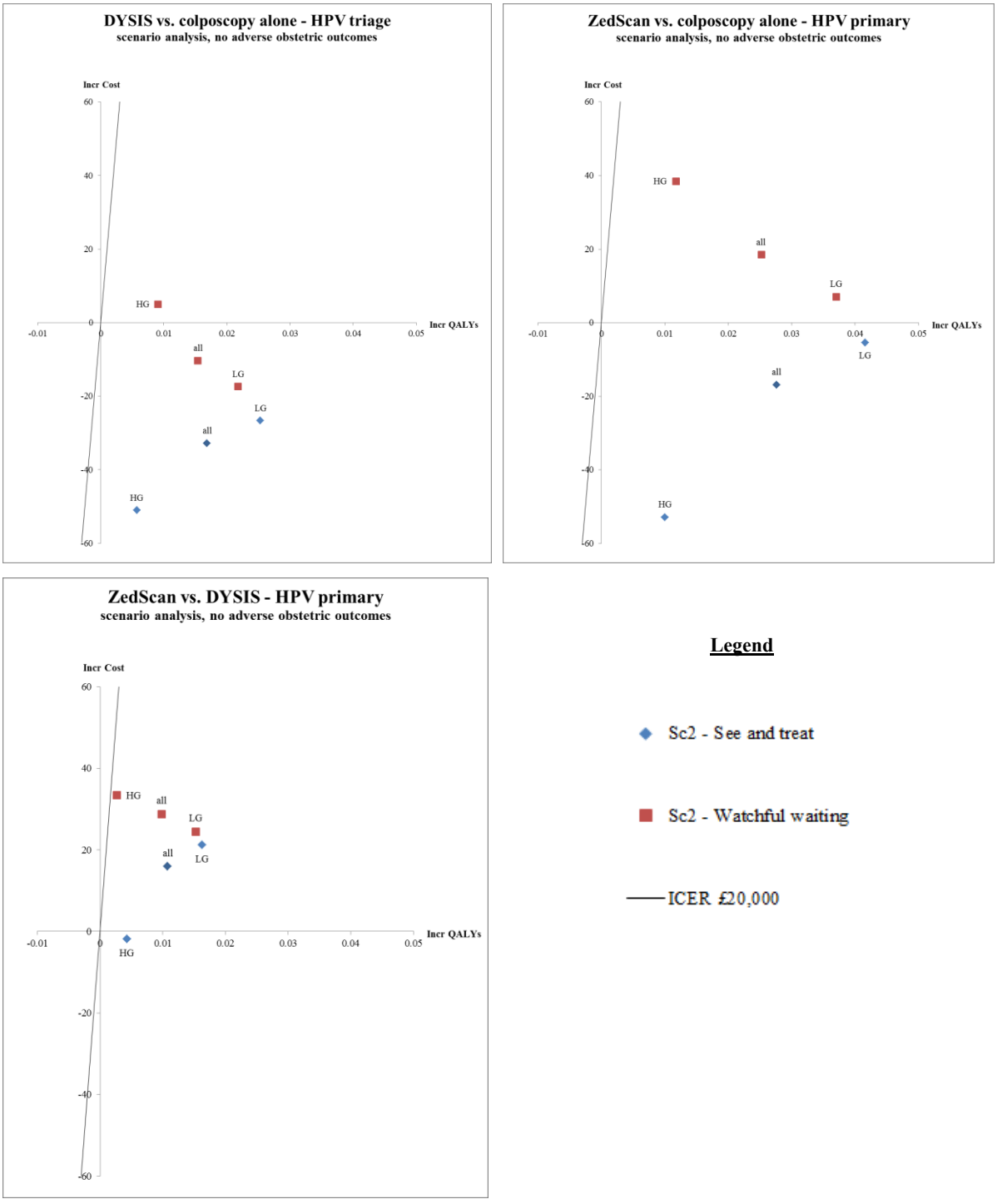


Figure 36 Scenario analysis, no adverse obstetric outcomes - HPV primary



6.6.3.3 Scenario 3: ZedScan was used alongside colposcopy at all appointments

Scenario 3 assumed that ZedScan was used alongside colposcopy at all appointments, including therapeutic colposcopies after confirmation by histology results. Since costs and QALYs were not altered for colposcopy alone and DYSIS compared to the base case, Figure 37 only presents the results for ZedScan vs. colposcopy alone and ZedScan vs. DYSIS under HPV triage and HPV primary. Detailed results are displayed in Appendix 10.10 (Table 128 to Table 131).

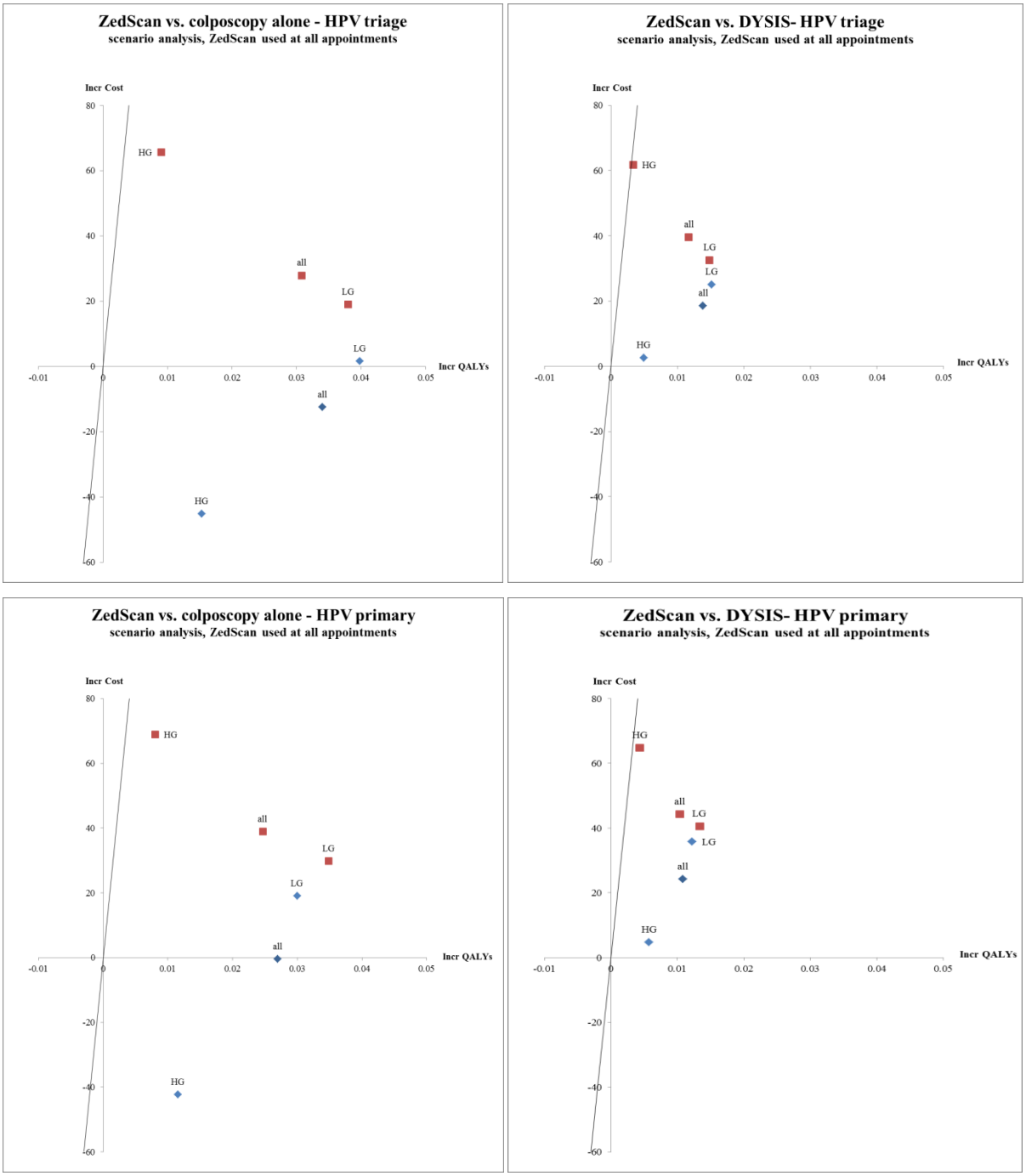
Since no additional benefit is associated with the use of ZedScan during therapeutic colposcopies the impact of scenario 3 is only an increase in the incremental cost of ZedScan compared to colposcopy alone and DYSIS.

- Overall, conclusions remain unchanged compared to the base case.

However, the impact of using ZedScan alongside colposcopy at all appointments varies according to reason for referral and types of clinics.

- The increase in cost was higher for HG referrals in Watchful waiting clinics: when ZedScan was compared to colposcopy alone the ICER was £7270 in HPV triage (Table 128) and £8557 under HPV primary (Table 130); when ZedScan was compared to DYSIS, the ICER reached £18,628 under HPV triage (Table 129) and £14,928 under HPV primary (Table 131).

Figure 37 Scenario analysis, Zedscan used alongside colposcopy at all appointments



6.7 Discussion of the independent economic assessment

Only two studies that reported on the cost effectiveness of DYSIS and Zedscan were included. Neither study was considered to fully inform the stated decision problem which includes the current HPV triage protocol (including test of cure) and also the proposed HPV primary screening protocol.

A *de-novo* decision analytic model (the 'York model') was developed using a patient-level state-transition modelling approach to estimate the cost-effectiveness of adjunctive colposcopy technologies (DYSIS with DYSISmap and ZedScan I) for people who are referred for colposcopy through the NHS Cervical Screening Programme under either HPV triage (including test of cure) or the HPV primary screening algorithm (including test of cure).

The York model was specifically developed to address the limitations of existing studies and concerns regarding the generalisability to both the HPV triage and HPV primary screening protocols. The main strength of the decision model is the linkage between the diagnostic accuracy of a given identification strategy, the impact on subsequent treatment decisions and the ultimate effect on health outcomes and costs. A potential limitation of the model is that the patient-level modelling approach precluded a probabilistic assessment of cost-effectiveness and hence decision uncertainty could also not be fully represented in our analyses. Although the inclusion of a probabilistic assessment was technically feasible, repeating simulations to appropriately represent second-order uncertainty was not considered feasible within the time frame. However, a broad range of scenario and sensitivity analyses were undertaken to address key assumptions and uncertainties.

The base case cost-effectiveness results showed that DYSIS routinely dominated colposcopy, i.e. was less costly and more effective than standard colposcopy. The only exception was for HG referrals in a Watchful waiting clinic setting, where the ICER of DYSIS varied between £675 and £1095 per QALY under HPV triage and primary protocols. ZedScan also dominated colposcopy alone for HG referrals in See and treat clinics. The ICER for ZedScan varied between £272 (LG referral in a Watchful waiting clinic; HPV triage) and £4922 per QALY (HG referral in a Watchful waiting clinic; HPV primary). These findings appeared robust to a wide range of sensitivity and scenario analyses. Only in one of the analyses did the ICER exceed a £20,000 per QALY threshold. This arose in a sensitivity analysis for ZedScan where the diagnostic performance of colposcopy was derived from a separate study to the base case analysis and only for HG referrals in a Watchful waiting clinic under HPV primary.

In the absence of a direct comparison between the alternative technologies, an indirect comparison was performed. However, these results should be considered exploratory in nature given the lack of a

robust direct comparison and the challenges identified more generally arising from the limitations in the evidence base for ZedScan. The base case cost-effectiveness results showed that ZedScan was always more effective but also more costly than DYSIS. The ICER ranged from £109 per QALY for HG referrals in See and treat clinics under HPV primary protocol to £9918 per QALY for HG referrals in Watchful waiting clinics under the HPV triage protocol. These findings appeared robust to a wide range of sensitivity and scenario analyses.

There remains uncertainty regarding the cost-effectiveness of ZedScan given the challenges of comparing it to colposcopy and DYSIS. Moreover, the cost-effectiveness results presented for the HPV primary screening protocols also require careful consideration. Our analysis is based on the current protocol and that the final HPV primary screening protocol may alter prior to HPV primary screening being rolled out nationally. Furthermore, key input data were derived from unpublished and preliminary results collected in the HPV pilot sites. Data collection is still ongoing and selection issues may limit the generalisability of the data used. Hence, the results under the HPV primary screening protocol should be considered exploratory and further analyses should ideally be undertaken when data collection has been completed and the implications of any selection effect is clearer.

6.8 Conclusions of the cost effectiveness section

The cost-effectiveness of both adjunctive technologies compared to standard colposcopy, under both the HPV triage and primary screening algorithms, appears favourable when compared against conventional threshold used to determine value in the NHS. However, the limitations and uncertainties in the evidence base identified for ZedScan need to be carefully considered. The cost-effectiveness of both adjunctive technologies under the HPV primary screening protocol should also be reassessed when additional data becomes available from the pilot sites.

7 Discussion

7.1 Statement of principal findings

7.1.1 Diagnostic accuracy

Nine studies compared adjunctive DYSIS (DYSISmap and DYSIS colposcope) with DYSIS video colposcopy alone. Adjunctive DYSIS use was found to have higher sensitivity to detect CIN2+ (81.25%, 95% CI 72.2 to 87.9) than standard colposcopy alone (57.91%, 95% CI 47.2 to 67.9) but lower specificity (70.40%, 95% CI 59.4 to 79.5) than colposcopy (87.41%, 95% CI 81.7 to 91.5). This difference appears to be because adjunctive DYSIS leads to more positive test results (i.e. more women are judged to have possible high-grade CIN).

Only two included studies investigated ZedScan; one was a study of a pre-commercial prototype. Results from the prototype study suggested that adjunctive ZedScan could improve diagnostic accuracy when compared to colposcopy alone (i.e. it could increase sensitivity at the same specificity as colposcopy or vice versa). [redacted]

Data on participant subgroups, including women with high-risk HPV or high-grade referrals were limited. The results suggested that colposcopy alone has poor sensitivity to detect high-grade CIN in women with low-grade referrals (e.g. mild dyskariosis). Adjunctive DYSIS and ZedScan appeared to improve diagnosis in low-grade referral cases. There was some limited evidence that the diagnostic accuracy of adjunctive DYSIS may be greater in women with high-risk HPV infection.

Sensitivity analyses identified that the specificity of all methods was strongly dependent on what reference standard was used in women with no colposcope-detected high-grade CIN. Specificity was much higher where no biopsies were performed in those women, suggesting a possible verification bias due to under-diagnosis of high-grade CIN. This means that the actual specificity of colposcopy and adjunctive colposcopy is uncertain, as it depends on the use of the reference standard. However the comparative results are valid, because any possible bias affects all methods equally.

7.1.2 Clinical effectiveness

Only three studies that reported data on our pre-specified clinical effectiveness outcomes were included. One study of ZedScan reported three adverse events, of which one was serious and two studies of DYSIS with DYSISmap reported that no adverse events occurred following colposcopy

examination. No data were reported on mortality, morbidity and health-related quality of life in studies of DYSIS and ZedScan.

7.1.3 Implementation

Five studies reported data on our pre-specified implementation outcomes, including four studies of DYSIS and one of ZedScan I.

There is reasonable evidence that DYSISmap as an adjunct to colposcopy is generally well received by patients referred for colposcopy and that patients are generally satisfied with the duration of examination. There is evidence that adjunctive DYSIS was generally perceived by clinicians to improve accuracy of colposcopy and confidence in their diagnostic decisions and biopsy site selection. There is evidence that adjunctive DYSIS was intuitive for clinicians with limited colposcopy experience and improved their evaluations. There is evidence that additional time required to use ZedScan is minimal in experienced colposcopists. However all included studies had significant limitations, therefore these findings need to be interpreted with caution.

No evidence was found for several of the pre-specified outcomes: successful database and record management, capacity to perform colposcopies, uptake and compliance. No evidence was found regarding training requirements for DYSIS. The limited evidence for ZedScan precludes conclusions for any of the implementation review pre-specified outcomes.

7.1.4 Cost effectiveness

Only two studies that reported on the cost effectiveness of DYSIS and Zedscan were included. Neither study was considered to fully inform the stated decision problem which includes the current HPV triage protocol (including test of cure) and also the proposed HPV primary screening protocol.

A *de-novo* decision analytic model (the 'York model') was developed using a patient-level state-transition modelling approach to estimate the cost-effectiveness of adjunctive colposcopy technologies (DYSIS with DYSISmap and ZedScan I) for people who are referred for colposcopy through the NHS Cervical Screening Programme under either HPV triage (including test of cure) or the HPV primary screening algorithm (including test of cure).

The York model provides a link between diagnostic test accuracy and final health outcomes expressed in terms of Quality-Adjusted Life Years (QALYs). The model provides a quantitative framework, using the best available evidence, to determine how the diagnostic performance of both adjunctive colposcopy technologies is likely to impact subsequent treatment and/or monitoring options and their effect on disease progression. The model also captures the potential impact of the technologies on unnecessary biopsies and excisions which may increase the risk of adverse obstetric outcomes.

The base case cost-effectiveness results showed that adjunctive DYSISmap routinely dominated (i.e. less costly and more effective) standard colposcopy. The only exception was for HG referrals in for in a Watchful waiting clinic setting, where the ICER of DYSISmap varied between £675 and £1095 per QALY under HPV triage and primary protocols. ZedScan I also dominated colposcopy alone for HG referrals in See and treat clinics. The ICER for ZedScan I varied between £272 (LG referral in a Watchful waiting clinic; HPV triage) and £4,922 per QALY (HG referral in a Watchful waiting clinic; HPV primary). These findings appeared robust to a wide range of sensitivity and scenario analyses.

7.2 Strengths and limitations of the assessment

7.2.1 Clinical effectiveness

Extensive literature searches were conducted with an attempt to maximise retrieval of potentially relevant studies. These included electronic searches of a variety of bibliographic databases as well as screening of clinical trial registers and conference proceedings to identify unpublished studies. The search strategy did not restrict by study design. The device manufactures and study authors were contacted to provide additional data, and the review includes additional data from published studies and data from as yet unpublished studies. The review process followed recommended methods to minimise the potential for error and/or bias. The quality of the included studies was assessed and accounted for when interpreting the review results. Appropriate synthesis methods were employed by taking into account the heterogeneity of study characteristics.

One study of DYSIS was at low risk of bias, and all other included studies were at high risk of bias. The evidence for Zedscan was particularly limited. Only one study of ZedScan I was available, and there was no evidence directly comparing ZedScan I with standard colposcopy. The evidence for ZedScan came mostly from a single centre and excluded relevant patient populations (including patients with transformation zone type 3), which limits the extent to which the evidence for ZedScan is applicable to the broader population of women referred through NHS cervical screening.

No studies directly compared DYSIS and ZedScan. Very little data on participant subgroups was available. In particular there was little data on diagnostic accuracy in women referred through HPV primary screening.

There was very limited evidence relating to the clinical effectiveness of adjunctive DYSIS or ZedScan, with little reporting of any potential adverse effects.

7.2.2 Cost effectiveness

The York model was specifically developed to address the limitations of existing studies and concerns regarding the generalisability to the current decision problem under both the HPV triage and HPV

primary screening protocols. The main strength of the decision model is directly addresses several of the key assumptions and areas of uncertainties identified in our review of previously published studies, including consideration of the potential impact of unnecessary treatment on adverse obstetric outcomes.

A potential limitation of the model is that the patient-level modelling approach precluded a probabilistic assessment of cost-effectiveness and hence decision uncertainty could also not be fully represented in our analyses. The decision to use a patient-level approach was taken with careful consideration and we consider that alternative modelling approaches were not appropriate given the high complexity that arises from interactions between the natural history model and the screening and treatment pathways and the need to characterise two separate screening paradigms. Although the inclusion of a probabilistic assessment was technically feasible, each analysis (i.e. for each type of clinic and for each of the different reasons for referral) required 500,000 simulations which took approximately 15 minutes. Repeating this simulation to appropriately represent second-order uncertainty was not considered feasible within the time frame. However, a broad range of scenario and sensitivity analyses were undertaken to address key assumptions and uncertainties.

7.3 Uncertainties

7.3.1 Clinical effectiveness

There was no data comparing ZedScan I to colposcopy, so any improvement in diagnostic accuracy with ZedScan I over colposcopy alone is uncertain. Due to design limitations the extent to which the evidence for ZedScan I is applicable to the broader population of women referred through NHS cervical screening is uncertain.

No studies compared DYSIS and ZedScan directly, limiting the possibility of comparing their diagnostic accuracies. Most studies were performed in women referred for colposcopy on the basis of cytology screening, so the diagnostic accuracy of all methods in women referred from HPV primary screening is uncertain, particularly as data on diagnostic accuracy in women with high-risk HPV infection was also limited.

The reference standard (histopathology of samples from punch biopsy or excision) was applied variably across studies. In particular, biopsies were not performed in women with normal colposcopy examination results in several DYSIS studies and in all ZedScan studies. This may have led to positive bias in estimates of diagnostic accuracy for both adjunctive colposcopy and colposcopy alone. Hence, the estimates of sensitivity and specificity reported may not be the same as diagnostic accuracy that will be observed in the UK.

