Title of the project

Adjunctive colposcopy technologies for assessing suspected cervical abnormalities: a systematic review and economic evaluation

Name of External Assessment Group (EAG) and project leads

Centre for Reviews and Dissemination and Centre for Health Economics - York EAG

Dr Mark Simmonds
Centre for Reviews and Dissemination
University of York
York YO10 5DD
Tel: 01904 321091
Email: mark.simmonds@york.ac.uk

Prof. Stephen Palmer
Centre for Health Economics
University of York
York YO10 5DD
Tel: 01904 321434
Email: stephen.palmer@york.ac.uk

Plain English Summary

In 2014, 3,224 people were diagnosed with cervical cancer in the UK, making it the 13th most common cancer in women, and 890 people died as a result of the disease. Cervical cancer is nearly always caused by sexually acquired infection with certain types of viruses, known as high-risk human papillomavirus.

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 by taking a sample of cells brushed from the cervix (liquid-based cytology). These cells are tested for possible changes that may or may not develop into cancer. 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. A colposcopy is a procedure to confirm whether there are abnormal cells on or in a woman's cervix, and is done by a colposcopist. A colposcopy is performed using a colposcope (a magnifier with a bright light), which allows the colposcopist to examine the cervix in detail. In any area that appears abnormal a sample of cervical cells (a biopsy) can be taken and sent to a laboratory to check whether these cells are normal, pre-cancerous or cancerous. In some cases, the clinician may decide to directly treat the patient during the examination, by making a small cut (excision) to the cervix to directly remove any suspicious cells.

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 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 been reviewed by NICE before. 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. The purpose of this project is to assess and compare the potential benefits and harms and value for money of the DYSIS with DYSISmap and Zedscan used alongside regular colposcopy for people referred for colposcopy as part of the cervical cancer screening programme.

Decision problem

The purpose of this assessment is 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).

Interventions

Adjunctive colposcopy technologies are intended for use in conjunction with conventional colposcopy to assist with the identification of cervical intraepithelial neoplasia during a colposcopy examination. Results from a colposcopy examination help determine whether further treatment or biopsies are required. However, colposcopy alone has limited accuracy and is subject to inter-observer and intra-observer variability,[1, 2] which may result in missed lesions, unnecessary biopsies and overtreatment. Adjunctive colposcopy technologies may result in more accurate detection of cervical abnormalities (particularly low-grade abnormalities) and therefore reduce the number of biopsies and follow-up colposcopy examinations. They may also help to select areas for biopsy with greater precision and help to facilitate more conservative patient management where appropriate.

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.

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.[3]

- 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).

Comparator technologies

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.[4-6] Details of referral cytology results, other clinical information, the type of management available, and the number of biopsies taken may also be relevant when interpreting the results of colposcopy. The previous assessment (DG4) 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).[7]

Population and relevant subgroups

Cervical cancer is the most common cancer in women aged 35 and under. In 2014, there were 3,224 new cases of cervical cancer, making it the 13th most common cancer in women.[8] In 2014, there were 890 deaths from the cervical cancer in the UK and the mortality rates are higher for the women living in the most deprived areas. However it is one of the less common (less than 1%) cancers, primarily due to the NHS cervical screening programme.[9]

Cervical cancer is linked to high risk human papillomavirus (hr-HPV) infection. There are around 12 types of hr-HPV.[10] Of those, HPV 16 and HPV 18 are associated with a large proportion of cervical cancers (around 70% in the UK). However, most HPV infections will not progress to CIN, and it 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 sex partners.[9] CIN is classified 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. [12] CIN 3 is considered to be pre-cancerous with the potential to progress to invasive cancer.[13] CIN 2 is also generally considered and managed as pre-cancerous, although the regression rate of CIN 2 in adult people is significant.[14] [15]

There is evidence to suggest that cellular changes caused by HPV 16 may be more apparent on colposcopy examination than cellular changes caused by other hr-HPV genotypes.[16] Therefore the accuracy of colposcopy, and the adjunctive technologies, may differ in these subgroups.

Place of the intervention in the care pathway

HPV immunisation

All girls aged 12 to 13 are offered HPV vaccination against HPV 16 and 18 genotypes since September 2008 (a catch-up programme was initially implemented for girls between 14 and 18 years old). 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. For this reason the impact of HPV vaccination will not be considered in this assessment.