7.3.2 Cost effectiveness

The uncertainties noted regarding the design limitations for the evidence of ZedScan also raise important uncertainties regarding the generalisability of the cost-effectiveness results for Zedscan to routine NHS usage.

The introduction of HPV primary screening will alter the population of women referred for colposcopy through the NHS cervical screening programme. However, the data is still incomplete especially for women referred at the third round and because the pilot sites were not randomly selected the data is subject to selection issues and especially variability in the prevalence of HPV and CIN lesions compared to the general population. The impact of these issues on the cost-effectiveness of the adjunctive technologies is not possible to determine. As a result, we would recommend that the cost-effectiveness analysis of the adjunctive technologies is updated when data collection from the HPV primary screening has been completed and the implications of any selection effects are clearer.

7.4 Other relevant factors

The population of women referred for colposcopy is likely to change significantly in the future as females who have received the HPV vaccine reach screening age. The implication of this for the cost-effectiveness of the adjunctive technologies has not been included in the current assessment.

8 Conclusions

8.1 Implications for service provision

The use of adjunctive DYSIS (DYSISmap with DYSIS video colposcope) increases sensitivity when compared to colposcopy alone, so it increases the number of high-grade CIN cases that are detected. However it also reduces specificity when compared to colposcopy, so more women with no or low-grade CIN will be incorrectly judged as possibly having high-grade CIN. This could lead to an increase in the number of unnecessary diagnostic biopsies, excisions and "see and treat" cases, although evidence as to whether this is actually the case is limited. It might therefore increase unnecessary anxiety, and complications in subsequent pregnancies in women who did not require treatment. The use of DYSIS is likely to be cost saving when compared to standard colposcopy

The limited evidence precludes any definitive conclusions regarding the diagnostic accuracy of ZedScan I, [redacted] It is, therefore, also likely to be cost saving compared to standard colposcopy. There is currently too little evidence to compare the relative diagnostic accuracy of ZedScan and DYSIS.

The introduction of any of these adjunctive technologies may require additional staff training which may impose additional costs that were not considered in the analysis.

8.2 Suggested research priorities

Given the limited evidence for ZedScan, further diagnostic accuracy studies of ZedScan I are needed, particularly to compare its diagnostic accuracy to standard colposcopy, and in groups independent of the manufacturers. Diagnostic accuracy studies comparing both DYSIS and ZedScan as adjunct to colposcopy directly and against colposcopy alone may also be useful.

As most current studies have been in women referred to colposcopy on the basis of cytology screening, diagnostic accuracy studies in women referred through HPV primary screening are needed to assess whether the new screening programme will alter diagnostic accuracy.

All future diagnostic accuracy studies should have robust designs with sufficient power, including consecutive patients from a representative population of NHS referrals, ensuring adequate blinding of all assessors, and taking biopsies in all women including those with no colposcopic evidence of CIN.

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10 Appendices

10.1 Literature search strategies

10.1.1 MEDLINE

Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R)

via Ovid http://ovidsp.ovid.com/

1946 to present

Searched on: 3rd January 2017

Records retrieved: 2505

An update search was carried out on 10th April 2017, retrieving 2436 records.

1 Cervix Uteri/ (27749)

2 cervix.ti,ab. (44380)

3 cervic$.ti,ab. (217889)

4 (endocervix or endo-cervix).ti,ab. (1165)

5 (endocervic$ or endo-cervic$).ti,ab. (5220)

6 (ectocervix or ecto-cervix).ti,ab. (402)

7 (ectocervic$ or ecto-cervic$).ti,ab. (654)

8 ((squamocolumnar or squamo-columnar) adj2 junction).ti,ab. (568)

9 transformation zone$.ti,ab. (1061)

10 or/1-9 (252639)

11 Colposcopy/ (6321)

12 Colposcopes/ (193)

13 Spectrum Analysis/ (47414)

14 Dielectric Spectroscopy/ (1674)

15 (colposcop$ adj4 (adjunct$ or digital$ or DSI or computer$ or video$ or alternative$ or conventional$)).ti,ab. (217)

16 (impedance adj2 spectroscop$).ti,ab. (5309)

17 (Dielectric adj2 Spectroscop$).ti,ab. (1232)

18 (impedance adj2 spectrometr$).ti,ab. (35)

19 (Dielectric adj2 Spectrometr$).ti,ab. (6)

20 (impedance adj2 spectrum analys$).ti,ab. (4)

21 (Dielectric adj2 Spectrum analys$).ti,ab. (0)

22 (telecolposcop$ or tele-colposcop$).ti,ab. (20)

23 (optical adj2 spectroscop$).ti,ab. (5149)

24 ((point or pencil or impedance) adj2 probe$).ti,ab. (546)

25 (microcolposcop$ or micro-colposcop$).ti,ab. (20)

26 (dysis or dysismap).ti,ab. (31)

27 dynamic spectral imaging.ti,ab. (16)

28 Zilico.ti,ab. (0)

29 (ZedScan or Zed Scan).ti,ab. (0)

30 (APX 100 or APX100).ti,ab. (2)

31 EIS.ti,ab. (3007)

32 epitheliometer$.ti,ab. (1)

33 MKIII.ti,ab. (33)

34 or/11-33 (66616)

35 10 and 34 (4876)

36 exp animals/ not humans/ (4837860)

37 35 not 36 (4845)

38 limit 37 to yr="2000 -Current" (2505)

Key:

/ = indexing term (MeSH heading)
exp = exploded indexing term (MeSH heading)
$ = truncation
ti,ab = terms in either title or abstract fields
adj2 = terms within two words of each other (any order)

10.1.2 Cochrane Central Register of Controlled Trials (CENTRAL)

via Wiley http://onlinelibrary.wiley.com/

Issue 1 of 12, November 2016

Searched on: 3rd January 2017

Records retrieved: 175

10.1.3 CENTRAL

An update search was carried out on 10th April 2017, retrieving 183 records from CENTRAL.

#1 MeSH descriptor: [Cervix Uteri] this term only 1031

#2 cervix:ti,ab,kw 4427

#3 cervic*:ti,ab,kw 11455

#4 (endocervix or endo-cervix):ti,ab,kw 49

#5 (endocervic* or endo-cervic*):ti,ab,kw 287
#6 (ectocervix or ecto-cervix):ti,ab,kw 19
#7 (ectocervic* or ecto-cervic*):ti,ab,kw 25
#8 ((squamocolumnar or squamo-columnar) near/2 junction):ti,ab,kw 23
#9 (transformation next zone*):ti,ab,kw 91
#10 {or #1-#9} 12900
#11 MeSH descriptor: [Colposcopy] this term only 353
#12 MeSH descriptor: [Colposcopes] this term only 10
#13 MeSH descriptor: [Spectrum Analysis] this term only 90
#14 MeSH descriptor: [Dielectric Spectroscopy] this term only 11
#15 (colposcop* near/4 (adjunct* or digital* or DSI or computer* or video* or alternative* or conventional*)):ti,ab,kw 35
#16 (impedance near/2 spectroscop*):ti,ab,kw 35
#17 (Dielectric near/2 Spectroscop*):ti,ab,kw 12
#18 (impedance near/2 spectrometr*):ti,ab,kw 1
#19 (Dielectric near/2 Spectrometr*):ti,ab,kw 0
#20 (impedance near/2 (spectrum next analys*)):ti,ab,kw 0
#21 (Dielectric near/2 (Spectrum next analys*)):ti,ab,kw 0
#22 (telecolposcop* or tele-colposcop*):ti,ab,kw 2
#23 (optical near/2 spectroscop*):ti,ab,kw 19
#24 ((point or pencil or impedance) near/2 probe*):ti,ab,kw 44
#25 (microcolposcop* or micro-colposcop*):ti,ab,kw 1
#26 (dysis or dysismap):ti,ab,kw 5
#27 (dynamic next spectral next imaging):ti,ab,kw 2
#28 Zilico:ti,ab,kw 1
#29 (ZedScan or Zed Scan):ti,ab,kw 0
#30 (APX 100 or APX100):ti,ab,kw 0
#31 EIS:ti,ab,kw 78
#32 epitheliometer*:ti,ab,kw 0
#33 MKIII:ti,ab,kw 3
#34 (157-#33) 637
#35 #10 and #34 304
#36 #10 and #34 Publication Year from 2000 to 2017 229
#37 #10 and #34 Publication Year from 2000 to 2017, in Cochrane Reviews (Reviews and Protocols) 2
#38 #10 and #34 Publication Year from 2000 to 2017, in Trials 175

Key:
MeSH descriptor = indexing term (MeSH heading)
* = truncation
ti,ab,kw = terms in either title or abstract or keyword fields
near/2 = terms within two words of each other (any order)
next = terms are next to each other

10.1.4 Cochrane Database of Systematic Reviews (CDSR)

via Wiley http://onlinelibrary.wiley.com/

Issue 1 of 12, January 2017

Searched on: 3rd January 2017

Records retrieved: 2

See above under CENTRAL for search strategy used.

An update search was carried out on 10th April 2017, retrieving 2 records from CDSR.

10.1.5 Cumulative Index to Nursing & Allied Health (CINAHL Plus)

via EBSCO https://www.ebscohost.com/

Inception to 2nd January 2017

Searched on: 3rd January 2017

Records retrieved: 762

An update search was carried out on 10th April 2017, retrieving 786 records.

S1	(MH "Cervix")	2,037
S2	TI cervix OR AB cervix	2,536
S3	TI cervic* OR AB cervic*	30,166
S4	TI (endocervix or endo-cervix) OR AB (endocervix or endo-cervix)	32
S5	TI (endocervic* or endo-cervic*) OR AB (endocervic* or endo-cervic*)	339
S6	TI (ectocervix or ecto-cervix) OR AB (ectocervix or ecto-cervix)	16
S7	TI (ectocervic* or ecto-cervic*) OR AB (ectocervic* or ecto-cervic*)	28
S8	TI ((squamocolumnar or squamo-columnar) N2 junction) OR AB ((squamocolumnar or squamo-columnar) N2 junction)	29

S9	TI transformation N1 zone* OR AB transformation N1 zone*	101
S10	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8 OR S9	32,130
S11	(MH "Colposcopy")	1,218
S12	(MH "Spectrum Analysis")	1,861
S13	TI (colposcop* N4 (adjunct* or digital* or DSI or computer* or video* or alternative* or conventional*)) OR AB (colposcop* N4 (adjunct* or digital* or DSI or computer* or video* or alternative* or conventional*))	53
S14	TI impedance N2 spectroscop* OR AB impedance N2 spectroscop*	80
S15	TI dielectric N2 spectroscop* OR AB dielectric N2 spectroscop*	9
S16	TI impedance N2 spectrometr* OR AB impedance N2 spectrometr*	3
S17	TI dielectric N2 spectrometr* OR AB dielectric N2 spectrometr*	4
S18	TI impedance N2 “spectrum analys*” OR AB impedance N2 “spectrum analys*”	2
S19	TI dielectric N2 “spectrum analys*” OR AB dielectric N2 “spectrum analys*”	2
S20	TI (telecolposcop* or tele-colposcop*) OR AB (telecolposcop* or tele-colposcop*)	7
S21	TI optical N2 spectroscop* OR AB optical N2 spectroscop*	105
S22	TI ((point or pencil or impedance) N2 probe*) OR AB ((point or pencil or impedance) N2 probe*)	37
S23	TI (microcolposcop* or micro-colposcop*) OR AB (microcolposcop* or micro-colposcop*)	1
S24	TI (dysis or dysismap) OR AB (dysis or dysismap)	9
S25	TI "dynamic spectral imaging" OR AB "dynamic spectral imaging"	5
S26	TI Zilico OR AB Zilico	0
S27	TI (ZedScan or Zed Scan) OR AB (ZedScan or Zed Scan)	0
S28	TI (APX 100 or APX100) OR AB (APX 100 or APX100)	1
S29	TI EIS OR AB EIS	287
S30	TI epitheliometer* OR AB epitheliometer*	0
S31	TI MKIII OR AB MKIII	3
S32	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	3,551
S33	S10 AND S32	838
S34	S10 AND S32 Limiters - Published Date: 20000101-20170131	762

Key:
MH = indexing term (CINAHL heading)
* = truncation
TI = terms in the title
AB = terms in the abstract

N2 = terms within two words of each other (any order)

10.1.6 Database of Abstracts of Reviews of Effects (DARE)

via http://www.crd.york.ac.uk/CRDWeb/

Inception – 31st March 2015

Searched on: 4th January 2017

Records retrieved: 16

As DARE closed on 31st March 2015, an update search was not carried out for this database.

1	(MeSH DESCRIPTOR Cervix Uteri) FROM 2000 TO 2017	67
2	(cervix) OR (cervic*) FROM 2000 TO 2017	1302
3	(endocervix) OR (endo-cervix) FROM 2000 TO 2017	0
4	(endocervic*) OR (endo-cervic*) FROM 2000 TO 2017	28
5	(ectocervix) OR (ecto-cervix) FROM 2000 TO 2017	0
6	(ectocervic*) OR (ecto-cervic*) FROM 2000 TO 2017	0
7	(((squamocolumnar or squamo-columnar) NEAR2 junction)) FROM 2000 TO 2017	1
8	((junction NEAR2 (squamocolumnar or squamo-columnar))) FROM 2000 TO 2017	0
9	(transformation zone*) FROM 2000 TO 2017	14
10	#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9	1308
11	(MeSH DESCRIPTOR Colposcopy) FROM 2000 TO 2017	55
12	(MeSH DESCRIPTOR Colposcopes) FROM 2000 TO 2017	3
13	(MeSH DESCRIPTOR Spectrum Analysis) FROM 2000 TO 2017	6
14	(MeSH DESCRIPTOR Dielectric Spectroscopy) FROM 2000 TO 2017	2
15	((colposcop* NEAR4 (adjunct* or digital* or DSI or computer* or video* or alternative* or conventional*))) FROM 2000 TO 2017	3
16	(((adjunct* or digital* or DSI or computer* or video* or alternative* or conventional*) NEAR4 colposcop*)) FROM 2000 TO 2017	12
17	(impedance NEAR2 spectroscop*) FROM 2000 TO 2017	0
18	(spectroscop* NEAR2 impedance) FROM 2000 TO 2017	0
19	(Dielectric NEAR2 Spectroscop*) FROM 2000 TO 2017	2
20	(Spectroscop* NEAR2 Dielectric) FROM 2000 TO 2017	0
21	(impedance NEAR2 spectrometr*) FROM 2000 TO 2017	0
22	(spectrometr* NEAR2 impedance) FROM 2000 TO 2017	0
23	(Dielectric NEAR2 Spectrometr*) FROM 2000 TO 2017	0

24	(Spectrometr* NEAR2 Dielectric) FROM 2000 TO 2017	0
25	(impedance NEAR2 spectrum analys*) FROM 2000 TO 2017	0
26	(spectrum analys* NEAR2 impedance) FROM 2000 TO 2017	0
27	(Dielectric NEAR2 Spectrum analys*) FROM 2000 TO 2017	0
28	(Spectrum analys* NEAR2 Dielectric) FROM 2000 TO 2017	0
29	(telecolposcop* or tele-colposcop*) FROM 2000 TO 2017	1
30	(optical NEAR2 spectroscop*) FROM 2000 TO 2017	2
31	(spectroscop* NEAR2 optical) FROM 2000 TO 2017	0
32	(((point or pencil or impedance) NEAR2 probe*)) FROM 2000 TO 2017	0
33	((probe* NEAR2 (point or pencil or impedance))) FROM 2000 TO 2017	0
34	(microcolposcop* or micro-colposcop*) FROM 2000 TO 2017	0
35	(dysis or dysismap) FROM 2000 TO 2017	3
36	(dynamic spectral imaging) FROM 2000 TO 2017	0
37	(Zilico) FROM 2000 TO 2017	1
38	(ZedScan or Zed Scan) FROM 2000 TO 2017	0
39	(APX 100 or APX100) FROM 2000 TO 2017	0
40	(EIS) FROM 2000 TO 2017	3
41	(epitheliometer*) FROM 2000 TO 2017	0
42	(MKIII) FROM 2000 TO 2017	0
43	#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	72
44	#10 AND #43	59
45	(*) IN DARE FROM 2000 TO 2017	43354
46	#44 AND #45	16
47	(*) IN NHSEED FROM 2000 TO 2017	14762
48	#44 AND #47	38
49	(*) IN HTA FROM 2000 TO 2017	14138
50	#44 AND #49	5

Key:

MeSH DESCRIPTOR = indexing term (MeSH heading)
* = truncation
NEAR2 = terms within two words of each other (order specified)

10.1.7 EMBASE

via Ovid http://ovidsp.ovid.com/

1974 to 2016 December 30

Searched on: 3rd January 2017

Records retrieved: 6177

An update search was carried out on 10th April 2017, retrieving 6300 records.

1 exp uterine cervix/ (27722)
2 cervix.ti,ab. (48465)
3 cervic$.ti,ab. (247849)
4 (endocervix or endo-cervix).ti,ab. (1296)
5 (endocervic$ or endo-cervic$).ti,ab. (6123)
6 (ectocervix or ecto-cervix).ti,ab. (458)
7 (ectocervic$ or ecto-cervic$).ti,ab. (663)
8 ((squamocolumnar or squamo-columnar) adj2 junction).ti,ab. (747)
9 transformation zone$.ti,ab. (1202)
10 or/1-9 (283656)
11 colposcopy/ (11114)
12 colposcope/ (251)
13 spectroscopy/ (95966)
14 electrochemical impedance spectroscopy/ (5008)
15 (colposcop$ adj4 (adjunct$ or digital$ or DSI or computer$ or video$ or alternative$ or conventional$)).ti,ab. (281)
16 (impedance adj2 spectroscop$).ti,ab. (4587)
17 (Dielectric adj2 Spectroscop$).ti,ab. (843)
18 (impedance adj2 spectrometr$).ti,ab. (40)
19 (Dielectric adj2 Spectrometr$).ti,ab. (10)
20 (impedance adj2 spectrum analys$).ti,ab. (7)
21 (Dielectric adj2 Spectrum analys$).ti,ab. (0)
22 (telecolposcop$ or tele-colposcop$).ti,ab. (20)
23 (optical adj2 spectroscop$).ti,ab. (3982)
24 ((point or pencil or impedance) adj2 probe$).ti,ab. (473)
25 (microcolposcop$ or micro-colposcop$).ti,ab. (31)
26 (dysis or dysismap).ti,ab,dv,dm. (111)
27 dynamic spectral imaging.ti,ab. (27)

28 Zilico.ti,ab,dm. (0)

29 (ZedScan or Zed Scan).ti,ab,dv. (3)

30 (APX 100 or APX100).ti,ab,dv. (4)

31 EIS.ti,ab. (3150)

32 epitheliometer$.ti,ab,dv. (1)

33 MKIII.ti,ab,dv. (48)

34 or/11-33 (117271)

35 10 and 34 (8853)

36 (animal/ or nonhuman/) not exp human/ (5039945)

37 35 not 36 (8818)

38 limit 37 to yr="2000 -Current" (6177)

Key:

/ = indexing term (Emtree heading)
exp = exploded indexing term (Emtree heading)
$ = truncation
ti,ab = terms in either title or abstract fields
dm = terms in device manufacturer field
dv = terms in the device trade name field
adj2 = terms within two words of each other (any order)

Health Management Information Consortium (HMIC)
via Ovid http://ovidsp.ovid.com/

1979-Nov 2016

Searched on: 3rd January 2017

Records retrieved: 19

An update search was carried out on 10th April 2017, retrieving 19 records.