Cervical screening

In England, women between the ages of 25 and 64 are invited for regular cervical screening every three years (if aged between 25 and 49 years) or every five years (if aged between 50 and 64 years) under the NHS Cervical Screening Programme. Cytological assessment is performed to detect nuclear abnormalities, which are described as dyskaryotic.[17] Grading systems for cervical cytology results 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) [18] and Solomon (2004)[19]

In 2014-15 a total of 4.31 million people aged 25 to 64 were invited for screening of which 3.12 million (around 73%) attended and 3.20 million samples were examined.[20] Of all people with an adequate test, 93.6% had a negative result and 6.4% had an abnormal result (from borderline change through to potential cervical cancer). 1.3% of people tested had a result that showed a high-grade abnormality. [20]

There were 198,216 referrals for colposcopy in 2014-15; 66.8% of these were as a result of screening and 20.2% were clinically indicated, 13% were referred for other reasons (e.g. CIN treatment follow-up). [20]

HR-HPV triage

The current management protocols for cervical cytology and management options for patients are outlined in Table 2. Under the hr-HPV triage protocol, people whose cervical samples indicate borderline changes or low-grade dyskaryosis are given a reflex hr-HPV 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 hr-HPV test.[17] National implementation of hr-HPV triage for people with borderline or low-grade cytology results and hr-HPV test of cure was completed in 2013.

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

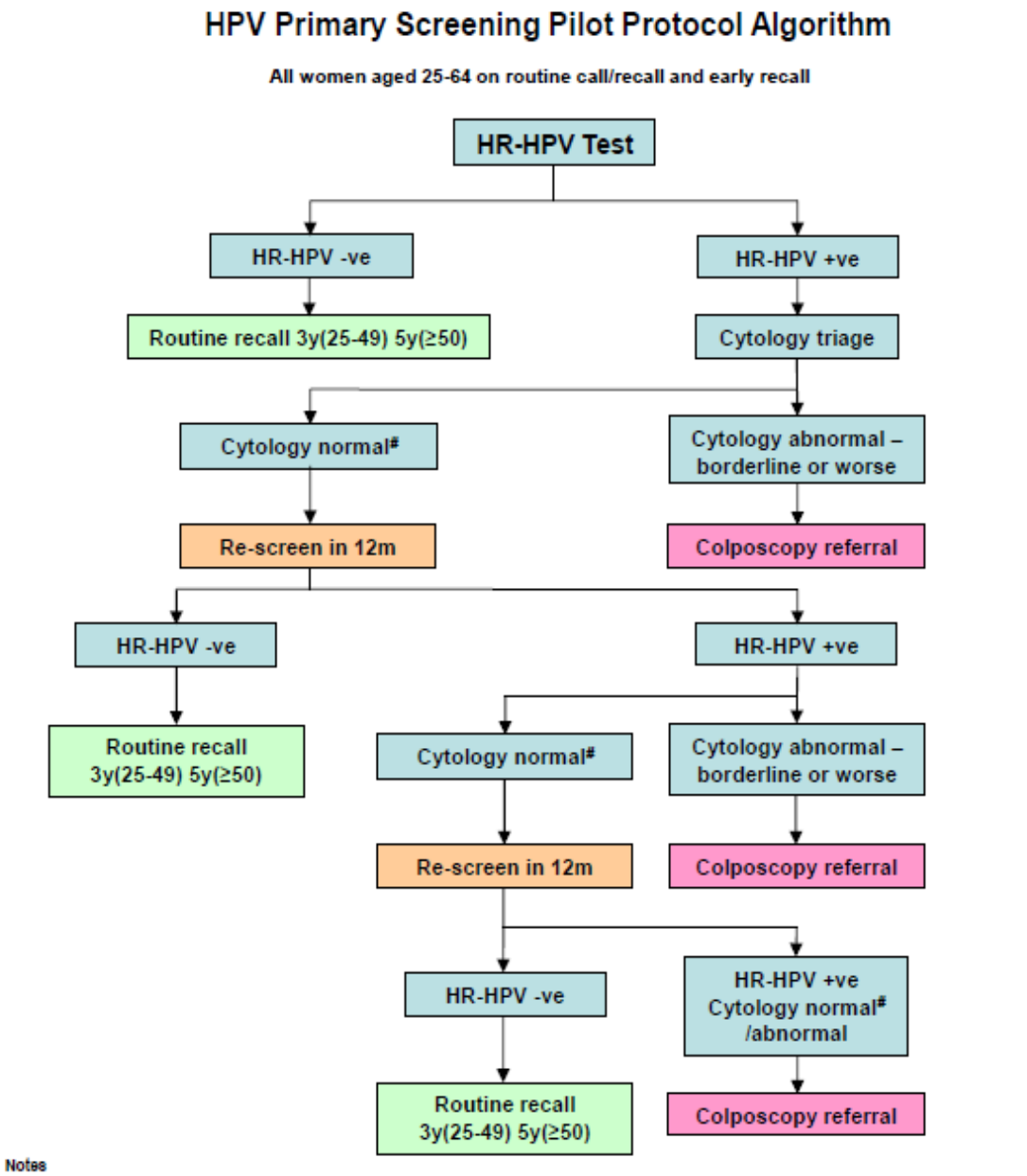
Source: NHSCSP publication 20[21]

HPV primary screening

Following the piloting of English HPV primary screening in six sites in England in 2013-2014,[22] the Department of Health announced a change to the cervical screening process in July 2016.[21] 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 hr-HPV, prior to cytology triage. The algorithm for the HPV primary screening pilots is shown below in Figure 1. In general, primary screening with hr-HPV 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.[23]

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.



Notes

1) Inadequate tests at any screening episode in the pathway will be repeated in 3 months. Three inadequate tests in a row will lead to a colposcopy referral.
2) Women entering the pilot under follow up for treatment for CIN will be given a 3 year recall if HR-HPV-ve and will be referred to colposcopy if HR-HPV+ve/any grade of cytology.
3) Women entering the pilot under follow up for CGIN or SMILE (complete excision margins) will follow the protocol for CGIN at their next two tests as detailed in the HPV Primary Screening Pilot Colposcopy Management Recommendations Algorithm.
4) Women in follow up for cervical cancer (who still have a cervix) and CGIN/SMILE (without complete excision margins) at a pilot site will be given annual HPV testing (instead of cytology) for 10 years.

#HPV16/18 recorded where available. Women testing HPV 16 or 18 positive/cytology normal at baseline and again at their first 12 month follow up test can be referred to colposcopy without further repeat tests.

Version 3.0 **January 2016**

Source: Public Health England[24]

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.

Colposcopy management and treatment

If an abnormality is detected during the colposcopy examination, the colposcopist may take a diagnostic biopsy or treat an abnormality during the first clinic appointment ("see and treat") by excising the area of abnormal cells where high grade changes are suspected.

In 2014-15, 61.7% of all people referred to colposcopy in England underwent a procedure or treatment at their first appointment. Diagnostic biopsy was the most common procedure (47.7%), followed by an excision (12.2%), with the most common excision being a large loop excision of the transformation zone (LLETZ).[20]

NHSCSP publication 20 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 low-grade colposcopic change and high grade dyskaryosis (severe), an excisional form of biopsy (rather than punch biopsy) is recommended.[21]

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, or destroying them in situ (ablation).

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 and will be performed under general anaesthesia. The depth of the excision depends on the nature of the cervical transformation zone.[21]

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.[25]