1 cervix uteri/ (18)

2 cervix.ti,ab. (136)

3 cervic$.ti,ab. (1398)

4 (endocervix or endo-cervix).ti,ab. (1)

5 (endocervic$ or endo-cervic$).ti,ab. (17)

6 (ectocervix or ecto-cervix).ti,ab. (0)

7 (ectocervic$ or ecto-cervic$).ti,ab. (1)

8 ((squamocolumnar or squamo-columnar) adj2 junction).ti,ab. (1)

9 transformation zone$.ti,ab. (6)

10 or/1-9 (1472)

11 colposcopy/ (49)

12 spectroscopy/ (20)

13 (colposcop$ adj4 (adjunct$ or digital$ or DSI or computer$ or video$ or alternative$ or conventional$)).ti,ab. (4)

14 (impedance adj2 spectroscop$).ti,ab. (0)

15 (Dielectric adj2 Spectroscop$).ti,ab. (0)

16 (impedance adj2 spectrometr$).ti,ab. (0)

17 (Dielectric adj2 Spectrometr$).ti,ab. (0)

18 (impedance adj2 spectrum analys$).ti,ab. (0)

19 (Dielectric adj2 Spectrum analys$).ti,ab. (0)

20 (telecolposcop$ or tele-colposcop$).ti,ab. (0)

21 (optical adj2 spectroscop$).ti,ab. (0)

22 ((point or pencil or impedance) adj2 probe$).ti,ab. (0)

23 (microcolposcop$ or micro-colposcop$).ti,ab. (0)

24 (dysis or dysismap).ti,ab. (0)

25 dynamic spectral imaging.ti,ab. (0)

26 Zilico.ti,ab. (0)

27 (ZedScan or Zed Scan).ti,ab. (0)

28 (APX 100 or APX100).ti,ab. (0)

29 EIS.ti,ab. (26)

30 epitheliometer$.ti,ab. (0)

31 MKIII.ti,ab. (0)

32 or/11-31 (97)

33 10 and 32 (36)

34 limit 33 to yr="2000 -Current" (19)

Key:

/ = indexing term
$ = truncation
ti,ab = terms in either title or abstract fields
adj2 = terms within two words of each other (any order)

10.1.8 Health Technology Assessment (HTA) database

via http://www.crd.york.ac.uk/CRDWeb/

Inception – 3rd January 2017

Searched on: 4th January 2017

Records retrieved: 5

See above under DARE for search strategy used.

An update search was carried out on 10th April 2017, retrieving 5 records.

10.1.9 NHS Economic Evaluations Database (NHS EED)

via http://www.crd.york.ac.uk/CRDWeb/

Inception – 31st March 2015

Searched on: 4th January 2017

Records retrieved: 38

See above under DARE for search strategy used.

As NHS EED closed on 31st March 2015, an update search was not carried out for this database.

10.1.10 PubMed

http://www.ncbi.nlm.nih.gov/pubmed/

Searched on: 4th January 2017

Records retrieved: 63

An update search was carried out on 10th April 2017, retrieving 59 records.

((((((((((((((((((((((((((("Colposcopy"[Mesh:NoExp]) OR "Colposcopes"[Mesh:NoExp]) OR "Spectrum Analysis"[Mesh:NoExp]) OR "Dielectric Spectroscopy"[Mesh:NoExp]) OR ((colposcop*[Title/Abstract]) AND (adjunct*[Title/Abstract] OR digital*[Title/Abstract] OR DSI[Title/Abstract] OR computer*[Title/Abstract] OR video*[Title/Abstract] OR alternative*[Title/Abstract] OR conventional*[Title/Abstract]))) OR ((impedance[Title/Abstract]) AND spectroscop*[Title/Abstract])) OR ((Dielectric[Title/Abstract]) AND Spectroscop*[Title/Abstract])) OR ((impedance[Title/Abstract]) AND spectrometr*[Title/Abstract])) OR ((impedance[Title/Abstract]) AND spectrum analys*[Title/Abstract])) OR ((Dielectric[Title/Abstract]) AND Spectrum analys*[Title/Abstract])) OR ((Dielectric[Title/Abstract]) AND Spectrometr*[Title/Abstract])) OR ((telecolposcop*[Title/Abstract] OR tele-colposcop*[Title/Abstract]))) OR ((optical[Title/Abstract]) AND spectroscop*[Title/Abstract])) OR (((point[Title/Abstract] OR pencil[Title/Abstract] OR impedance[Title/Abstract])) AND probe*[Title/Abstract])) OR ((microcolposcop*[Title/Abstract] OR micro-colposcop*[Title/Abstract]))) OR ((dysis[Title/Abstract] OR dysismap[Title/Abstract]))) OR dynamic

spectral imaging[Title/Abstract]) OR Zilico[Title/Abstract]) OR ((ZedScan[Title/Abstract] OR Zed Scan[Title/Abstract]))) OR (("APX 100"[Title/Abstract] OR APX100[Title/Abstract]))) OR EIS[Title/Abstract]) OR epitheliometer*[Title/Abstract]) OR MKIII[Title/Abstract])) AND ((((("Cervix Uteri"[Mesh:NoExp]) OR ((((((cervix[Title/Abstract]) OR cervic*[Title/Abstract]) OR (endocervix[Title/Abstract] OR endo-cervix[Title/Abstract])) OR (endocervic*[Title/Abstract] OR endo-cervic*[Title/Abstract])) OR (ectocervix[Title/Abstract] OR ecto-cervix[Title/Abstract])) OR (ectocervic*[Title/Abstract] OR ecto-cervic*[Title/Abstract]))) OR (((squamocolumnar[Title/Abstract] OR squamo-columnar[Title/Abstract])) AND junction[Title/Abstract])) OR (("transformation zone"[Title/Abstract]) OR "transformation zones"[Title/Abstract])))) AND ((pubstatusaheadofprint OR publisher[sb] OR pubmednotmedline[sb])))) AND ("2000/01/01"[Date - Publication] : "3000"[Date - Publication]))) NOT ((animals [mh] NOT humans [mh]))

The above search strategy incorporates the following search line to limit to studies found in PubMed but not available in Ovid MEDLINE: (pubstatusaheadofprint OR publisher[sb] OR pubmednotmedline[sb]).(158)

Key:

[Mesh] = exploded indexing term (MeSH heading)
[Mesh:noexp] = indexing term (MeSH heading) not exploded
* = truncation
" " = phrase search
[Title/Abstract]) = terms in either title or abstract fields

10.1.11 Science Citation Index
via Web of Science, Thomson Reuters

http://thomsonreuters.com/thomson-reuters-web-of-science/

1900 – 2nd January 2017

Searched on: 3rd January 2017

Records retrieved: 279

An update search was carried out on 10th April 2017, retrieving 286 records.

30 279 #28 AND #8
Indexes=SCI-EXPANDED Timespan=2000-2017
29 318 #28 AND #8

28 91,903 #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
27 64 TS=MKIII
26 2 TS=epitheliometer*
25 20,286 TS=EIS
24 2 TS=("APX 100" or APX100)
23 1 TS=(ZedScan or "Zed Scan")
22 0 TS=Zilico
21 20 TS="dynamic spectral imaging"
20 75 TS=(dysis or dysismap)
19 15 TS=(microcolposcop* or micro-colposcop*)
18 4,324 TS=((point or pencil or impedance) NEAR/2 probe*)
17 31,129 TS=(optical NEAR/2 spectroscop*)
16 20 TS=(telecolposcop* or tele-colposcop*)
15 8 TS=(Dielectric NEAR/2 "Spectrum analys*")
14 35 TS=(impedance NEAR/2 "spectrum analys*")
13 89 TS=(Dielectric NEAR/2 Spectrometr*)
12 225 TS=(impedance NEAR/2 spectrometr*)
11 7,615 TS=(Dielectric NEAR/2 Spectroscop*)
10 44,134 TS=(impedance NEAR/2 spectroscop*)
9 198 TS=(colposcop* NEAR/4 (adjunct* or digital* or DSI or computer* or video* or alternative* or conventional*))
8 197,500 #7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
7 1,431 TS="transformation zone*"
6 448 TS=((squamocolumnar or squamo-columnar) NEAR/2 junction)
5 457 TS=(ectocervic* or ecto-cervic*)
4 248 TS=(ectocervix or ecto-cervix)
3 3,940 TS=(endocervic* or endo-cervic*)
2 754 TS=(endocervix or endo-cervix)
1 194,743 TS=(cervix or cervic*)

Key:

TS= topic tag; searches terms in title, abstract, author keywords and keywords plus fields
* = truncation
" " = phrase search
NEAR/2 = terms within 2 words of each other (any order)

10.1.12 On-going, unpublished or grey literature search strategies

10.1.12.1 ClinicalTrials.gov
https://clinicaltrials.gov/

Searched on: 4th January 2017

Records retrieved: 173

169 studies found for: (Cervix OR cervical) AND (Colposcopy OR spectroscopy OR spectrometry OR "spectrum analysis")

4 studies found for: dysis OR dysismap OR "dynamic spectral imaging" OR Zilico OR ZedScan OR Zed Scan OR "APX 100" OR APX100 OR epitheliometer OR MKIII

An update search was carried out on 10th April 2017, retrieving 8 new records.

10.1.12.2 Conference Proceedings Citation Index: Science
via Web of Science, Thomson Reuters

http://thomsonreuters.com/thomson-reuters-web-of-science/

1990 – 2nd January 2017

Searched on: 3rd January 2017

Records retrieved: 62

An update search was carried out on 10th April 2017, retrieving 63 records.

30 62 #28 AND #8

Indexes=CPCI-S Timespan=2000-2017

29 67 #28 AND #8

28 20,223 #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

27 27 TS=MKIII

26 0 TS=epitheliometer*

25 3,376 TS=EIS

24 0 TS=("APX 100" or APX100)

23 0 TS=(ZedScan or "Zed Scan")

# 22	0	TS=Zilico
# 21	4	TS="dynamic spectral imaging"
# 20	32	TS=(dysis or dysismap)
# 19	0	TS=(microcolposcop* or micro-colposcop*)
# 18	1,606	TS=((point or pencil or impedance) NEAR/2 probe*)
# 17	8,132	TS=(optical NEAR/2 spectroscop*)
# 16	3	TS=(telecolposcop* or tele-colposcop*)
# 15	3	TS=(Dielectric NEAR/2 "Spectrum analys*")
# 14	15	TS=(impedance NEAR/2 "spectrum analys*")
# 13	19	TS=(Dielectric NEAR/2 Spectrometr*)
# 12	51	TS=(impedance NEAR/2 spectrometr*)
# 11	2,063	TS=(Dielectric NEAR/2 Spectroscop*)
# 10	7,234	TS=(impedance NEAR/2 spectroscop*)
# 9	38	TS=(colposcop* NEAR/4 (adjunct* or digital* or DSI or computer* or video* or alternative* or conventional*))
# 8	16,544	#7 OR #6 OR #5 OR #4 OR #3 OR #2 OR #1
# 7	135	TS="transformation zone*"
# 6	60	TS=((squamocolumnar or squamo-columnar) NEAR/2 junction)
# 5	36	TS=(ectocervic* or ecto-cervic*)
# 4	20	TS=(ectocervix or ecto-cervix)
# 3	400	TS=(endocervic* or endo-cervic*)
# 2	54	TS=(endocervix or endo-cervix)
# 1	16,171	TS=(cervix or cervic*)

Key:

TS= topic tag; searches terms in title, abstract, author keywords and keywords plus fields
* = truncation
" " = phrase search
NEAR/2 = terms within 2 words of each other (any order)

10.1.12.3 EU Clinical Trials Register
https://www.clinicaltrialsregister.eu/ctr-search/search

Searched on: 4th January 2017

Records retrieved: 15

1. 15 result(s) found for: (Cervix OR cervical) AND (Colposcopy OR spectroscopy OR spectrometry OR "spectrum analysis")

2. Dysis OR dysismap OR "dynamic spectral imaging" – 0 results

3. Zilico OR ZedScan OR "Zed Scan" OR "APX 100" OR APX100 OR epitheliometer OR MKIII – 0 results

An update search was carried out on 10th April 2017, retrieving 16 records.

10.1.12.4 PROSPERO
http://www.crd.york.ac.uk/PROSPERO/
Searched on: 4th January 2017
Records retrieved: 4

An update search was carried out on 10th April 2017, retrieving 3 new records.

#1 MeSH DESCRIPTOR Cervix Uteri 10
#2 cervix OR cervic* 399
#3 endocervix OR endo-cervix 1
#4 endocervic* OR endo-cervic* 4
#5 ectocervix OR ecto-cervix 0
#6 ectocervic$ or ecto-cervic$ 0
#7 ectocervic* OR ecto-cervic* 0
#8 squamocolumnar OR squamo-columnar 1
#9 transformation zone* 3
#10 #1 OR #2 OR #3 OR #4 OR #5 OR #7 OR #8 OR #9 400
#11 MeSH DESCRIPTOR colposcopy 2
#12 MeSH DESCRIPTOR Colposcopes 0
#13 MeSH DESCRIPTOR Spectrum Analysis 1
#14 MeSH DESCRIPTOR Dielectric Spectroscopy 0
#15 (colposcop* AND (adjunct* OR digital* OR DSI OR computer* OR video* OR alternative* OR conventional*)) 3
#16 ((impedance OR Dielectric) AND (spectroscop* OR spectrometr* OR spectrum analys*)) 1
#17 telecolposcop* OR tele-colposcop* 0
#18 telecolposcop* OR tele-colposcop* 0
#19 optical AND spectroscop* 5

#20 ((point OR pencil OR impedance) AND probe*) 16

#21 microcolposcop* OR micro-colposcop* 1

#22 dysis OR dysismap 2

#23 dynamic spectral imaging 1

#24 Zilico 1

#25 ZedScan OR Zed Scan 0

#26 APX 100 OR APX100 1

#27 EIS 1

#28 epitheliometer* 0

#29 MKIII 0

#30 #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #19 OR #20 OR #21 OR #18 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 26

#31 #30 AND #10 4

Key:

MeSH DESCRIPTOR = indexing term (MeSH heading)
* = truncation

10.1.12.5 WHO International Clinical Trials Registry Platform
http://www.who.int/ictrp/search/en/

Searched on: 4th January 2017

Records retrieved: 17

1. cervix OR cervical (Condition field) AND Colposcopy OR spectroscopy OR spectrometry OR spectrum analysis (Intervention field) – 16 records retrieved.

2. dysis OR dysismap OR dynamic spectral imaging OR Zilico OR ZedScan OR Zed Scan OR APX 100 OR APX100 OR epitheliometer OR MKIII (Intervention field) - 1 record retrieved.

An update search was carried out on 10th April 2017, retrieving 15 records.

Guideline searches

The following websites were all searched on 10th January 2017. An update search was carried out on 10th April 2017, however no new guidelines were identified.

10.1.12.6 Scottish Intercollegiate Guidelines Network (SIGN)
www.sign.ac.uk

Search of website using terms "colposcopy", "DySIS", "ZedScan", "Zed Scan". Also browsed all guidelines. No new guidance found

10.1.12.7 National Institute for Health and Clinical Excellence (NICE)
https://www.nice.org.uk/

Search of website using terms "colposcopy", "DySIS", "ZedScan", "Zed Scan". Also browsed documents within the cervical cancer guidance section. 4 relevant guidance documents found.

10.1.12.8 National Guideline Clearinghouse
https://www.guideline.gov/

Searched using terms "colposcopy OR DySIS OR ZedScan OR Zed Scan", limited to publications from 2011 to 2017. 19 results browsed for relevance. 8 relevant guidelines found.

10.1.12.9 NHS Evidence
https://www.evidence.nhs.uk/

Searched using terms "colposcopy OR dysis OR ZedScan OR Zed Scan". Filtered results by guidance and by date 01/01/2011 to 10/01/2017. 40 records retrieved and downloaded.

10.1.12.10 TRIP database
https://www.tripdatabase.com/

Searched using terms "colposcopy OR dysis OR ZedScan OR Zed Scan". Filtered results by guidelines, 48 records retrieved and browsed for relevance. 1 relevant record found after duplicates removed.

10.1.12.11 Public Health England
https://www.gov.uk/search

Search of website using terms "colposcopy", "DySIS", "ZedScan", "Zed Scan" filtered by Public Health England. 9 results retrieved and browsed for relevance. 7 relevant documents found.

10.1.12.12 Royal College of Obstetricians and Gynaecologists

https://www.rcog.org.uk/en/guidelines-research-services/guidelines/

Search of all guidelines using terms "colposcopy", "DySIS", "ZedScan", "Zed Scan". 8 records retrieved and browsed for relevance. 1 relevant report found.

10.1.12.13 The British Society for Colposcopy and Cervical Pathology

https://www.bsccp.org.uk/

Search of website using terms "colposcopy", "DySIS", "ZedScan", "Zed Scan" using website general search box. 110 results returned and browsed for relevance. No guidelines found.

10.1.13 Additional searches

The following search strategies were used to identify systematic reviews or meta-analyses examining the diagnostic test accuracy of cervical screening or HPV testing.

10.1.13.1 MEDLINE (Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R))

via Ovid http://ovidsp.ovid.com/

1946 to present

Searched on: 29th March 2017

Records retrieved: 267

1 Uterine Cervical Neoplasms/ (67631)

2 Cervical Intraepithelial Neoplasia/ (8926)

3 exp Uterine Cervical Dysplasia/ (4058)

4 Cervix Uteri/ (25999)

5 ((cervix or cervic*) adj3 (cancer* or neoplas* or carcinoma* or adenocarcinoma* or tumour* or tumor* dysplas* or dyskaryo* or precancer* or pre-cancer*)).ti,ab. (65985)

6 ((cervix or cervic*) adj3 (abnormal* or lesion* or atypical or squamous)).ti,ab. (13430)

7 (cervix or cervic*).ti,ab. (227836)

8 (LSIL or HSIL or ASCUS or ASC-US or ASC-H or ASC).ti,ab. (8776)

9 ((intraepithelial or intra-epithelial) adj2 lesion$).ti,ab. (4844)
10 (atypical adj2 squamous).ti,ab. (1989)
11 8 or 9 or 10 (12051)
12 7 and 11 (5015)
13 (CIN or CIN1* or CIN2* or CIN3* or CIN 1* or CIN 2* or CIN 3* or CIN I* or CIN II* or CIN III* or CINI* or CINII* or CINIII* or CGIN*).ti,ab. (10256)
14 1 or 2 or 3 or 4 or 5 or 6 or 12 or 13 (114337)
15 exp Papillomavirus Infections/ (28658)
16 Papillomaviridae/ (21795)
17 exp Alphapapillomavirus/ (6098)
18 (human* adj2 (papillomavirus* or papillomaviridae or papilloma virus*)).ti,ab. (33953)
19 (HPV* or hrHPV* or hr-HPV*).ti,ab. (35059)
20 or/15-19 (53740)
21 Vaginal Smears/ (21441)
22 Papanicolaou Test/ (5902)
23 Cytological Techniques/ (10199)
24 Cytodiagnosis/ (15335)
25 Mass Screening/ (92108)
26 "Early Detection of Cancer"/ (15713)
27 DNA Probes, HPV/ (1080)
28 Human Papillomavirus DNA Tests/ (340)
29 ((vagina* or pap or papanicolaou) adj2 smear*).ti,ab. (9876)
30 ((pap or papanicolaou) adj2 (test* or analys* or screen*)).ti,ab. (4980)
31 cytolog*.ti,ab. (85141)
32 or/21-31 (214406)
33 14 and 32 (26028)
34 20 and 32 (10837)
35 (screen* adj3 (cervic* or cervix)).ti,ab. (9587)
36 ((cervic* or cervix) adj2 smear$).ti,ab. (4102)
37 ((HPV* or hrHPV* or hr-HPV*) adj4 (screen* or test* or detect* or triage*)).ti,ab. (11312)
38 (human* adj2 (papillomavirus* or papillomaviridae or papilloma virus*) adj2 (screen* or test* or detect* or triage*)).ti,ab. (3300)
39 35 or 36 or 37 or 38 (22413)
40 33 or 34 or 39 (36627)
41 systematic$ review$.ti,ab. (103638)

42 meta-analysis as topic/ (15759)
43 meta-analytic$.ti,ab. (5302)
44 meta-analysis.ti,ab,pt. (116352)
45 metanalysis.ti,ab. (157)
46 metaanalysis.ti,ab. (1389)
47 meta analysis.ti,ab. (94402)
48 meta-synthesis.ti,ab. (524)
49 metasynthesis.ti,ab. (231)
50 meta synthesis.ti,ab. (524)
51 meta-regression.ti,ab. (4549)
52 metaregression.ti,ab. (442)
53 meta regression.ti,ab. (4549)
54 (synthes$ adj3 literature).ti,ab. (2221)
55 (synthes$ adj3 evidence).ti,ab. (6509)
56 integrative review.ti,ab. (1692)
57 data synthesis.ti,ab. (9772)
58 (research synthesis or narrative synthesis).ti,ab. (1591)
59 (systematic study or systematic studies).ti,ab. (9808)
60 (systematic comparison$ or systematic overview$).ti,ab. (2592)
61 evidence based review.ti,ab. (1694)
62 comprehensive review.ti,ab. (10438)
63 critical review.ti,ab. (13445)
64 quantitative review.ti,ab. (583)
65 structured review.ti,ab. (641)
66 realist review.ti,ab. (158)
67 realist synthesis.ti,ab. (118)
68 or/41-67 (239126)
69 review.pt. (2263518)
70 medline.ab. (84579)
71 pubmed.ab. (65446)
72 cochrane.ab. (51941)
73 embase.ab. (54367)
74 cinahl.ab. (17283)
75 psyc?lit.ab. (937)
76 psyc?info.ab. (17111)
77 (literature adj3 search$).ab. (41423)