Follow-up and test of cure

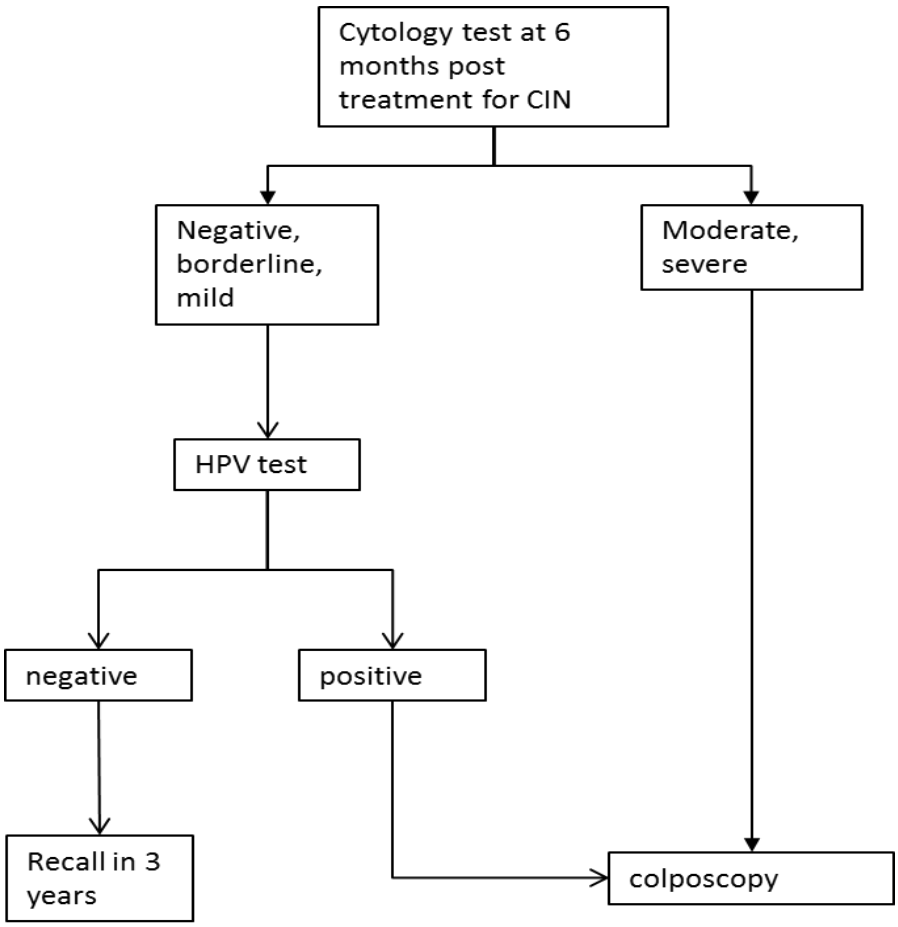
Post-colposcopy follow-up depends on whether treatment has been performed or whether surveillance has been recommended. Surveillance can be done within the colposcopy service or within the community.

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.[21] 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 2 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.[26]

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.[17] Under HPV primary screening, test of cure differs and is described in the NHS cancer screening programme's pilot.[26]

Figure 2 Test of cure algorithm



Personal communication, adapted from NHSCSP publication 20[17]

People who have been treated for CGIN will also have test of cure at 6 months post treatment; if this sample is reported as cytology normal and HPV not detected, a second test of cure sample will be advised in a further 12 months (18 months post treatment). If the second sample is cytology and HPV negative, discharge to recall in 3 years will be advised. People who have abnormal cytology or a HPV positive result at either scheduled test of cure should be referred back to colposcopy for further management.

Objectives

The aim of the project is to determine the clinical and cost-effectiveness of adjunctive colposcopy technologies (DYSIS with 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:

Clinical effectiveness

- To perform a systematic review and meta-analysis of the diagnostic accuracy of adjunctive colposcopy technologies (DYSIS with DYSISmap and ZedScan I) in conjunction with standard colposcopy for the examination of the uterine cervix of the people who are referred for colposcopy
- 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.

Cost-effectiveness

- 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.

- 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).

Methodology

Systematic review of diagnostic accuracy and clinical effectiveness

The review will be conducted following the general principles recommended in CRD's guidance [27] and the PRISMA statement.[28]

Literature searching

Searches of the literature will be conducted in order to identify studies and other relevant literature in the following key areas:

Extensive searches of the literature relating to the specified technologies (DYSIS with DYSISmap, Zedscan) will be conducted. Searches for studies for cost and quality of life data will also be included, as determined by the model.

The following databases will be searched: MEDLINE, PubMed, EMBASE, CINAHL, Health Management Information Consortium (HMIC), ISI Science Citation Index, Cochrane Database of

Systematic Reviews (CDSR), CENTRAL, Database of Abstracts of Reviews of Effects (DARE), Health Technology Assessment (HTA) Database, and NHS Economic Evaluation Database (NHS EED).

Ongoing and unpublished studies will be searched for using appropriate sources, including ClinicalTrials.gov, Conference Proceedings Citation Index: Science, EU Clinical Trials Register, PROSPERO, WHO International Clinical Trials Registry Platform portal and manufacturer websites. 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) will also be consulted.