78 (database$ adj3 search$).ab. (39606)
79 (bibliographic adj3 search$).ab. (1816)
80 (electronic adj3 search$).ab. (14770)
81 (electronic adj3 database$).ab. (18516)
82 (computeri?ed adj3 search$).ab. (3229)
83 (internet adj3 search$).ab. (2468)
84 included studies.ab. (13602)
85 (inclusion adj3 studies).ab. (10824)
86 inclusion criteria.ab. (57533)
87 selection criteria.ab. (25429)
88 predefined criteria.ab. (1537)
89 predetermined criteria.ab. (904)
90 (assess$ adj3 (quality or validity)).ab. (58471)
91 (select$ adj3 (study or studies)).ab. (51767)
92 (data adj3 extract$).ab. (43710)
93 extracted data.ab. (10058)
94 (data adj2 abstracted).ab. (4252)
95 (data adj3 abstraction).ab. (1226)
96 published intervention$.ab. (143)
97 ((study or studies) adj2 evaluat$).ab. (145298)
98 (intervention$ adj2 evaluat$).ab. (8561)
99 confidence interval$.ab. (314381)
100 heterogeneity.ab. (125402)
101 pooled.ab. (65443)
102 pooling.ab. (9876)
103 odds ratio$.ab. (205883)
104 (Jadad or coding).ab. (150343)
105 or/70-104 (1105052)
106 69 and 105 (179404)
107 review.ti. (354575)
108 107 and 105 (85749)
109 (review$ adj4 (papers or trials or studies or evidence or intervention$ or evaluation$)).ti,ab. (142763)
110 68 or 106 or 108 or 109 (418128)
111 letter.pt. (964951)

112 editorial.pt. (434093)

113 comment.pt. (685970)

114 111 or 112 or 113 (1570204)

115 110 not 114 (408039)

116 exp animals/ not humans/ (4364879)

117 115 not 116 (396895)

118 40 and 117 (921)

119 limit 118 to yr="2014 -Current" (267)

Key:

/ = indexing term (MeSH heading)
exp = exploded indexing term (MeSH heading)
* = truncation
$ = truncation
? = optional wildcard – stands for zero or one character
.ti,ab. = terms in either title or abstract fields
.pt. = publication type
adj = terms next to each other (order specified)
adj2 = terms within two words of each other (any order)

10.1.13.2 Cochrane Database of Systematic Reviews (CDSR)
via Wiley http://onlinelibrary.wiley.com/

Issue 3 of 12, March 2017

Searched on: 29th March 2017

Records retrieved: 20

#1 MeSH descriptor: [Uterine Cervical Neoplasms] this term only 1975

#2 MeSH descriptor: [Cervical Intraepithelial Neoplasia] this term only 518

#3 MeSH descriptor: [Uterine Cervical Dysplasia] explode all trees 129

#4 MeSH descriptor: [Cervix Uteri] this term only 1045

#5 ((cervix or cervic*) near/3 (cancer* or neoplas* or carcinoma* or adenocarcinoma* or tumour* or tumor* dysplas* or dyskaryo* or precancer* or pre-cancer*)):ti,ab,kw 3701

#6 ((cervix or cervic*) near/3 (abnormal* or lesion* or atypical or squamous)):ti,ab,kw 725

#7 (cervix or cervic*):ti,ab,kw 13509

#8 (LSIL or HSIL or ASCUS or ASC-US or ASC-H or ASC):ti,ab,kw 383

#9 ((intraepithelial or intra-epithelial) near/2 lesion*):ti,ab,kw 217

#10 (atypical near/2 squamous):ti,ab,kw 118

#11 #8 or #9 or #10 521

#12 #7 and #11 270

#13 (CIN or CIN1* or CIN2* or CIN3* or CIN 1* or CIN 2* or CIN 3* or CIN I* or CIN II* or CIN III* or CINI* or CINII* or CINIII* or CGIN*):ti,ab,kw 1165

#14 #1 or #2 or #3 or #4 or #5 or #6 or #12 or #13 5623

#15 MeSH descriptor: [Papillomavirus Infections] explode all trees 1107

#16 MeSH descriptor: [Papillomaviridae] this term only 419

#17 MeSH descriptor: [Alphapapillomavirus] explode all trees 220

#18 (human* near/2 (papillomavirus* or papillomaviridae or papilloma next virus*)):ti,ab,kw 1353

#19 (HPV* or hrHPV* or hr-HPV*):ti,ab,kw 1438

#20 #15 or #16 or #17 or #18 or #19 2137

#21 MeSH descriptor: [Vaginal Smears] explode all trees 802

#22 MeSH descriptor: [Papanicolaou Test] this term only 228

#23 MeSH descriptor: [Cytological Techniques] this term only 82

#24 MeSH descriptor: [Cytodiagnosis] this term only 120

#25 MeSH descriptor: [Mass Screening] this term only 4758

#26 MeSH descriptor: [Early Detection of Cancer] this term only 955

#27 MeSH descriptor: [DNA Probes, HPV] this term only 16

#28 MeSH descriptor: [Human Papillomavirus DNA Tests] this term only 8

#29 ((vagina* or pap or papanicolaou) near/2 (smear*)):ti,ab,kw 1139

#30 ((pap or papanicolaou) near/2 (test* or analys* or screen*)):ti,ab,kw 581

#31 cytolog*:ti,ab,kw 2751

#32 #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 8679

#33 #14 and #32 1330

#34 #20 and #32 666

#35 (screen* near/2 (cervic* or cervix)):ti,ab,kw 730

#36 ((cervic* or cervix) near/2 smear*):ti,ab,kw 189

#37 ((HPV* or hrHPV* or hr-HPV*) near/4 (screen* or test* or detect* or triage*)):ti,ab,kw 519

#38 (human* near/2 (papillomavirus* or papillomaviridae or papilloma next virus*) near/2 (screen* or test* or detect* or triage*)):ti,ab,kw 240

#39 #35 or #36 or #37 or #38 1211

#40 #33 or #34 or #39 1740

Key:
MeSH descriptor = indexing term (MeSH heading)
* = truncation
ti,ab,kw = terms in either title or abstract or keyword fields
near/2 = terms within two words of each other (any order)

next = terms are next to each other

10.1.13.3 Database of Abstracts of Reviews of Effects (DARE)
via http://www.crd.york.ac.uk/CRDWeb/

Inception – 31st March 2015

Searched on: 29th March 2017

Records retrieved: 128

1 MeSH DESCRIPTOR Uterine Cervical Neoplasms 540

2 MeSH DESCRIPTOR Cervical Intraepithelial Neoplasia 136

3 MeSH DESCRIPTOR Uterine Cervical Dysplasia EXPLODE ALL TREES 22

4 MeSH DESCRIPTOR Cervix Uteri 89

5 (((cervix or cervic*) ADJ3 (cancer* or neoplas* or carcinoma* or adenocarcinoma* or tumour* or tumor* dysplas* or dyskaryo* or precancer* or pre-cancer*))) 693

6 (((cancer* or neoplas* or carcinoma* or adenocarcinoma* or tumour* or tumor* dysplas* or dyskaryo* or precancer* or pre-cancer*) ADJ3 (cervix or cervic*))) 168

7 (((cervix or cervic*) ADJ3 (abnormal* or lesion* or atypical or squamous))) 60

8 (((abnormal* or lesion* or atypical or squamous) ADJ3 (cervix or cervic*))) 43

9 ((cervix or cervic*)) AND (LSIL or HSIL or ASCUS or ASC-US or ASC-H or ASC) 41

10 ((cervix or cervic*)) 1481

11 (((intraepithelial or intra-epithelial) ADJ2 lesion*)) 66

12 ((lesion* ADJ2 (intraepithelial or intra-epithelial))) 0

13 ((atypical ADJ2 squamous)) 36

14 ((squamous ADJ2 atypical)) 1

15 #11 OR #12 OR #13 OR #14 76

16 #10 AND #15 73

17 ((CIN or CIN1* or CIN2* or CIN3* or CIN 1* or CIN 2* or CIN 3* or CIN I* or CIN II* or CIN III* or CINI* or CINII* or CINIII* or CGIN*)) 111

18 #1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #16 OR #17 801

19 MeSH DESCRIPTOR Papillomavirus Infections EXPLODE ALL TREES 283

20 MeSH DESCRIPTOR Papillomaviridae 114

21 MeSH DESCRIPTOR Alphapapillomavirus EXPLODE ALL TREES 54

22 ((human* ADJ2 (papillomavirus* or papillomaviridae or papilloma virus*))) 304

23 (((papillomavirus* or papillomaviridae or papilloma virus*) ADJ2 human*)) 35

24 (HPV* or hrHPV* or hr-HPV*) 259

25 #19 OR #20 OR #21 OR #22 OR #23 OR #24 409

26 MeSH DESCRIPTOR Vaginal Smears EXPLODE ALL TREES 213
27 MeSH DESCRIPTOR Papanicolaou Test 56
28 MeSH DESCRIPTOR Cytological Techniques 34
29 MeSH DESCRIPTOR Cytodiagnosis 40
30 MeSH DESCRIPTOR Mass Screening 2100
31 MeSH DESCRIPTOR Early Detection of Cancer 273
32 MeSH DESCRIPTOR DNA Probes, HPV 6
33 MeSH DESCRIPTOR Human Papillomavirus DNA Tests 6
34 (((vagina* or pap or papanicolaou) ADJ2 smear*)) 258
35 ((smear* ADJ2 (vagina* or pap or papanicolaou))) 10
36 (((pap or papanicolaou) ADJ2 (test* or analys* or screen*))) 128
37 (((test* or analys* or screen*) ADJ2 (pap or papanicolaou))) 63
38 (cytolog*) 483
39 #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 2727
40 #18 AND #39 393
41 #25 AND #39 233
42 ((screen* ADJ3 (cervic* or cervix))) 142
43 (((cervic* or cervix) ADJ3 screen*)) 264
44 (((cervic* or cervix) ADJ3 smear*)) 81
45 ((smear* ADJ2 (cervic* or cervix))) 18
46 (((HPV* or hrHPV* or hr-HPV*) ADJ4 (screen* or test* or detect* or triage*))) 135
47 (((screen* or test* or detect* or triage*) ADJ4 (HPV* or hrHPV* or hr-HPV*))) 92
48 ((papillomavirus* or papillomaviridae or papilloma virus*) ADJ2 (screen* or test* or detect* or triage*)) 115
49 (((screen* or test* or detect* or triage*) ADJ2 (papillomavirus* or papillomaviridae or papilloma virus*))) 75
50 (human) 3164
51 #48 OR #49 144
52 #50 AND #51 123
53 #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #52 392
54 #40 OR #41 OR #53 472
55 (*) IN DARE 45418
56 #54 AND #55 128
57 (*) IN HTA 16846

58 #54 AND #57 108

Key:

MeSH DESCRIPTOR = indexing term (MeSH heading)
* = truncation
ADJ2 = terms within two words of each other (order specified)

10.1.13.4 EMBASE
via Ovid http://ovidsp.ovid.com/

1974 to 2017 March 28

Searched on: 29th March 2017

Records retrieved: 676

1 exp uterine cervix tumor/ (101917)

2 exp uterine cervix dysplasia/ (5017)

3 exp uterine cervix/ (28075)

4 ((cervix or cervic*) adj3 (cancer* or neoplas* or carcinoma* or adenocarcinoma* or tumour* or tumor* dysplas* or dyskaryo* or precancer* or pre-cancer*)).ti,ab. (81511)

5 ((cervix or cervic*) adj3 (abnormal* or lesion* or atypical or squamous)).ti,ab. (17047)

6 (cervix or cervic*).ti,ab. (279094)

7 (LSIL or HSIL or ASCUS or ASC-US or ASC-H or ASC).ti,ab. (12691)

8 ((intraepithelial or intra-epithelial) adj2 lesion$).ti,ab. (6060)

9 (atypical adj2 squamous).ti,ab. (2491)

10 7 or 8 or 9 (16616)

11 6 and 10 (6886)

12 (CIN or CIN1* or CIN2* or CIN3* or CIN 1* or CIN 2* or CIN 3* or CIN I* or CIN II* or CIN III* or CINI* or CINII* or CINIII* or CGIN*).ti,ab. (14461)

13 1 or 2 or 3 or 4 or 5 or 11 or 12 (147667)

14 exp papillomavirus infection/ (25629)

15 papillomaviridae/ (816)

16 exp alphapapillomavirus/ (12821)

17 wart virus/ (37172)

18 (human* adj2 (papillomavirus* or papillomaviridae or papilloma virus*)).ti,ab. (39987)

19 (HPV* or hrHPV* or hr-HPV*).ti,ab. (45330)

20 14 or 15 or 16 or 17 or 18 or 19 (71133)

21 vagina smear/ (10593)

22 papanicolaou test/ (15851)
23 uterine cervix cytology/ (12091)
24 cytology/ (382601)
25 cancer screening/ (66243)
26 early cancer diagnosis/ (1191)
27 Human papillomavirus DNA test/ (1518)
28 DNA probe/ (27048)
29 screening test/ (65290)
30 diagnostic accuracy/ (217693)
31 diagnostic test accuracy study/ (75141)
32 ((vagina* or pap or papanicolaou) adj2 smear*).ti,ab. (11672)
33 ((pap or papanicolaou) adj2 (test* or analys* or screen*)).ti,ab. (6474)
34 cytolog*.ti,ab. (105880)
35 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 (854789)
36 13 and 35 (36343)
37 20 and 35 (17008)
38 (screen* adj3 (cervic* or cervix)).ti,ab. (11964)
39 ((cervic* or cervix) adj2 smear$).ti,ab. (4794)
40 ((HPV* or hrHPV* or hr-HPV*) adj4 (screen* or test* or detect* or triage*)).ti,ab. (14930)
41 (human* adj2 (papillomavirus* or papillomaviridae or papilloma virus*) adj2 (screen* or test* or detect* or triage*)).ti,ab. (3861)
42 38 or 39 or 40 or 41 (28042)
43 36 or 37 or 42 (49894)
44 systematic$ review$.ti,ab. (127491)
45 systematic$ literature review$.ti,ab. (9255)
46 "systematic review"/ (159479)
47 "systematic review (topic)"/ (28244)
48 meta analysis/ (161820)
49 "meta analysis (topic)"/ (39256)
50 meta-analytic$.ti,ab. (5990)
51 meta-analysis.ti,ab. (121194)
52 metanalysis.ti,ab. (390)
53 metaanalysis.ti,ab. (5712)
54 meta analysis.ti,ab. (121194)
55 meta-synthesis.ti,ab. (482)

56 metasynthesis.ti,ab. (226)
57 meta synthesis.ti,ab. (482)
58 meta-regression.ti,ab. (5717)
59 metaregression.ti,ab. (735)
60 meta regression.ti,ab. (5717)
61 (synthes$ adj3 literature).ti,ab. (2538)
62 (synthes$ adj3 evidence).ti,ab. (7290)
63 (synthes$ adj2 qualitative).ti,ab. (1370)
64 integrative review.ti,ab. (1388)
65 data synthesis.ti,ab. (11134)
66 (research synthesis or narrative synthesis).ti,ab. (1581)
67 (systematic study or systematic studies).ti,ab. (10580)
68 (systematic comparison$ or systematic overview$).ti,ab. (2810)
69 (systematic adj2 search$).ti,ab. (19687)
70 systematic$ literature research$.ti,ab. (218)
71 (review adj3 scientific literature).ti,ab. (1419)
72 (literature review adj2 side effect$).ti,ab. (12)
73 (literature review adj2 adverse effect$).ti,ab. (2)
74 (literature review adj2 adverse event$).ti,ab. (12)
75 (evidence-based adj2 review).ti,ab. (3042)
76 comprehensive review.ti,ab. (12025)
77 critical review.ti,ab. (14564)
78 critical analysis.ti,ab. (7278)
79 quantitative review.ti,ab. (653)
80 structured review.ti,ab. (841)
81 realist review.ti,ab. (141)
82 realist synthesis.ti,ab. (95)
83 (pooled adj2 analysis).ti,ab. (13908)
84 (pooled data adj6 (studies or trials)).ti,ab. (2176)
85 (medline and (inclusion adj3 criteria)).ti,ab. (17624)
86 (search adj (strateg$ or term$)).ti,ab. (27662)
87 or/44-86 (397542)
88 medline.ab. (101252)
89 pubmed.ab. (83024)
90 cochrane.ab. (65587)
91 embase.ab. (67292)

92 cinahl.ab. (19062)
93 psyc?lit.ab. (977)
94 psyc?info.ab. (15707)
95 lilacs.ab. (5248)
96 (literature adj3 search$).ab. (51495)
97 (database$ adj3 search$).ab. (48637)
98 (bibliographic adj3 search$).ab. (2080)
99 (electronic adj3 search$).ab. (17339)
100 (electronic adj3 database$).ab. (24395)
101 (computeri?ed adj3 search$).ab. (3688)
102 (internet adj3 search$).ab. (3184)
103 included studies.ab. (16745)
104 (inclusion adj3 studies).ab. (13046)
105 inclusion criteria.ab. (94570)
106 selection criteria.ab. (27646)
107 predefined criteria.ab. (2021)
108 predetermined criteria.ab. (1098)
109 (assess$ adj3 (quality or validity)).ab. (74945)
110 (select$ adj3 (study or studies)).ab. (65709)
111 (data adj3 extract$).ab. (57099)
112 extracted data.ab. (12500)
113 (data adj2 abstracted).ab. (6653)
114 (data adj3 abstraction).ab. (1741)
115 published intervention$.ab. (167)
116 ((study or studies) adj2 evaluat$).ab. (198404)
117 (intervention$ adj2 evaluat$).ab. (11277)
118 confidence interval$.ab. (367946)
119 heterogeneity.ab. (154328)
120 pooled.ab. (88249)
121 pooling.ab. (12583)
122 odds ratio$.ab. (252412)
123 (Jadad or coding).ab. (172491)
124 evidence-based.ti,ab. (104203)
125 or/88-124 (1482382)
126 review.pt. (2263944)

127 125 and 126 (181834)

128 review.ti. (404112)

129 125 and 128 (105785)

130 (review$ adj10 (papers or trials or trial data or studies or evidence or intervention$ or evaluation$ or outcome$ or findings)).ti,ab. (413152)

131 (retriev$ adj10 (papers or trials or studies or evidence or intervention$ or evaluation$ or outcome$ or findings)).ti,ab. (21339)

132 87 or 127 or 129 or 130 or 131 (776417)

133 letter.pt. (983216)

134 editorial.pt. (537824)

135 133 or 134 (1521040)

136 132 not 135 (761183)

137 (animal/ or nonhuman/) not exp human/ (5103479)

138 136 not 137 (735678)

139 43 and 138 (2214)

140 limit 139 to yr="2014 -Current" (676)

Key:

/ = indexing term (Emtree heading)
exp = exploded indexing term (Emtree heading)
* = truncation
$ = truncation
ti,ab = terms in either title or abstract fields
adj = terms next to each other (order specified)
adj2 = terms within two words of each other (any order)
.pt. = publication type
? = optional wildcard – stands for zero or one character

10.1.13.5 Health Technology Assessment (HTA) database
via http://www.crd.york.ac.uk/CRDWeb/

Inception – 28th March 2017

Searched on: 29th March 2017

Records retrieved: 108

See above under DARE for search strategy used.

References

Wade R, Spackman E, Corbett M, Walker S, Light K, Naik R, Sculpher M, Eastwood A. Adjunctive colposcopy technologies for examination of the uterine cervix--DySIS, LuViva Advanced Cervical

Scan and Niris Imaging System: a systematic review and economic evaluation. *Health Technol Assess* 2013;17:1-240.

Duffy S, de Kock S, Misso K, Noake C, Ross J, Stirk L. Supplementary searches of PubMed to improve currency of MEDLINE and MEDLINE In-Process searches via Ovid. *J Med Libr Assoc* 2016;104:309-312.

10.2 Included studies

1. Budithi S, Peevor RJ, Pugh D, Papagiannakis E, Durman A, Banu N, et al. Evaluating colposcopy with dynamic spectral imaging during routine practice at five colposcopy clinics in Wales: clinical performance. Unknown. In press?

2. Budithi S, Peevor R, Pugh D, Papagiannakis M, Leeson S, editors. DySIS service evaluation in Wales. Patient and colposcopist feedback. BSCCP 2016, 13-15 April 2016; 2016; Bradford. Order (DYSIS)

3. Budithi S, Peevor R, Pugh D, Papagiannakis M, Leeson S, editors. DySIS service evaluation in Wales. Final data from 5 sites. BSCCP 2016, 13-15 April 2016; 2016; Bradford. Order (DYSIS)

4. Budithi S, Peevor R, Pugh D, Papagiannakis M, Leeson S, editors. DySIS service evaluation in Wales. A report of preliminary data from 2 sites. BSCCP 2015, 15-17 April 2015; 2015; Nottingham, UK. Order (DYSIS)

5. Budithi S, Peevor R, Papagiannakis E, Leeson S. Dysis colposcopy service evaluation in Wales. A report of preliminary data from four sites. Int J Gynecol Cancer. 2015;25(Suppl 1 9):968.

6. Coronado PJ, Fasero M. Colposcopy combined with dynamic spectral imaging. A prospective clinical study. Eur J Obstet Gynecol Reprod Biol. 2016;196:11-6.

7. Coronado PJ, Fasero M. Correlating the accuracy of colposcopy with practitioner experience when diagnosing cervical pathology using the dynamic spectral imaging system. Gynecol Obstet Invest. 2014;78(4):224-9.

8. Coronado P, Fasero M, Papagiannakis M, editors. Value of the dynamic spectral imaging map in the diagnosis of cervical intraepithelial neoplasia. IFPC 15th World Congress for Cervical Pathology and Colposcopy, 26-30 May 2014; 2014; London, UK. Order (DYSIS)

9. Coronado P, Fasero M, Rincon JA, Papagiannakis M, Herraiz M, editors. Colposcopy accuracy using the Dynamic Spectral Imaging System (DySIS) by colposcopist experience. 6th Congress of the European Federation for Colposcopy and Cervical Pathology, 5-7 September 2013; 2013; Prague, Czech Republic. Order (DYSIS)

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10.3 Excluded studies

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Founta (2013) Using DySIS to triage different patient groups in a colposcopy clinic: Preliminary results of an ongoing study. In: 2013 7th Hellenic & 3rd Turkish Joint Congress on Colposcopy and Cervical Pathology, Athens, Greece

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10.4 CIN and cancer prevalence

Table 62 Histology confirmed CIN & cancer prevalence in diagnostic accuracy studies

	N	Normal	CIN1 prevalence	CIN1- prevalence	CIN2 prevalence	CIN2+ prevalence	CIN3 prevalence	>CIN 3
Budithi (2016) {#3485)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Coronado (2016)(47)	443	66.1%	24.6%	90.7%	3.2%	9.3%	6.1%	1.1%
Founta (unpublished)(51)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Louwers (2011)	239	NR	NR	NR	NR	45.2%	NR	[redacted]
Natsis (2016)(74)	287 (+948 ctrl group)	NR	NR	NR	NR	17.1%	NR	NR
Roensbo (2015)(79)	239	71.5%	NR	71.5%	NR	28.5%	0.0%	NR
Salter (2017) (IMPROVE-COLPO) (80)	210	56.7%	28.6%	85.2%	9.0%	14.8%	5.7%	0.5%*
Soutter (2009)(88)	308	NR	NR	76.6%	8.4%	23.4%	14.9%	1.0%
Tidy (2013)(94)	196	NR	NR	55.6%	NR	44.4%	NR	NR

Tidy (forthcoming)(103)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tsetsa (2012) (112)	54	NR	NR	NR	NR	NR	NR	NR

*Prevalence was 0.4% in a linked ongoing study including a total of 1839 patients across two arms by Livingston (2016)(84)

10.5 Patient selection criteria and test failures

Table 63 Patient selection criteria in the diagnostic accuracy studies, test failures rates with reasons

Study	Inclusion criteria	Exclusion criteria	Test failure (n, %)	Reasons for test failures
Budithi 2016(42)	Women referred to the colposcopy clinic due to abnormal cervical cytology, abnormal appearing cervix or postcoital bleeding	Non-cervical disease (e.g. vulval and vaginal referrals) and pregnant women exclude from analyses.	26 (6.2%)	Missing colposcopic impression and DSI map (25), missing histology data (1)
Coronado (2016)(47), Spain	Women aged ≥18 referred for colposcopy following Spanish national guidance.*	NR	36 (8.1%)	Excessive movements during the measurement
Founta (unpublished) (51)	Women referred to the colposcopy clinic with negative cytology and testing positive for HR-HPV either 6 months after treatment or in the context of the catch-up programme and who underwent DySIS colposcopy	NR	3 (2.9%)	Poor quality imaging due to user errors
Louwers (2011)(57)	Women aged ≥18 with abnormal cervical cytology** or follow-up of a cervical intraepithelial neoplasia (CIN) grade 1 or 2 lesion.	Previous surgery on the cervix, pelvic radiotherapy. Current pregnancy and pregnancy in the last 3 months.	25 (9.5%)	7 DYSIS did not start, 9 no map, 9 exam data not saved
Natsis (2016)(74)	NR	NR	NR	NR
Roensbo (2015)(79)	Women age ≥18 with adequate DySIS colposcopy (such as sufficient view of the cervix and no patient movement resulting in adequate DySIS analysis)	NR	28 (9.8%)	48 women were excluded due to: biopsies not sent separately (28), not possible to classify the biopsy (6), technical difficulties (9), others (5).

Study	Inclusion criteria	Exclusion criteria	Test failure (n, %)	Reasons for test failures
Salter (2017)(80)	NR	NR	NR	NR
Soutter (2009)(88)	Cervical smear showing squamous or glandular cell dyskaryosis or borderline nuclear change (ASCUS or AGUS); or symptoms of postcoital bleeding, postmenopausal bleeding, or intermenstrual bleeding	Self-referring women without an abnormal smear, an inadequate or an inflammatory smear, any other clinical indication for referral to colposcopy, pregnancy, previous pelvic radiotherapy, or any woman for whom any prolongation of the examination was thought to be inadvisable.	139 (31%)	Software problems (15), no biopsy (23), unsatisfactory view (45) in 45 women, not eligible (6), 5% acetic acid (1), lost data form (1), lost biopsy slides (5), blood or mucus (1), biopsies from wrong point (3), excessive movement (2), problem with acetic acid-faulty nozzles (37)
Tidy (2013)(94)	Women referred with abnormal cervical cytology	Type 3 transformation zone, pregnancy and active menstruation,	Phase 1: 33 (15.4%); phase 2: 19 (8.8%)	Phase 1: 31 "as part of training", 2 incomplete clinical data. Phase 2: Biopsy not coincident with EIS reading or inadequate for histological examination n = 14 Failure of EIS device n = 5 12, incl. 9 had incomplete clinical data, one did not meet the inclusion criteria, one was unable to complete the colposcopic examination and one was excluded because of a protocol violation. In five cases the device exhibited technical problems that prevented the collection of EIS data. Additionally, 110/7706 (1.4%) recorded measurements were unacceptable when the spectra were visually reviewed.
Tidy (forthcoming) (103)	Women referred to the colposcopy clinic with abnormal cervical cytology from the national cervical screening programme. Adequate colposcopic examination, i.e. type 1 or 2 transformation zone with the upper extent of the lesion seen.	Type 3 transformation zone, pregnancy	73 (5.6%)	73 were not considered analysable: 61 related to the use of ZedScan, mainly occurred in the early stages of adopting the device and were a combination of device failures and user errors, 7 had problems unrelated to ZedScan (e.g. discomfort due to speculum), 5 had incomplete data or self-reported as pregnant.
Tsetsa	NR	NR	NR	NR

10.6 ZedScan I algorithm

[redacted]

Figure 38

Figure 38 ZedScan I diagnostic flow chart

10.7 Quality assessment of diagnostic accuracy studies

Risk of bias and concerns about applicability of all included studies included in the diagnostic accuracy review was performed using a modified version of the Quality Assessment tool of Diagnostic Accuracy Studies (QUADAS-2) checklist. The modified version of the QUADAS-2 tool used in Wade (2013)(30) and further described elsewhere(36) to assess risk of bias in comparative diagnostic accuracy studies (i.e. a comparison of the index test with both standard care and the gold standard) was used. Further questions, presented in Table 64, were added to the following domains: index/comparator test (1 question), flow and timing (2 questions) and other concerns (3 questions). A question about the predicted direction of bias, similar to that used in the Cochrane ROBINS-I tool(159) for domains classed at high risk of bias was also added. Full results of the QUADAS-2 quality assessment are reported in Table 65 to Table 70.

Table 64 Additional QUADAS-2 questions

Question	Domain	Difference with Wade 2013(30)
Were the comparator test results interpreted and recorded without knowledge of the adjunctive technology results?	Index /comparator test	New
Were additional biospsies taken on random sites or sites with no apparent anormality with colposcopy?	Flow and timing	New
Did all patients receive a reference standard?	Flow and timing	New
Any concerns about the size/power of the study?	Other concerns	New, replaced “Was a sample size calculation used?”
Did the index test manufacturer have any involvement in the design, conduct of the study and/or in the interpretation of the results?	Other concerns	New
Was it a multi-centre study, and were several colposcopists involved?	Other concerns	New

Table 65 Patient selection

Short Title	Was a consecutive or random sample of patients enrolled?	Was a case-control design avoided?	Did the study avoid inappropriate exclusions?	Risk: Could the selection of patients have introduced bias?	Is there concern that the included patients do not match the review question?
Budithi (unpublished)(42)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Coronado (2016)(47)	Yes	Yes	Yes 36 cases (8.1%) with DSI map not calculated due to excessive movement. No other exclusions	Low	High Low prevalence of hr-HPV, referred following Spanish guidelines*
Founta (unpublished)(51)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Louwers (2011)(57)	Yes	Yes	Yes Excluded current pregnancy and pregnancy in the last 3 months, previous cervix surgery or pelvic radiotherapy N	Low (ITT population	High Not HPV-primary, 66.1% hr-HPV positive

Natsis (2016)(74)	Unclear	Yes	Unclear	Unclear conference abstract of ongoing study	Low Relevant subgroup Low-grade cytology & hr-HPV, England
Roensbo (2015)(79)	Unclear NR	Yes	Unclear "Sufficient view of the cervix" was required, with no further details reported.	Unclear Unclear if consecutive patients were recruited and unclear definition of inclusion criterion	Unclear No data on hr-HPV prevalence or whether participants underwent hr-HPV screening/triage
Salter (2016)(80)	Unclear	Yes	Unclear	Unclear	Unclear No data on hr-HPV prevalence
Soutter (2009)(88)	Yes	Yes	Unclear Issues relating to the software, speculum and a batch of faulty disposable nozzles, leading to the exclusion of a large proportion of eligible participants (31%)	Unclear Unclear if there were systematic differences in relevant baseline characteristics between included and excluded participants	Unclear No data on hr-HPV prevalence and cytology results
Tidy (2013)(94)	No "non-consecutive"	Yes	Unclear	High non consecutive selection of patients, exclusion of women with active menstruation Predicted direction of bias: Favours index test (menstruation affects spectroscopy)	High non consecutive selection of patients

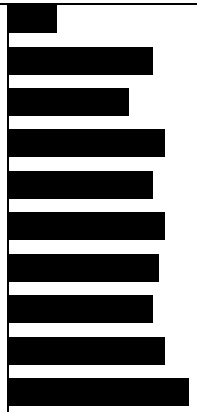
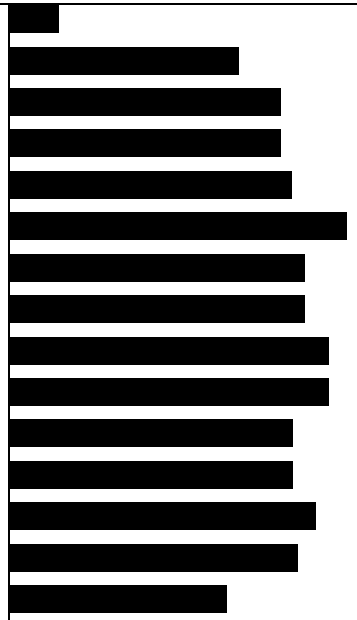
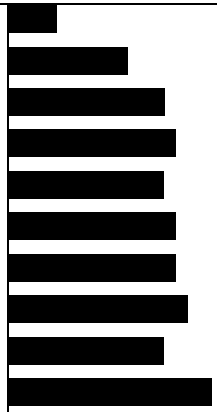
Tidy (forthcoming)(103)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tsetsa (2012)(112)	Unclear	Yes	Unclear	Unclear	Unclear

Table 66 Index and comparator tests- risk of bias

Study	Were the index test results interpreted without knowledge of the results of the reference standard?	Were the comparator test results interpreted and recorded without knowledge of the adjunctive technology results?	If a threshold was used, was it pre-specified?	Were the colposcopists undertaking the tests experienced in colposcopy?	Were the colposcopists undertaking the new technologies given training/experience in the new technology?	RISK Could the conduct or interpretation of the index test have introduced bias?	RISK Could the conduct or interpretation of the comparator test have introduced bias?
Budithi (unpublished)(42)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Coronado (2016)(47)	Yes	Unclear Performed before DYSIS map, but no reporting of measures to ensure the two	Yes	Yes	Unclear	Low	Unclear Unclear if colposcopy results were interpreted and recorded independently of

		were recorded independently.					knowledge of index test results
Founta (unpublished)(51)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Louwers (2011)(57)	Yes	Yes	Yes	Yes	Yes	Low	Low
Natsis (2016)(74)	Yes	No	Unclear	Unclear	Unclear	Unclear Insufficient information (conference abstract)	Unclear Insufficient information (conference abstract)
Roensbo (2015)(79)	Yes	No Clinicians were not blinded to DYSIS map results when performing colposcopy.	Unclear	Partly Almost 50% of colposcopies were performed by colposcopists with low experience (general practitioner residents), although one of two licensed and experienced	Unclear The DySIS colposcope had been in use in the outpatient clinic for 2 months before study initiation, but it is unclear whether all colposcopists had received sufficient	High 50% of colposcopies performed by colposcopists with low experience (although all supervised by experienced and licenced nurse). Unclear whether colposcopists were	High Colposcopists not blinded to DYSIS map results, low experience of colposcopists who performed almost 50% of colposcopies

				nurses supervised all examinations. Licensed and experienced nurses performed all other colposcopies.	training.	sufficiently trained with adjunctive technology.	
Salter (2016)(80)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear
Soutter (2009)(88)	Yes	Yes done independently by a separate blinded colposcopist	Yes specified following training on 82 patients, prior to starting test on actual study population. CB value of 553	Yes UK colposcopists all experienced & accredited by BSCCP. Colposcopists in Greek clinic were similarly experienced.	Unclear Unclear if all colposcopists were involved in the training group	Low	Low
Tidy (2013)(94)	Unclear (phase 2); no (phase 1):colposcopic impression and histological data used concurrently	Yes the colposcopist was blinded at all times to the EIS result to prevent bias #3544	No The cut-off points were further tested and refined in post-hoc analyses during phase 2"on pragmatic grounds".	Yes	Yes	High The cut-off points were further tested and refined in post-hoc analyses during phase 2"on pragmatic grounds".	Low The colposcopist was blinded at all times to the EIS result to prevent bias #3544

Tidy (forthcoming)(103)							
Tsetsa (2012)(112)	Unclear	Unclear	Unclear	Unclear	Unclear	Unclear Each patient was examined 3 times with three different concentrations of acetic acid (min 45 minutes between examinations). It is not clear whether colposcopists were blinded to the results of	Unclear

						examinations using different concentrations.	

Table 67 Index and comparator tests- applicability concerns

Study	Were relevant clinical data available to colposcopist during the examination (cytology/pap & HPV test results)?	Was the execution of the intervention technology as it would be in practice?	Was the execution of the comparator technology as it would be in practice?	Applicability concern: Is there concern that the INDEX test, its conduct, or interpretation differ from the review question?	Applicability concern: Is there concern that the COMPARATOR test, its conduct, or interpretation differ from the review question?
Budithi (unpublished)(42)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Coronado (2016)(47)	Yes	Yes	Yes	Low	Low
Founta (unpublished)(51)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Louwers (2011)(57)	Unclear Presumably yes	Yes	No Use of multiple/random biopsies in all patients	Low	High
Natsis (2016)(74)	Yes likely	Unclear	Unclear	Unclear Insufficient information (conference	Unclear Insufficient information (conference

				abstract of ongoing study)	abstract of ongoing study)
Roensbo (2015)(79)	Unclear	No DYSIS map not used as adjunct to colposcopy. Areas with weaker acetowhitening (dark blue & green on DYSISmap) were treated as ”suspicious for high grade disease”	No High number of biopsies performed (3 to 5 in all participants) and use of random biopsies.	High DYSIS map not used as adjunct to colposcopy. Areas with less acetowhitening on the DYSIS map treated as potential CIN2+	High Differs significantly from standard UK practice due to number of biopsies performed (3 to 5 in all participants) and use of random biopsies.
Salter (2016)(80)	Unclear	Unclear	Unclear	Unclear DySIS medical played a role in study conduct so use of index test likely to have been consistent with other trials, but information too sparse.	Unclear
Soutter (2009)(88)	Yes	No Pre-commercial prototype, with different DYSISmap algorithm	No Biopsies performed in all patients, including those with normal TZ colposcopy result	High Pre-commercial prototype, with different DYSISmap algorithm	High
Tidy (2013)(94)	Yes	No	Yes	High Prototype used with video display	Low

		Prototype version with [redacted] and with video display		and different cut-offs to Zedscan I	
Tidy (forthcoming)(103)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tsetsa (2012)(112)	Unclear	No Patients were examined three times using different concentrations of acetic acid	Unclear	High Patients were examined three times using different concentrations of acetic acid	High Patients were examined three times using different concentrations of acetic acid

Table 68 Reference standard

Short Title	Is the reference standard likely to correctly classify the target condition?	Were the reference standard results interpreted without	RISK Could the reference standard, its conduct, or its	Was the execution of the reference standard as it would	CONCERN Is there concern that the target condition as defined by the reference

		knowledge of the results of the index test?	**interpretation have introduced bias?**	**be in practice (e.g. performed by experienced pathologists)?**	**standard does not match the review question?**
Budithi (unpublished)(42)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Coronado (2016)(47)	No*	Unclear	High*	Yes	Low
Founta (unpublished)(51)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Louwers (2011)(57)	No*	Yes All histology independently reviewed by a specialist pathologist. In case of disagreement between original assessment and review a third expert reviewer graded the lesion (19.0% of all tissue samples), blinded to all previous results, and the majority	High*	Yes	Low

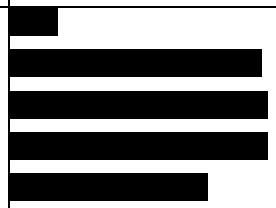
		decision dertermined the diagnosis.			
Natsis (2016)(74)	No*	Unclear	High*	Unclear	Unclear Insufficient information (conference abstract of ongoing study)
Roensbo (2015)(79)	No*	Unclear	High*	Yes	Low
Salter (2016)(80)	No*	Unclear	High*	Unclear	Unclear
Soutter (2009)(88)	No*	Yes "Histopathologists were unaware of the DySIS result and the histopathology reports of the other pathologists."	High*	Yes	Low
Tidy (2013)(94)	No*	Unclear	High*	Yes	Low

Tidy (forthcoming)(103)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Tsetsa (2012)(112)	No*	Unclear	High*	Unclear	Unclear

* Histology mostly based on biopsies, which have limited accuracy. The direction of bias is unclear.

Table 69 Flow and timing

Short Title	**Was there an appropriate interval between index test(s) and reference standard?**	**Did all patients receive a reference standard?**	**Did the patients who received a ref. standard all receive the same ref. standard? (e.g. histology based on punch biopsy vs. LLETZ)**	**Were additional biospsies taken on random sites or seemingly normal sites?**	**Were all patients included in the analysis?**	**RISK Could the patient flow have introduced bias?**
Budithi (unpublished)(42)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]

						
Coronado (2016)(47)	Yes	No	No An endocervical curettage was performed when the transformation zone was type 3. A LEEP was performed on all CIN2+ cases diagnosed by a punch biopsy, on all women referred with a HSIL Pap that had transformation zone type 3 and on all cases of biopsy-confirmed CIN1 that was persistent for more than 2 years.	No	No 8.1% excluded. Reasons for exclusion appeared appropriate	High High risk of verification bias due to absence of biopsy for lower risk patients. May positively bias sensitivity estimates.
Founta (unpublished)(51)						
Louwers (2011)(57)	Yes	Yes	No All histology, mostly	Yes One additional control biopsy of	No 9.5% excluded. Reasons for	Low

			through biopsy (89%), others via LLETZ	apparently normal cervical tissue on the opposite side of abnormal looking lesion(s), or 1 biopsy at 12 o'clock if both colposcopy and DYSIS found no abnormal sites	exclusion appeared appropriate	
Natsis (2016)(74)	Unclear	No 80.8% in DYSIS group, 85.9% in control group.	Unclear Unclear how many, if any, underwent LLETZ	Unclear unlikely (not UK practice)	Unclear insufficient information	High Risk of verification bias
Roensbo (2015)(79)	Yes	Yes	Yes	Yes Biopsies taken according to cliniciansjudgement/randomly. All participants received between three and five biopsies.	No 9.8% excluded. Reasons for exclusion appeared appropriate	High Exclusion of significant proportion of enrolled participants
Salter (2016)(80)	Unclear	No	Unclear	No	Unclear	Unclear
Soutter (2009)(88)	Yes	Yes	No most from punch biopsies, others from treatment and	Yes All received biopsies. Random biopsies taken from 115 sites thought by the colposcopist to be normal, metaplasia, or	No. 31% excluded. Main reasons: unsatisfactory view (10%) problem with acetic acid-faulty nozzles (8.3%)	High High proportion of patients were included, although it is unclear whether there were any systematic differences

			follow-up biopsies	human papillomavirus infection or with CB values less than 500, and 101 treatment or follow-up biopsies. The sensitivities of colposcopy and DySIS were 48.6% and 79.2%, respectively. If the cases of high-grade disease detected by biopsies taken to limit verification bias were excluded, the sensitivities would have seemed to be 55.6% and 83.8%, respectively.		in baseline characteristics between patients included and excluded from the analyses
Tidy (2013)(94)	Yes	No "biopsies taken as clinically indicated"	No	No	No Twelve women were excluded in phase 2: nine had incomplete clinical data, one did not meet the inclusion criteria, one was unable to complete the colposcopic examination and one was excluded because of a protocol violation. In five cases the device exhibited technical problems that prevented the collection of EIS data. Additionally, 110/7706 (1.4%) recorded measurements were unacceptable when the spectra were visually reviewed.	High risk of verification bias: biopsies only performed in patients with suspected abnormalities based on examination

Tidy (forthcoming)(103)						
Tsetsa (2012)(112)	Unclear	Unclear	Unclear Potentially no - loop excisions and punch biopsies were taken.	No	No	Unclear

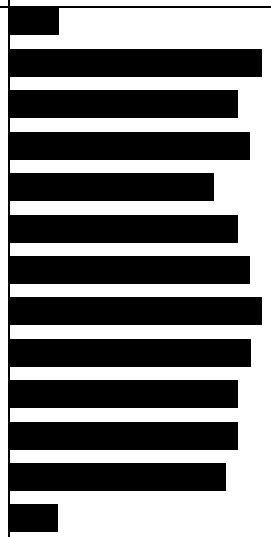
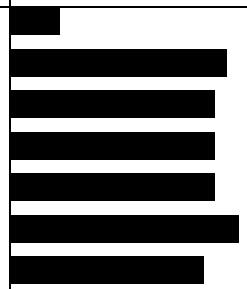
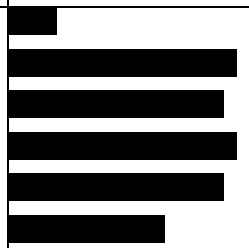
Table 70 Additional issues and overall quality

Study	Were the data analysed by lesion, patient or both?	Were results for all pre-specified outcomes reported?	Did the index test manufacturer have any involvement in the design, conduct of the study and/or in the interpretation of the results?	Any concerns about the size/power of the study?	Was it a multi-centre study, and were several colposcopists involved?	Overall quality
Budithi (unpublished)(42)						

						[redacted]
Coronado (2016)(47)	Patient	Unclear no protocol found	UNo	No	No One centre, one colposcopist	Unsound High risk of verification bias (no biopsy for all participants), limited applicability (population and single centre/colposcopist)
Founta (unpublished)(51)	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
Louwers (2011)(57)	Patient	Unclear No protocol found Sensitivity & specificity, n and reasons for exclusions all reported	Yes Role in the study design and critically appraised the manuscript	No	Yes	Sound
Natsis (2016)(74)	Patient	Unclear no protocol found	Yes	No	Yes	Unsound Ongoing study, conference abstract, with significant proportion of patients (18.6%) who did not

						receive a biopsy.
Roensbo (2015)(79)	Patient	Unclear no protocol found	No	No	No Single centre, multiple colposcopists with variable levels of experience	Unsound 1) almost 50% of colposcopies performed by colposcopists with low experience (although supervised by experienced nurses) 2) lack of blinding of colposcopists to initial DYSIS map results 3) exclusion of 17% of participants following enrollment, including due to protocol failures
Salter (2016)(80)	Patient	Yes	Yes Specific role unclear	No	Yes	Unsound Conference abstract of ongoing study, limited data on diagnostic accuracy (full diagnostic accuracy data only reported for a small subgroup of 2 colposcopy clinics).

Soutter (2009)(88)	Patient	Unclear protocol not found	Yes Contributed to the study design and the writing of the report. The collection and collation of the data were supervised by the principal investigator and corresponding author. The analysis of data was undertaken by the principal investigator. Corresponding author is a member of the speakers bureau of Forth Photonics (manufacturer). Principal investigator has an ownership interest in Forth Photonics	No	Yes	Unsound due exclusion of large proportion of participants (31%). Significant applicability concerns (FPC-03 prototype used)
Tidy (2013)(94)	Patient	Unclear no protocol found	Yes 1st and 2nd authors hold patents related to the technology. They are shareholders in Zilico Ltd and receive consultancy fees. Another author is also a shareholder. A 4th author is	No	Yes	Unsound High risk of verification bias, selection bias, significant concerns about applicability (patient selection and use of pre-commercial prototype)

			a medical advisor to Zilico Ltd and receives consultancy fees.			
Tidy (forthcoming)(103)						
Tsetsa (2012)(112)	Patient	Unclear no protocol found	Yes No formal declaration, though E. Papagiannakis is an employee of DySIS Medical.	Yes small study (n=54)	No	Unsound Conference abstract, small study with little information available

10.8 Quality assessment of implementation studies

Table 71 Budithi (2016): quality assessment

	Yes	No	Can't tell
Was the objective clearly stated?	x		
Was the setting clearly described?	x		
Were the methods described clearly enough to permit other researchers to duplicate the study?	x		
Was the survey sample likely to be representative of the population to which the findings are referred?	x		
Was the questionnaire described adequately?	x		
Have the validity and reliability of the questionnaire been established?		x	
Was the sample size based on pre-study considerations of statistical power?		x	
Was statistical significance assessed appropriately?		x	
Were all relevant confounding factors adjusted/accounted for?		x	
Did the results address the objective?	x		
Was a satisfactory response rate achieved?			x
Were the results clearly and logically presented?	x		
Were the tables and figures appropriate?	x		
Were the numbers consistent in the text and the tables?		x*	
Were confidence intervals given for the main results?		x	

* Multiple small discrepancies

Table 72 Coronado (2014): quality assessment

	Yes	No	Can't tell
Was the objective clearly stated?	x		
Was the setting clearly described?	x		
Were the methods described clearly enough to permit other researchers to duplicate the study?	x		
Was the survey sample likely to be representative of the population to which the findings are referred?			x*
Was the questionnaire described adequately?	x		
Have the validity and reliability of the questionnaire been established?		x[#]	
Was the sample size based on pre-study considerations of statistical power?		x	
Was statistical significance assessed appropriately?	x		
Were all relevant confounding factors adjusted/accounted for?	x[±]		
Did the results address the objective?	x		
Was a satisfactory response rate achieved?	x		
Were the results clearly and logically presented?	x		
Were the tables and figures appropriate?	x		
Were the numbers consistent in the text and the tables?	x		

Were confidence intervals given for the main results?	x		

*Colposcopists from a single centre; # only internal consistency was assessed, which was high (Cronbach's α= 0.9691); ± colposcopist experience accounted for

Table 73 Louwers (2015): quality assessment

	Yes	**No**	**Can't tell**
Was the objective clearly stated?	x		
Was the setting clearly described?	x		
Were the methods described clearly enough to permit other researchers to duplicate the study?	x		
Was the survey sample likely to be representative of the population to which the findings are referred?	x		
Was the questionnaire described adequately?	x		
Have the validity and reliability of the questionnaire been established?		x	
Was the sample size based on pre-study considerations of statistical power?		x	
Was statistical significance assessed?		x	
Were all relevant confounding factors adjusted/accounted for?	x*		
Were the statistical methods used appropriately?	x		
Did the results address the objective?	x		
Was a satisfactory response rate achieved?	x		

Were the results clearly and logically presented?	x		
Were the tables and figures appropriate?	x		
Were the numbers consistent in the text and the tables?	x		
Were confidence intervals given for the main results?		x	

*age, education, number of pregnancies and sexual behaviour

Table 74 Lowe (2016): quality assessment

	Yes	**No**	**Can't tell**
Was the objective clearly stated?	x		
Was the setting clearly described?	x		
Were the methods described clearly enough to permit other researchers to duplicate the study?	x		
Was the survey sample likely to be representative of the population to which the findings are referred?			x
Was the questionnaire described adequately?	x		
Have the validity and reliability of the questionnaire been established?		x	
Was the sample size based on pre-study considerations of statistical power?		x	
Was statistical significance assessed?		x	
Were all relevant confounding factors adjusted/accounted for?		x	
Were the statistical methods used appropriately?		x	

Did the results address the objective?	x		
Was a satisfactory response rate achieved?			x
Were the results clearly and logically presented?	x		
Were the tables and figures appropriate?	x		
Were the numbers consistent in the text and the tables?	x		
Were confidence intervals given for the main results?		x	

10.9 Quality assessment of cost-effectiveness studies

Table 75 Quality assessment of studies included in the economic review using the checklist of Drummond and Jefferson (1996)

Criteria	Wade, 2013 (30)	Whyte, 2013 (128)
The research question is stated	Y	Y
The economic importance of the research question is stated	Y	Y
The viewpoint(s) of the analysis are clearly stated and justified	Y	Y
The rationale for choosing alternative programmes or interventions compared is stated	Y	Partial
The alternatives being compared are clearly described	Y	Y
The form of economic evaluation used is stated	Y	Y
The choice of form of economic evaluation is justified in relation to the question addressed	Y	N
The source(s) of effectiveness estimates used are stated	Y	Y
Details of the design and results of the effectiveness study are given (if based on a single study)	Partial	Partial

Criteria	Wade, 2013 (30)	Whyte, 2013 (128)
Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies)	NA	NA
The primary outcome measure(s) for the economic evaluation are clearly stated	Y	Y
Methods to value benefits are stated	Y	Y
Details of the subjects from whom valuations were obtained are given	N	N
Productivity changes (if included) are reported separately	NA	NA
The relevance of productivity changes to the study question is discussed	NA	NA
Quantities of resource use are reported separately from their unit costs	Y	Y
Methods for the estimation of quantities and unit costs are described	Y	Y
Currency and price date are recorded	Y	N
Details of currency of price adjustments for inflation or currency conversion are given	Y	N
Details of any model used are given	Y	Y
The choice of model used and the key parameters on which it is based are justified	Y	Y
Time horizon of costs and benefits is stated	Y	Y
The discount rate(s) are stated	Y	Y
The choice of discount rate(s) is justified	Y	Y

10.10 Sensitivity and scenario analyses results

10.10.1 SA1: Diagnostic accuracy from Louwers (2011) for colposcopy and DYSIS

Table 76 SA1, HPV triage – DYSIS vs. colposcopy alone

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	Colposcopy alone	916.73	19.16145			
	DYSIS	880.39	19.18359	-36.35	0.02214	Dominant
LG referrals	Colposcopy alone	806.20	19.15627			
	DYSIS	778.57	19.18554	-27.63	0.02928	Dominant
HG referrals	Colposcopy alone	1155.24	19.15946			
	DYSIS	1099.83	19.17080	-55.41	0.01134	Dominant
Watchful Waiting clinics						
All referrals	Colposcopy alone	964.91	19.15709			
	DYSIS	949.98	19.17972	-14.93	0.02263	Dominant
LG referrals	Colposcopy alone	826.11	19.15563			
	DYSIS	809.60	19.18314	-16.51	0.02751	Dominant
HG referrals	Colposcopy alone	1257.65	19.15866			
	DYSIS	1259.59	19.16660	1.94	0.00794	245

Table 77 SA1, HPV primary – DYSIS vs. colposcopy alone

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	Colposcopy alone	864.77	19.17079			
	DYSIS	832.84	19.18872	-31.93	0.01794	Dominant
LG referrals	Colposcopy alone	746.32	19.18168			
	DYSIS	722.98	19.20610	-23.34	0.02442	Dominant
HG referrals	Colposcopy alone	1144.79	19.16330			
	DYSIS	1087.97	19.16779	-56.81	0.00448	Dominant
Watchful Waiting clinics						
All referrals	Colposcopy alone	906.82	19.17033			
	DYSIS	897.72	19.18658	-9.10	0.01625	Dominant
LG referrals	Colposcopy alone	764.55	19.17674			
	DYSIS	748.24	19.20428	-16.31	0.02754	Dominant
HG referrals	Colposcopy alone	1243.12	19.15871			
	DYSIS	1246.03	19.16275	2.92	0.00404	722

10.10.2 SA2: Additional data from Louwers (2011) for colposcopy and DYSIS

Table 78 SA2, HPV triage – DYSIS vs. colposcopy alone

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	Colposcopy alone	915.59	19.16400			
	DYSIS	877.11	19.18527	-38.47	0.02126	Dominant
LG referrals	Colposcopy alone	803.82	19.15971			
	DYSIS	775.53	19.18647	-28.30	0.02676	Dominant
HG referrals	Colposcopy alone	1158.06	19.16338			
	DYSIS	1095.93	19.17186	-62.14	0.00848	Dominant
Watchful Waiting clinics						
All referrals	Colposcopy alone	961.66	19.16057			
	DYSIS	948.72	19.18188	-12.94	0.02131	Dominant
LG referrals	Colposcopy alone	823.01	19.16003			
	DYSIS	808.43	19.18335	-14.59	0.02332	Dominant
HG referrals	Colposcopy alone	1255.99	19.16118			
	DYSIS	1256.93	19.16619	0.94	0.00501	188

Table 79 SA2, HPV primary– DYSIS vs. colposcopy alone

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	Colposcopy alone	862.25	19.17320			
	DYSIS	829.31	19.19171	-32.94	0.01850	Dominant
LG referrals	Colposcopy alone	741.00	19.18583			
	DYSIS	720.31	19.20695	-20.69	0.02112	Dominant
HG referrals	Colposcopy alone	1146.90	19.16260			
	DYSIS	1083.95	19.16881	-62.95	0.00621	Dominant
Watchful Waiting clinics						
All referrals	Colposcopy alone	901.92	19.17230			
	DYSIS	895.97	19.18840	-5.95	0.01609	Dominant
LG referrals	Colposcopy alone	759.00	19.18034			
	DYSIS	746.69	19.20509	-12.31	0.02475	Dominant
HG referrals	Colposcopy alone	1240.88	19.16197			
	DYSIS	1244.50	19.16419	3.62	0.00222	1633

10.10.3 SA3: Diagnostic accuracy from Tidy (2013) for colposcopy

Table 80 SA3, HPV triage – ZedScan vs. colposcopy alone

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	Colposcopy alone	873.87	19.17860			
	ZedScan	885.91	19.19901	12.04	0.02041	590
LG referrals	Colposcopy alone	768.32	19.17826			
	ZedScan	789.30	19.20307	20.98	0.02482	845
HG referrals	Colposcopy alone	1101.18	19.16626			
	ZedScan	1091.97	19.17651	-9.22	0.01024	Dominant
Watchful Waiting clinics						
All referrals	Colposcopy alone	933.64	19.17676			
	ZedScan	965.87	19.19363	32.23	0.01687	1910
LG referrals	Colposcopy alone	790.35	19.17872			
	ZedScan	823.19	19.20082	32.85	0.02210	1486
HG referrals	Colposcopy alone	1243.40	19.16514			
	ZedScan	1288.82	19.16911	45.42	0.00397	11,448

Table 81 SA3, HPV primary – ZedScan vs. colposcopy alone

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	Colposcopy alone	822.80	19.18722			
	ZedScan	844.41	19.20206	21.61	0.01483	1457
LG referrals	Colposcopy alone	708.37	19.20451			
	ZedScan	744.85	19.22007	36.49	0.01557	2344
HG referrals	Colposcopy alone	1088.46	19.16641			
	ZedScan	1082.27	19.17347	-6.19	0.00707	Dominant
Watchful Waiting clinics						
All referrals	Colposcopy alone	876.13	19.18917			
	ZedScan	918.78	19.19977	42.65	0.01060	4023
LG referrals	Colposcopy alone	726.69	19.19959			
	ZedScan	770.26	19.21984	43.57	0.02025	2152
HG referrals	Colposcopy alone	1228.18	19.16472			
	ZedScan	1276.58	19.16668	48.39	0.00196	24,686

10.10.4 SA4.1 DYSIS: lower bound specificity (2.5%) and correlated sensitivity

Table 82 SA4.1, HPV triage – DYSIS vs. colposcopy alone

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	Colposcopy alone	903.55	19.16672			
	DYSIS	873.06	19.18922	-30.48	0.02250	Dominant
LG referrals	Colposcopy alone	793.82	19.16515			
	DYSIS	771.78	19.19215	-22.03	0.02700	Dominant
HG referrals	Colposcopy alone	1139.70	19.16221			
	DYSIS	1087.56	19.17411	-52.13	0.01190	Dominant
Watchful Waiting clinics						
All referrals	Colposcopy alone	953.16	19.16161			
	DYSIS	946.17	19.18190	-6.98	0.02029	Dominant
LG referrals	Colposcopy alone	812.81	19.16406			
	DYSIS	804.49	19.18743	-8.33	0.02337	Dominant
HG referrals	Colposcopy alone	1252.23	19.16011			
	DYSIS	1258.67	19.16576	6.44	0.00565	1140

Table 83 SA4.1, HPV primary– DYSIS vs. colposcopy alone

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	Colposcopy alone	850.17	19.17452			
	DYSIS	825.20	19.19201	-24.97	0.01749	Dominant
LG referrals	Colposcopy alone	731.84	19.18497			
	DYSIS	718.51	19.20383	-13.33	0.01885	Dominant
HG referrals	Colposcopy alone	1126.46	19.16164			
	DYSIS	1075.05	19.16989	-51.41	0.00825	Dominant
Watchful Waiting clinics						
All referrals	Colposcopy alone	894.53	19.17496			
	DYSIS	894.58	19.19188	0.05	0.01692	3
LG referrals	Colposcopy alone	748.21	19.18388			
	DYSIS	744.58	19.20499	-3.63	0.02112	Dominant
HG referrals	Colposcopy alone	1237.65	19.15840			
	DYSIS	1245.44	19.16424	7.79	0.00584	1334

10.10.5 SA4.2 DYSIS: upper bound specificity (97.5%) and correlated sensitivity

Table 84 SA4.2, HPV triage – DYSIS vs. colposcopy alone

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	Colposcopy alone	902.94	19.16637			
	DYSIS	874.62	19.18261	-28.33	0.01624	Dominant
LG referrals	Colposcopy alone	794.28	19.16183			
	DYSIS	771.24	19.18206	-23.04	0.02023	Dominant
HG referrals	Colposcopy alone	1139.09	19.16116			
	DYSIS	1099.15	19.16860	-39.94	0.00744	Dominant
Watchful Waiting clinics						
All referrals	Colposcopy alone	952.89	19.16303			
	DYSIS	940.43	19.18000	-12.46	0.01696	Dominant
LG referrals	Colposcopy alone	812.37	19.16024			
	DYSIS	794.50	19.18385	-17.87	0.02360	Dominant
HG referrals	Colposcopy alone	1251.78	19.15972			
	DYSIS	1256.10	19.16660	4.32	0.00688	628

Table 85 SA4.2, HPV primary – DYSIS vs. colposcopy alone

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	Colposcopy alone	849.66	19.17576			
	DYSIS	826.70	19.18872	-22.96	0.01296	Dominant
LG referrals	Colposcopy alone	733.04	19.19014			
	DYSIS	715.06	19.20599	-17.98	0.01585	Dominant
HG referrals	Colposcopy alone	1126.83	19.16170			
	DYSIS	1087.79	19.16707	-39.04	0.00537	Dominant
Watchful Waiting clinics						
All referrals	Colposcopy alone	894.39	19.17731			
	DYSIS	887.97	19.19055	-6.42	0.01323	Dominant
LG referrals	Colposcopy alone	748.25	19.18760			
	DYSIS	733.48	19.20442	-14.77	0.01681	Dominant
HG referrals	Colposcopy alone	1237.22	19.16004			
	DYSIS	1241.84	19.16457	4.62	0.00453	1021

10.10.6 SA4.3 ZedScan: lower bound specificity (2.5%) and upper bound sensitivity (97.5%)

Table 86 SA4.3, HPV triage – ZedScan vs. colposcopy alone

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	Colposcopy alone	903.55	19.16672			
	ZedScan	885.01	19.20070	-18.54	0.03398	Dominant
LG referrals	Colposcopy alone	793.82	19.16515			
	ZedScan	788.41	19.20559	-5.40	0.04044	Dominant
HG referrals	Colposcopy alone	1139.70	19.16221			
	ZedScan	1089.75	19.17831	-49.95	0.01611	Dominant
Watchful Waiting clinics						
All referrals	Colposcopy alone	953.16	19.16161			
	ZedScan	967.10	19.19443	13.94	0.03282	425
LG referrals	Colposcopy alone	812.81	19.16406			
	ZedScan	822.94	19.20219	10.12	0.03814	265
HG referrals	Colposcopy alone	1252.23	19.16011			
	ZedScan	1289.12	19.16965	36.88	0.00954	3865

Table 87 SA4.3, HPV primary – ZedScan vs. colposcopy alone

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	Colposcopy alone	850.17	19.17452			
	ZedScan	843.97	19.20515	-6.20	0.03063	Dominant
LG referrals	Colposcopy alone	731.84	19.18497			
	ZedScan	745.03	19.21610	13.19	0.03112	424
HG referrals	Colposcopy alone	1126.46	19.16164			
	ZedScan	1079.65	19.17438	-46.81	0.01274	Dominant
Watchful Waiting clinics						
All referrals	Colposcopy alone	894.53	19.17496			
	ZedScan	920.70	19.20378	26.17	0.02881	908
LG referrals	Colposcopy alone	748.21	19.18388			
	ZedScan	770.96	19.21819	22.74	0.03431	663
HG referrals	Colposcopy alone	1237.65	19.15840			
	ZedScan	1278.66	19.16758	41.00	0.00918	4466

10.10.7 SA4.4 ZedScan: upper bound specificity (97.5%) and lower bound sensitivity (2.5%)

Table 88 SA4.4, HPV triage – ZedScan vs. colposcopy alone

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	Colposcopy alone	902.94	19.16637			
	ZedScan	886.84	19.19761	-16.10	0.03124	Dominant
LG referrals	Colposcopy alone	794.28	19.16183			
	ZedScan	788.79	19.20177	-5.49	0.03994	Dominant
HG referrals	Colposcopy alone	1139.09	19.16116			
	ZedScan	1095.33	19.17545	-43.76	0.01429	Dominant
Watchful Waiting clinics						
All referrals	Colposcopy alone	952.89	19.16303			
	ZedScan	966.94	19.19209	14.05	0.02906	484
LG referrals	Colposcopy alone	812.37	19.16024			
	ZedScan	822.06	19.19885	9.70	0.03861	251
HG referrals	Colposcopy alone	1251.78	19.15972			
	ZedScan	1289.24	19.16956	37.46	0.00984	3805

Table 89 SA4.4, HPV primary – ZedScan vs. colposcopy alone

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	Colposcopy alone	849.66	19.17576			
	ZedScan	844.47	19.20290	-5.20	0.02714	Dominant
LG referrals	Colposcopy alone	733.04	19.19014			
	ZedScan	745.03	19.21860	11.99	0.02846	421
HG referrals	Colposcopy alone	1126.83	19.16170			
	ZedScan	1085.86	19.17054	-40.97	0.00884	Dominant
Watchful Waiting clinics						
All referrals	Colposcopy alone	894.39	19.17731			
	ZedScan	918.89	19.20128	24.50	0.02396	1022
LG referrals	Colposcopy alone	748.25	19.18760			
	ZedScan	768.47	19.22001	20.22	0.03241	624
HG referrals	Colposcopy alone	1237.22	19.16004			
	ZedScan	1277.83	19.16834	40.61	0.00830	4891

10.10.8 SA5.1: Number of patients per colposcope per year: -50% compared to base case

Table 90 SA5.1, HPV triage – DYSIS vs. colposcopy alone

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	Colposcopy alone	903.28	19.16500			
	DYSIS	879.49	19.18516	-23.79	0.02016	Dominant
LG referrals	Colposcopy alone	793.97	19.16330			
	DYSIS	777.71	19.18794	-16.26	0.02464	Dominant
HG referrals	Colposcopy alone	1139.13	19.16122			
	DYSIS	1098.77	19.17156	-40.36	0.01034	Dominant
Watchful Waiting clinics						
All referrals	Colposcopy alone	953.02	19.16286			
	DYSIS	949.78	19.18194	-3.24	0.01908	Dominant
LG referrals	Colposcopy alone	812.85	19.16283			
	DYSIS	806.96	19.18601	-5.89	0.02318	Dominant
HG referrals	Colposcopy alone	1252.07	19.16008			
	DYSIS	1266.47	19.16580	14.40	0.00571	2521

Table 91 SA5.1, HPV triage – ZedScan vs. colposcopy alone

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	Colposcopy alone	903.28	19.16500			
	ZedScan	886.72	19.19901	-16.56	0.03401	Dominant
LG referrals	Colposcopy alone	793.97	19.16330			
	ZedScan	790.09	19.20307	-3.88	0.03978	Dominant
HG referrals	Colposcopy alone	1139.13	19.16122			
	ZedScan	1092.79	19.17651	-46.34	0.01529	Dominant
Watchful Waiting clinics						
All referrals	Colposcopy alone	953.02	19.16286			
	ZedScan	966.69	19.19363	13.68	0.03078	444
LG referrals	Colposcopy alone	812.85	19.16283			
	ZedScan	824.01	19.20082	11.16	0.03799	294
HG referrals	Colposcopy alone	1252.07	19.16008			
	ZedScan	1289.67	19.16911	37.60	0.00903	4164

Table 92 SA5.1, HPV triage - ZedScan vs. DYSIS

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	DYSIS	879.49	19.18516			
	ZedScan	886.72	19.19901	7.22	0.01385	522
LG referrals	DYSIS	777.71	19.18794			
	ZedScan	790.09	19.20307	12.38	0.01514	818
HG referrals	DYSIS	1098.77	19.17156			
	ZedScan	1092.79	19.17651	-5.99	0.00495	Dominant
Watchful Waiting clinics						
All referrals	DYSIS	949.78	19.18194			
	ZedScan	966.69	19.19363	16.91	0.01170	1446
LG referrals	DYSIS	806.96	19.18601			
	ZedScan	824.01	19.20082	17.05	0.01481	1151
HG referrals	DYSIS	1266.47	19.16580			
	ZedScan	1289.67	19.16911	23.19	0.00332	6994

Table 93 SA5.1, HPV primary - DYSIS vs. colposcopy alone

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	Colposcopy alone	850.08	19.17506			
	DYSIS	833.46	19.19120	-16.62	0.01614	Dominant
LG referrals	Colposcopy alone	732.33	19.19008			
	DYSIS	723.49	19.20787	-8.85	0.01779	Dominant
HG referrals	Colposcopy alone	1126.93	19.16192			
	DYSIS	1087.72	19.16774	-39.22	0.00581	Dominant
Watchful Waiting clinics						
All referrals	Colposcopy alone	894.41	19.17511			
	DYSIS	898.26	19.18937	3.85	0.01426	270
LG referrals	Colposcopy alone	748.86	19.18496			
	DYSIS	746.49	19.20646	-2.37	0.02150	Dominant
HG referrals	Colposcopy alone	1236.94	19.15863			
	DYSIS	1252.13	19.16234	15.19	0.00371	4097

Table 94 SA5.1, HPV primary - ZedScan vs. colposcopy alone

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	Colposcopy alone	850.08	19.17506			
	ZedScan	845.31	19.20206	-4.77	0.02700	Dominant
LG referrals	Colposcopy alone	732.33	19.19008			
	ZedScan	745.76	19.22007	13.43	0.03000	448
HG referrals	Colposcopy alone	1126.93	19.16192			
	ZedScan	1083.15	19.17347	-43.78	0.01155	Dominant
Watchful Waiting clinics						
All referrals	Colposcopy alone	894.41	19.17511			
	ZedScan	919.71	19.19977	25.30	0.02466	1026
LG referrals	Colposcopy alone	748.86	19.18496			
	ZedScan	771.19	19.21984	22.33	0.03487	640
HG referrals	Colposcopy alone	1236.94	19.15863			
	ZedScan	1277.49	19.16668	40.56	0.00805	5036

Table 95 SA5.1, HPV primary - ZedScan vs. DYSIS

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	DYSIS	833.46	19.19120			
	ZedScan	845.31	19.20206	11.85	0.01085	1092
LG referrals	DYSIS	723.49	19.20787			
	ZedScan	745.76	19.22007	22.28	0.01220	1825
HG referrals	DYSIS	1087.72	19.16774			
	ZedScan	1083.15	19.17347	-4.56	0.00574	Dominant
Watchful Waiting clinics						
All referrals	DYSIS	898.26	19.18937			
	ZedScan	919.71	19.19977	21.45	0.01040	2063
LG referrals	DYSIS	746.49	19.20646			
	ZedScan	771.19	19.21984	24.70	0.01338	1846
HG referrals	DYSIS	1252.13	19.16234			
	ZedScan	1277.49	19.16668	25.36	0.00434	5838

10.10.9 SA5.2: Number of patients per colposcope per year: +50% compared to base case

Table 96 SA5.2, HPV triage – DYSIS vs. colposcopy alone

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	Colposcopy alone	903.28	19.16500			
	DYSIS	869.96	19.18516	-33.32	0.02016	Dominant
LG referrals	Colposcopy alone	793.97	19.16330			
	DYSIS	768.29	19.18794	-25.68	0.02464	Dominant
HG referrals	Colposcopy alone	1139.13	19.16122			
	DYSIS	1088.98	19.17156	-50.15	0.01034	Dominant
Watchful Waiting clinics						
All referrals	Colposcopy alone	953.02	19.16286			
	DYSIS	938.51	19.18194	-14.50	0.01908	Dominant
LG referrals	Colposcopy alone	812.85	19.16283			
	DYSIS	796.97	19.18601	-15.87	0.02318	Dominant
HG referrals	Colposcopy alone	1252.07	19.16008			
	DYSIS	1252.41	19.16580	0.34	0.00571	59

Table 97 SA5.2, HPV triage – ZedScan vs. colposcopy alone

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	Colposcopy alone	903.28	19.16500			
	ZedScan	885.66	19.19901	-17.63	0.03401	Dominant
LG referrals	Colposcopy alone	793.97	19.16330			
	ZedScan	789.04	19.20307	-4.93	0.03978	Dominant
HG referrals	Colposcopy alone	1139.13	19.16122			
	ZedScan	1091.71	19.17651	-47.42	0.01529	Dominant
Watchful Waiting clinics						
All referrals	Colposcopy alone	953.02	19.16286			
	ZedScan	965.60	19.19363	12.59	0.03078	409
LG referrals	Colposcopy alone	812.85	19.16283			
	ZedScan	822.93	19.20082	10.08	0.03799	265
HG referrals	Colposcopy alone	1252.07	19.16008			
	ZedScan	1288.55	19.16911	36.47	0.00903	4040

Table 98 SA5.2, HPV triage - ZedScan vs DYSIS

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	DYSIS	869.96	19.18516			
	ZedScan	885.66	19.19901	15.70	0.01385	1134
LG referrals	DYSIS	768.29	19.18794			
	ZedScan	789.04	19.20307	20.75	0.01514	1371
HG referrals	DYSIS	1088.98	19.17156			
	ZedScan	1091.71	19.17651	2.72	0.00495	550
Watchful Waiting clinics						
All referrals	DYSIS	938.51	19.18194			
	ZedScan	965.60	19.19363	27.09	0.01170	2316
LG referrals	DYSIS	796.97	19.18601			
	ZedScan	822.93	19.20082	25.96	0.01481	1752
HG referrals	DYSIS	1252.41	19.16580			
	ZedScan	1288.55	19.16911	36.13	0.00332	10,896

Table 99 SA5.2, HPV primary - DYSIS vs. colposcopy alone

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	Colposcopy alone	850.08	19.17506			
	DYSIS	822.80	19.19120	-27.28	0.01614	Dominant
LG referrals	Colposcopy alone	732.33	19.19008			
	DYSIS	712.78	19.20787	-19.55	0.01779	Dominant
HG referrals	Colposcopy alone	1126.93	19.16192			
	DYSIS	1077.20	19.16774	-49.74	0.00581	Dominant
Watchful Waiting clinics						
All referrals	Colposcopy alone	894.41	19.17511			
	DYSIS	885.97	19.18937	-8.44	0.01426	Dominant
LG referrals	Colposcopy alone	748.86	19.18496			
	DYSIS	735.30	19.20646	-13.56	0.02150	Dominant
HG referrals	Colposcopy alone	1236.94	19.15863			
	DYSIS	1237.28	19.16234	0.35	0.00371	94

Table 100 SA5.2, HPV primary - ZedScan vs. colposcopy alone

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	Colposcopy alone	850.08	19.17506			
	ZedScan	844.12	19.20206	-5.96	0.02700	Dominant
LG referrals	Colposcopy alone	732.33	19.19008			
	ZedScan	744.56	19.22007	12.23	0.03000	408
HG referrals	Colposcopy alone	1126.93	19.16192			
	ZedScan	1081.99	19.17347	-44.94	0.01155	Dominant
Watchful Waiting clinics						
All referrals	Colposcopy alone	894.41	19.17511			
	ZedScan	918.48	19.19977	24.07	0.02466	976
LG referrals	Colposcopy alone	748.86	19.18496			
	ZedScan	769.96	19.21984	21.10	0.03487	605
HG referrals	Colposcopy alone	1236.94	19.15863			
	ZedScan	1276.28	19.16668	39.35	0.00805	4886

Table 101 SA5.2, HPV primary - ZedScan vs. DYSIS

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	DYSIS	822.80	19.19120			
	ZedScan	844.12	19.20206	21.33	0.01085	1965
LG referrals	DYSIS	712.78	19.20787			
	ZedScan	744.56	19.22007	31.78	0.01220	2604
HG referrals	DYSIS	1077.20	19.16774			
	ZedScan	1081.99	19.17347	4.79	0.00574	835
Watchful Waiting clinics						
All referrals	DYSIS	885.97	19.18937			
	ZedScan	918.48	19.19977	32.52	0.01040	3127
LG referrals	DYSIS	735.30	19.20646			
	ZedScan	769.96	19.21984	34.66	0.01338	2591
HG referrals	DYSIS	1237.28	19.16234			
	ZedScan	1276.28	19.16668	39.00	0.00434	8977

10.10.10 SA6: Costs of diagnostic biopsy and LLETZ

Table 102 SA6, HPV triage – DYSIS vs. colposcopy alone

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	Colposcopy alone	1142.55	19.16500			
	DYSIS	1133.92	19.18516	-8.64	0.02016	Dominant
LG referrals	Colposcopy alone	933.40	19.16330			
	DYSIS	939.31	19.18794	5.91	0.02464	240
HG referrals	Colposcopy alone	1595.81	19.16122			
	DYSIS	1555.78	19.17156	-40.03	0.01034	Dominant
Watchful Waiting clinics						
All referrals	Colposcopy alone	1191.48	19.16286			
	DYSIS	1198.24	19.18194	6.76	0.01908	355
LG referrals	Colposcopy alone	945.18	19.16283			
	DYSIS	955.93	19.18601	10.75	0.02318	464
HG referrals	Colposcopy alone	1721.66	19.16008			
	DYSIS	1732.53	19.16580	10.87	0.00571	1903

Table 103 SA6, HPV triage – ZedScan vs. colposcopy alone

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	Colposcopy alone	1142.55	19.16500			
	ZedScan	1162.49	19.19901	19.94	0.03401	586
LG referrals	Colposcopy alone	933.40	19.16330			
	ZedScan	977.37	19.20307	43.97	0.03978	1105
HG referrals	Colposcopy alone	1595.81	19.16122			
	ZedScan	1561.11	19.17651	-34.70	0.01529	Dominant
Watchful Waiting clinics						
All referrals	Colposcopy alone	1191.48	19.16286			
	ZedScan	1235.83	19.19363	44.35	0.03078	1441
LG referrals	Colposcopy alone	945.18	19.16283			
	ZedScan	996.19	19.20082	51.02	0.03799	1343
HG referrals	Colposcopy alone	1721.66	19.16008			
	ZedScan	1770.28	19.16911	48.62	0.00903	5385

Table 104 SA6, HPV triage - ZedScan vs DYSIS

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	DYSIS	1133.92	19.18516			
	ZedScan	1162.49	19.19901	28.57	0.01385	2064
LG referrals	DYSIS	939.31	19.18794			
	ZedScan	977.37	19.20307	38.06	0.01514	2515
HG referrals	DYSIS	1555.78	19.17156			
	ZedScan	1561.11	19.17651	5.33	0.00495	1077
Watchful Waiting clinics						
All referrals	DYSIS	1198.24	19.18194			
	ZedScan	1235.83	19.19363	37.58	0.01170	3213
LG referrals	DYSIS	955.93	19.18601			
	ZedScan	996.19	19.20082	40.26	0.01481	2718
HG referrals	DYSIS	1732.53	19.16580			
	ZedScan	1770.28	19.16911	37.75	0.00332	11,383

Table 105 SA6, HPV primary - DYSIS vs. colposcopy alone

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	Colposcopy alone	1080.43	19.17506			
	DYSIS	1079.04	19.19120	-1.39	0.01614	Dominant
LG referrals	Colposcopy alone	865.95	19.19008			
	DYSIS	878.28	19.20787	12.33	0.01779	693
HG referrals	Colposcopy alone	1587.75	19.16192			
	DYSIS	1549.14	19.16774	-38.61	0.00581	Dominant
Watchful Waiting clinics						
All referrals	Colposcopy alone	1125.28	19.17511			
	DYSIS	1140.86	19.18937	15.59	0.01426	1093
LG referrals	Colposcopy alone	877.84	19.18496			
	DYSIS	892.41	19.20646	14.57	0.02150	678
HG referrals	Colposcopy alone	1712.09	19.15863			
	DYSIS	1724.71	19.16234	12.62	0.00371	3402

Table 106 SA6, HPV primary - ZedScan vs. colposcopy alone

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	Colposcopy alone	1080.43	19.17506			
	ZedScan	1113.02	19.20206	32.59	0.02700	1207
LG referrals	Colposcopy alone	865.95	19.19008			
	ZedScan	927.00	19.22007	61.05	0.03000	2035
HG referrals	Colposcopy alone	1587.75	19.16192			
	ZedScan	1556.56	19.17347	-31.18	0.01155	Dominant
Watchful Waiting clinics						
All referrals	Colposcopy alone	1125.28	19.17511			
	ZedScan	1184.20	19.19977	58.92	0.02466	2390
LG referrals	Colposcopy alone	877.84	19.18496			
	ZedScan	941.93	19.21984	64.09	0.03487	1838
HG referrals	Colposcopy alone	1712.09	19.15863			
	ZedScan	1766.12	19.16668	54.03	0.00805	6709

Table 107 SA6, HPV primary - ZedScan vs. DYSIS

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	DYSIS	1079.04	19.19120			
	ZedScan	1113.02	19.20206	33.98	0.01085	3131
LG referrals	DYSIS	878.28	19.20787			
	ZedScan	927.00	19.22007	48.72	0.01220	3992
HG referrals	DYSIS	1549.14	19.16774			
	ZedScan	1556.56	19.17347	7.43	0.00574	1295
Watchful Waiting clinics						
All referrals	DYSIS	1140.86	19.18937			
	ZedScan	1184.20	19.19977	43.34	0.01040	4168
LG referrals	DYSIS	892.41	19.20646			
	ZedScan	941.93	19.21984	49.52	0.01338	3701
HG referrals	DYSIS	1724.71	19.16234			
	ZedScan	1766.12	19.16668	41.41	0.00434	9531

Table 108 SA7.1, HPV primary - DYSIS vs. colposcopy alone

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	Colposcopy alone	869.15	19.17797			
	DYSIS	843.81	19.19374	-25.34	0.01577	Dominant
LG referrals	Colposcopy alone	761.78	19.18360			
	DYSIS	748.31	19.19999	-13.47	0.01639	Dominant
HG referrals	Colposcopy alone	1109.78	19.16614			
	DYSIS	1063.28	19.17235	-46.50	0.00622	Dominant
Watchful Waiting clinics						
All referrals	Colposcopy alone	916.54	19.17587			
	DYSIS	911.90	19.19021	-4.64	0.01433	Dominant
LG referrals	Colposcopy alone	780.26	19.18110			
	DYSIS	772.76	19.19683	-7.50	0.01573	Dominant
HG referrals	Colposcopy alone	1224.74	19.15938			
	DYSIS	1229.50	19.16602	4.75	0.00663	716

Table 109 SA7.1, HPV primary - ZedScan vs. colposcopy alone

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	Colposcopy alone	869.15	19.17797			
	ZedScan	864.85	19.20464	-4.30	0.02668	Dominant
LG referrals	Colposcopy alone	761.78	19.18360			
	ZedScan	779.52	19.21213	17.74	0.02853	622
HG referrals	Colposcopy alone	1109.78	19.16614			
	ZedScan	1065.96	19.17820	-43.81	0.01206	Dominant
Watchful Waiting clinics						
All referrals	Colposcopy alone	916.54	19.17587			
	ZedScan	948.19	19.19542	31.64	0.01954	1619
LG referrals	Colposcopy alone	780.26	19.18110			
	ZedScan	808.42	19.20864	28.16	0.02754	1023
HG referrals	Colposcopy alone	1224.74	19.15938			
	ZedScan	1265.75	19.17010	41.00	0.01072	3826

Table 110 SA7.1, HPV primary - ZedScan vs. DYSIS

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	DYSIS	843.81	19.19374			
	ZedScan	864.85	19.20464	21.03	0.01091	1929
LG referrals	DYSIS	748.31	19.19999			
	ZedScan	779.52	19.21213	31.21	0.01214	2571
HG referrals	DYSIS	1063.28	19.17235			
	ZedScan	1065.96	19.17820	2.69	0.00585	459
Watchful Waiting clinics						
All referrals	DYSIS	911.90	19.19021			
	ZedScan	948.19	19.19542	36.28	0.00521	6965
LG referrals	DYSIS	772.76	19.19683			
	ZedScan	808.42	19.20864	35.66	0.01181	3021
HG referrals	DYSIS	1229.50	19.16602			
	ZedScan	1265.75	19.17010	36.25	0.00408	8878

Table 111 SA7.2, HPV primary - DYSIS vs. colposcopy alone

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	Colposcopy alone	840.64	19.18448			
	DYSIS	813.05	19.20309	-27.59	0.01861	Dominant
LG referrals	Colposcopy alone	718.86	19.19501			
	DYSIS	705.08	19.20804	-13.78	0.01303	Dominant
HG referrals	Colposcopy alone	1130.13	19.15967			
	DYSIS	1082.72	19.16813	-47.42	0.00846	Dominant
Watchful Waiting clinics						
All referrals	Colposcopy alone	882.93	19.17807			
	DYSIS	876.39	19.19619	-6.54	0.01812	Dominant
LG referrals	Colposcopy alone	735.43	19.19023			
	DYSIS	725.96	19.20749	-9.47	0.01726	Dominant
HG referrals	Colposcopy alone	1243.76	19.16096			
	DYSIS	1250.08	19.16665	6.31	0.00570	1109

Table 112 SA7.2, HPV primary - ZedScan vs. colposcopy alone

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	Colposcopy alone	840.64	19.18448			
	ZedScan	832.59	19.21357	-8.05	0.02909	Dominant
LG referrals	Colposcopy alone	718.86	19.19501			
	ZedScan	731.56	19.21836	12.69	0.02336	543
HG referrals	Colposcopy alone	1130.13	19.15967			
	ZedScan	1084.55	19.17361	-45.59	0.01394	Dominant
Watchful Waiting clinics						
All referrals	Colposcopy alone	882.93	19.17807			
	ZedScan	908.53	19.20169	25.60	0.02362	1084
LG referrals	Colposcopy alone	735.43	19.19023			
	ZedScan	756.10	19.21774	20.67	0.02751	751
HG referrals	Colposcopy alone	1243.76	19.16096			
	ZedScan	1285.29	19.16882	41.53	0.00786	5285

Table 113 SA7.2, HPV primary - ZedScan vs. DYSIS

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	DYSIS	813.05	19.20309			
	ZedScan	832.59	19.21357	19.54	0.01047	1866
LG referrals	DYSIS	705.08	19.20804			
	ZedScan	731.56	19.21836	26.47	0.01033	2564
HG referrals	DYSIS	1082.72	19.16813			
	ZedScan	1084.55	19.17361	1.83	0.00548	334
Watchful Waiting clinics						
All referrals	DYSIS	876.39	19.19619			
	ZedScan	908.53	19.20169	32.14	0.00550	5848
LG referrals	DYSIS	725.96	19.20749			
	ZedScan	756.10	19.21774	30.13	0.01025	2940
HG referrals	DYSIS	1250.08	19.16665			
	ZedScan	1285.29	19.16882	35.22	0.00216	16,277

10.10.11 Sc1: Time horizon of three years

Table 114 Sc1, HPV triage – DYSIS vs. colposcopy alone

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	Colposcopy alone	411.06	2.57359			
	DYSIS	427.74	2.57234	16.69	-0.00126	Dominated
LG referrals	Colposcopy alone	265.59	2.58218			
	DYSIS	303.39	2.58039	37.80	-0.00180	Dominated
HG referrals	Colposcopy alone	732.77	2.55474			
	DYSIS	703.19	2.55461	-29.58	-0.00012	236,692
Watchful Waiting clinics						
All referrals	Colposcopy alone	446.62	2.57361			
	DYSIS	478.14	2.57239	31.53	-0.00122	Dominated
LG referrals	Colposcopy alone	265.84	2.58217			
	DYSIS	303.98	2.58039	38.14	-0.00178	Dominated
HG referrals	Colposcopy alone	839.24	2.55471			
	DYSIS	857.51	2.55450	18.27	-0.00021	Dominated

Table 115 Sc1, HPV triage – ZedScan vs. colposcopy alone

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	Colposcopy alone	411.06	2.57359			
	ZedScan	463.86	2.57147	52.80	-0.00213	Dominated
LG referrals	Colposcopy alone	265.59	2.58218			
	ZedScan	353.48	2.57909	87.89	-0.00310	Dominated
HG referrals	Colposcopy alone	732.77	2.55474			
	ZedScan	710.95	2.55448	-21.82	-0.00026	85,045
All referrals	Colposcopy alone	446.62	2.57361			
	ZedScan	524.47	2.57138	77.85	-0.00223	Dominated
LG referrals	Colposcopy alone	265.84	2.58217			
	ZedScan	354.30	2.57911	88.47	-0.00306	Dominated
HG referrals	Colposcopy alone	839.24	2.55471			
	ZedScan	893.65	2.55427	54.41	-0.00043	Dominated

Table 116 Sc1, HPV triage - ZedScan vs. DYSIS

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	DYSIS	427.74	2.57234			
	ZedScan	463.86	2.57147	36.12	-0.00087	Dominated
LG referrals	DYSIS	303.39	2.58039			
	ZedScan	353.48	2.57909	50.09	-0.00130	Dominated
HG referrals	DYSIS	703.19	2.55461			
	ZedScan	710.95	2.55448	7.76	-0.00013	Dominated
All referrals	DYSIS	478.14	2.57239			
	ZedScan	524.47	2.57138	46.33	-0.00101	Dominated
LG referrals	DYSIS	303.98	2.58039			
	ZedScan	354.30	2.57911	50.32	-0.00128	Dominated
HG referrals	DYSIS	857.51	2.55450			
	ZedScan	893.65	2.55427	36.14	-0.00022	Dominated

Table 117 Sc1, HPV primary – DYSIS vs. colposcopy alone

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	Colposcopy alone	405.17	2.57372			
	DYSIS	421.20	2.57260	16.04	-0.00112	Dominated
LG referrals	Colposcopy alone	258.89	2.58240			
	DYSIS	294.60	2.58084	35.71	-0.00156	Dominated
HG referrals	Colposcopy alone	750.87	2.55375			
	DYSIS	721.01	2.55363	-29.85	-0.00012	250,587
All referrals	Colposcopy alone	434.14	2.57402			
	DYSIS	464.91	2.57287	30.77	-0.00115	Dominated
LG referrals	Colposcopy alone	259.32	2.58242			
	DYSIS	295.66	2.58084	36.34	-0.00158	Dominated
HG referrals	Colposcopy alone	855.70	2.55383			
	DYSIS	873.31	2.55372	17.61	-0.00012	Dominated

Table 118 Sc1, HPV primary – ZedScan vs. colposcopy alone

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	Colposcopy alone	405.17	2.57372			
	ZedScan	457.63	2.57189	52.47	-0.00183	Dominated
LG referrals	Colposcopy alone	258.89	2.58240			
	ZedScan	343.76	2.57972	84.87	-0.00268	Dominated
HG referrals	Colposcopy alone	750.87	2.55375			
	ZedScan	727.65	2.55354	-23.22	-0.00021	110,371
Watchful Waiting clinics						
All referrals	Colposcopy alone	434.14	2.57402			
	ZedScan	510.68	2.57211	76.54	-0.00190	Dominated
LG referrals	Colposcopy alone	259.32	2.58242			
	ZedScan	345.24	2.57973	85.92	-0.00269	Dominated
HG referrals	Colposcopy alone	855.70	2.55383			
	ZedScan	909.58	2.55349	53.89	-0.00034	Dominated

Table 119 Sc1, HPV primary - ZedScan vs. DYSIS

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	DYSIS	421.20	2.57260			
	ZedScan	457.63	2.57189	36.43	-0.00070	Dominated
LG referrals	DYSIS	294.60	2.58084			
	ZedScan	343.76	2.57972	49.16	-0.00112	Dominated
HG referrals	DYSIS	721.01	2.55363			
	ZedScan	727.65	2.55354	6.63	-0.00009	Dominated
Watchful Waiting clinics						
All referrals	DYSIS	464.91	2.57287			
	ZedScan	510.68	2.57211	45.77	-0.00076	Dominated
LG referrals	DYSIS	295.66	2.58084			
	ZedScan	345.24	2.57973	49.58	-0.00112	Dominated
HG referrals	DYSIS	873.31	2.55372			
	ZedScan	909.58	2.55349	36.27	-0.00023	Dominated

Table 120 Sc1, HPV triage - Secondary outcomes

	Strategy	Missed CIN2+	Develop Cancer	Die from cancer	LLETZ	Unnecessary treatment (Clear, HPV)	Unnecessary treatment (CIN1)	Unnecessary diagnostic biopsy	Pre-term delivery
See and Treat clinics									
All referrals	Colposcopy alone	53	8	0.8	335	3	3	81	2.3
	DYSIS	24	5	0.7	373	7	8	162	2.6
	ZedScan	3	3	0.6	399	9	11	220	2.7
LG referrals	Colposcopy alone	71	10	0.5	97	0	0	72	0.7
	DYSIS	32	6	0.3	140	0	0	175	0.9
	ZedScan	4	3	0.2	172	0	0	248	1.1
HG referrals	Colposcopy alone	15	5	1.5	852	9	10	98	6.1
	DYSIS	7	4	1.5	877	21	24	135	6.2
	ZedScan	1	4	1.4	894	29	34	160	6.4
Watchful Waiting clinics									
All referrals	Colposcopy alone	53	8	0.8	328	0	0	85	2.4
	DYSIS	24	5	0.7	358	0	0	171	2.5
	ZedScan	3	3	0.6	380	0	0	233	2.7
LG referrals	Colposcopy alone	71	10	0.5	97	0	0	72	0.7
	DYSIS	32	6	0.3	140	0	0	175	0.9
	ZedScan	4	3	0	172	0	0	249	1.1
HG referrals	Colposcopy alone	15	5	1.5	833	0	0	107	5.9
	DYSIS	7	4	1.5	834	0	0	158	5.9
	ZedScan	1	4	1.5	835	0	0	193	6.0

Table 121 Sc1, HPV primary - Secondary outcomes

	Strategy	Missed CIN2+	Develop Cancer	Die from cancer	LLETZ	Unnecessary treatment (Clear, HPV)	Unnecessary treatment (CIN1)	Unnecessary diagnostic biopsy	Pre-term delivery
See and Treat clinics									
All referrals	Colposcopy alone	51	8	0.8	316	3	3	87	2
	DYSIS	23	5	0.7	351	6	6	180	3
	ZedScan	3	3	0.6	375	9	8	245	3
LG referrals	Colposcopy alone	66	9	0.4	90	0	0	83	0.7
	DYSIS	30	5	0.3	129	0	0	198	1.0
	ZedScan	3	3	0.1	158	0	0	280	1.2
HG referrals	Colposcopy alone	15	5	1.7	856	9	9	100	6.2
	DYSIS	7	4	1.7	880	22	21	137	6.3
	ZedScan	1	4	1.6	895	30	28	162	6.4
Watchful Waiting clinics									
All referrals	Colposcopy alone	51	8	0.8	311	0	0	90	2.2
	DYSIS	23	5	0.7	339	0	0	187	2.4
	ZedScan	3	3	0.6	360	0	0	256	2.6
LG referrals	Colposcopy alone	66	9	0.4	90	0	0	83	0.7
	DYSIS	30	5	0.3	129	0	0	198	1.0
	ZedScan	3	3	0.1	158	0	0	280	1.2
HG referrals	Colposcopy alone	15	5	1.7	840	0	0	109	5.9
	DYSIS	7	4	1.7	841	0	0	160	5.9
	ZedScan	1	4	1.7	842	0	0	196	6.0

10.10.12 Sc2: Adverse obstetric outcomes were excluded

Table 122 Sc2, HPV triage – DYSIS vs. colposcopy alone

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	Colposcopy alone	812.38	19.16794			
	DYSIS	772.72	19.18643	-39.66	0.01849	Dominant
LG referrals	Colposcopy alone	764.95	19.16568			
	DYSIS	731.55	19.19163	-33.40	0.02595	Dominant
HG referrals	Colposcopy alone	916.64	19.16996			
	DYSIS	864.11	19.17924	-52.53	0.00928	Dominant
Watchful Waiting clinics						
All referrals	Colposcopy alone	866.34	19.17183			
	DYSIS	851.85	19.18963	-14.49	0.01781	Dominant
LG referrals	Colposcopy alone	785.18	19.16212			
	DYSIS	762.82	19.18799	-22.36	0.02587	Dominant
HG referrals	Colposcopy alone	1040.04	19.17105			
	DYSIS	1045.25	19.17569	5.21	0.00464	1122

Table 123 Sc2, HPV triage – ZedScan vs. colposcopy alone

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	Colposcopy alone	812.38	19.16794			
	ZedScan	777.24	19.19700	-35.14	0.02906	Dominant
LG referrals	Colposcopy alone	764.95	19.16568			
	ZedScan	742.35	19.20822	-22.60	0.04254	Dominant
HG referrals	Colposcopy alone	916.64	19.16996			
	ZedScan	858.46	19.18343	-58.18	0.01348	Dominant
All referrals	Colposcopy alone	866.34	19.17183			
	ZedScan	871.25	19.19886	4.91	0.02703	182
LG referrals	Colposcopy alone	785.18	19.16212			
	ZedScan	778.96	19.20125	-6.22	0.03912	Dominant
HG referrals	Colposcopy alone	1040.04	19.17105			
	ZedScan	1074.92	19.17690	34.87	0.00585	5959

Table 124 Sc2, HPV triage - ZedScan vs. DYSIS

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	DYSIS	772.72	19.18643			
	ZedScan	777.24	19.19700	4.51	0.01057	427
LG referrals	DYSIS	731.55	19.19163			
	ZedScan	742.35	19.20822	10.80	0.01659	651
HG referrals	DYSIS	864.11	19.17924			
	ZedScan	858.46	19.18343	-5.65	0.00419	Dominant
All referrals	DYSIS	851.85	19.18963			
	ZedScan	871.25	19.19886	19.40	0.00922	2104
LG referrals	DYSIS	762.82	19.18799			
	ZedScan	778.96	19.20125	16.14	0.01325	1218
HG referrals	DYSIS	1045.25	19.17569			
	ZedScan	1074.92	19.17690	29.66	0.00121	24,493

Table 125 Sc2, HPV primary – DYSIS vs. colposcopy alone

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	DYSIS	761.64	19.18569			
	ZedScan	728.86	19.20253	-32.77	0.01684	Dominant
LG referrals	DYSIS	704.53	19.17840			
	ZedScan	677.83	19.20372	-26.70	0.02532	Dominant
HG referrals	DYSIS	901.67	19.16787			
	ZedScan	850.67	19.17360	-51.00	0.00574	Dominant
Watchful Waiting clinics						
All referrals	DYSIS	810.71	19.18529			
	ZedScan	800.40	19.20069	-10.31	0.01540	Dominant
LG referrals	DYSIS	720.52	19.18218			
	ZedScan	703.09	19.20395	-17.43	0.02177	Dominant
HG referrals	DYSIS	1025.10	19.16717			
	ZedScan	1030.11	19.17627	5.01	0.00910	550

Table 126 Sc2, HPV primary – ZedScan vs. colposcopy alone

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	Colposcopy alone	761.64	19.18569			
	ZedScan	744.76	19.21330	-16.88	0.02761	Dominant
LG referrals	Colposcopy alone	704.53	19.17840			
	ZedScan	699.06	19.22000	-5.47	0.04160	Dominant
HG referrals	Colposcopy alone	901.67	19.16787			
	ZedScan	848.84	19.17787	-52.83	0.01000	Dominant
Watchful Waiting clinics						
All referrals	Colposcopy alone	810.71	19.18529			
	ZedScan	829.20	19.21050	18.49	0.02522	733
LG referrals	Colposcopy alone	720.52	19.18218			
	ZedScan	727.58	19.21922	7.06	0.03704	191
HG referrals	Colposcopy alone	1025.10	19.16717			
	ZedScan	1063.51	19.17891	38.40	0.01174	3272

Table 127 Sc2, HPV primary – ZedScan vs. DYSIS

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	Colposcopy alone	728.86	19.20253			
	DYSIS	744.76	19.21330	15.89	0.01077	1476
LG referrals	Colposcopy alone	677.83	19.20372			
	DYSIS	699.06	19.22000	21.23	0.01628	1304
HG referrals	Colposcopy alone	850.67	19.17360			
	DYSIS	848.84	19.17787	-1.83	0.00427	Dominant
All referrals	Colposcopy alone	800.40	19.20069			
	DYSIS	829.20	19.21050	28.79	0.00981	2934
LG referrals	Colposcopy alone	703.09	19.20395			
	DYSIS	727.58	19.21922	24.49	0.01527	1603
HG referrals	Colposcopy alone	1030.11	19.17627			
	DYSIS	1063.51	19.17891	33.40	0.00264	12,663

10.10.13 Sc3: ZedScan was used alongside colposcopy at all appointments

Table 128 Sc3, HPV triage – ZedScan vs. colposcopy alone

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	Colposcopy alone	903.28	19.16500			
	ZedScan	890.89	19.19901	-12.40	0.03401	Dominant
LG referrals	Colposcopy alone	793.97	19.16330			
	ZedScan	795.63	19.20307	1.65	0.03978	42
HG referrals	Colposcopy alone	1139.13	19.16122			
	ZedScan	1094.01	19.17651	-45.12	0.01529	Dominant
All referrals	Colposcopy alone	953.02	19.16286			
	ZedScan	980.93	19.19363	27.92	0.03078	907
LG referrals	Colposcopy alone	812.85	19.16283			
	ZedScan	831.92	19.20082	19.07	0.03799	502
HG referrals	Colposcopy alone	1252.07	19.16008			
	ZedScan	1317.70	19.16911	65.63	0.00903	7270

Table 129 Sc3, HPV triage – ZedScan vs. DYSIS

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	DYSIS	872.34	19.18516			
	ZedScan	890.89	19.19901	18.54	0.01385	1339
LG referrals	DYSIS	770.65	19.18794			
	ZedScan	795.63	19.20307	24.98	0.01514	1651
HG referrals	DYSIS	1091.43	19.17156			
	ZedScan	1094.01	19.17651	2.58	0.00495	521
All referrals	DYSIS	941.33	19.18194			
	ZedScan	980.93	19.19363	39.60	0.01170	3385
LG referrals	Colposcopy alone	799.47	19.18601			
	ZedScan	831.92	19.20082	32.45	0.01481	2191
HG referrals	DYSIS	1255.93	19.16580			
	ZedScan	1317.70	19.16911	61.78	0.00332	18,628

Table 130 Sc3, HPV primary- ZedScan vs. Colposcopy alone

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	Colposcopy alone	850.08	19.17506			
	ZedScan	849.70	19.20206	-0.38	0.02700	Dominant
LG referrals	Colposcopy alone	732.33	19.19008			
	ZedScan	751.31	19.22007	18.98	0.03000	633
HG referrals	Colposcopy alone	1126.93	19.16192			
	ZedScan	1084.58	19.17347	-42.35	0.01155	Dominant
All referrals	Colposcopy alone	894.41	19.17511			
	ZedScan	933.32	19.19977	38.91	0.02466	1578
LG referrals	Colposcopy alone	748.86	19.18496			
	ZedScan	778.64	19.21984	29.78	0.03487	854
HG referrals	Colposcopy alone	1236.94	19.15863			
	ZedScan	1305.85	19.16668	68.91	0.00805	8557

Table 131 Sc3, HPV primary - ZedScan vs. DYSIS

	Strategy	Cost	QALYs	Incr. cost	Incr. QALYs	ICER
See and Treat clinics						
All referrals	DYSIS	825.46	19.19120			
	ZedScan	849.70	19.20206	24.24	0.01085	2233
LG referrals	DYSIS	715.46	19.20787			
	ZedScan	751.31	19.22007	35.85	0.01220	2938
HG referrals	DYSIS	1079.83	19.16774			
	ZedScan	1084.58	19.17347	4.75	0.00574	829
All referrals	DYSIS	889.04	19.18937			
	ZedScan	933.32	19.19977	44.28	0.01040	4259
LG referrals	DYSIS	738.10	19.20646			
	ZedScan	778.64	19.21984	40.54	0.01338	3030
HG referrals	DYSIS	1240.99	19.16234			
	ZedScan	1305.85	19.16668	64.85	0.00434	14,928