Where necessary, relevant guidelines will be identified through searching additional resources, including, National Institute for Health and Clinical Excellence (NICE) website, NHS Evidence, National Guideline Clearinghouse, Public Health England, BSCCP, Royal College of Obstetricians and Gynaecologists, Scottish Intercollegiate Guidelines Network (SIGN), and the TRIP database.

The searches will combine terms for cervix with terms for the technologies being assessed. The searches will be based on those used for the original review (DG4), updated to reflect the changed scope in this new review. The results of this new search will be de-duplicated against the results from the DG4 review, so papers already screened it that original review will not be screened again. Studies included in the DG4 review will be re-assessed for inclusion in this review. Reference lists of recent systematic reviews will be assessed and the abstracts of relevant conferences will be searched, where possible, for additional relevant studies. Searches will be limited by date, according to the date of development of the new technologies. No limits relating to language or study design will be applied to the searches.

Pragmatic supplementary searches for primary and secondary data (including existing systematic reviews) will be carried out as necessary, depending on the gaps and limitations identified during the review of clinical and economic evidence and during the development of the model. Where needed, targeted searches will be conducted to identify unpublished data and other grey literature, such as national audit data, Health and Social Care information Centre (HSCIC) data, or data from sentinel (pilot) sites. We will also work with relevant experts at the start of the project to identify relevant UK data sources and will make contact with investigators and manufacturers with a view to securing access to this data should this be required. Data submitted to NICE as part of this assessment will also be used as relevant.

Contact with study authors and manufacturers

It is anticipated that many studies may not report sufficient data in publications to perform full syntheses or fully populate economic models. Therefore, study authors and DYSIS and Zedscan manufacturers will be contacted to seek detailed diagnostic and other clinical data as appropriate.

Data requested will include:

- Full diagnostic data with results for adjunctive colposcopy, standard colposcopy and histology (normal, CIN 1, CIN 2, CIN 3, cancer).
- All other eligible clinical outcomes not reported in publications.

Requests will also be made to identify and obtain relevant data from unpublished studies from the manufacturers. It is anticipated that any contact with manufacturers will be made via the diagnostic team at NICE. Any confidential data will be held on a secure server at York, and clearly marked in the report.

Additional data

Data will be requested from the NHSCSP HPV screening pilot (Sentinel Sites), if it is determined that this pilot recorded data relevant to this assessment. This may include:

- Numbers of people receiving standard colposcopy, DYSIS (with DYSISmap) or Zedscan.
- Diagnostic results of colposcopies, sufficient to calculate diagnostic accuracy.

Studies of DYSIS and Zedscan may not report data on all the outcomes of interest listed above, or sufficient data to populate the economic models. It is anticipated that this may be the case for long-term outcomes such as morbidity, mortality or quality of life. Where appropriate, relevant data will be taken from the wider literature on colposcopy and cervical cancer treatment. Systematic reviews of relevant topics will be preferred, but other sources of data, such as audit data or primary studies, will also be considered.

Study selection

Two reviewers will independently screen all titles and abstracts. Full papers of any titles/abstracts that may be relevant will be obtained where possible, and the relevance of each study assessed independently by two reviewers according to the criteria below. Any discrepancies will be resolved by consensus and, if necessary, a third reviewer will be consulted. Eligible studies which are available only as conference abstracts will be included (and attempts will be made to contact authors for further data).

The following eligibility criteria will be used to identify relevant studies:

Participants

Studies of people referred for colposcopy through a cervical screening programme, due to a suspected abnormality resulting from liquid-based cytology, Pap smear test, or HPV test. Studies that also include people referred for colposcopy because of symptoms indicative of cervical cancer (e.g. post-coital bleeding) or people referred for follow-up of CIN will be included; however, studies that only include people referred for colposcopy because of symptoms indicative of cervical cancer or for follow-up of CIN will be excluded.

The following specific subgroups of people will be considered if data are available:

- people known to have HPV genotype 16 or other hr-HPV
- low grade dyskaryosis or less vs. high-grade dyskaryosis (moderate) or worse
- people with a recent CIN diagnosis (such that they would be in the “test of cure” pathway in the UK)

As the focus of this assessment is on people receiving colposcopy after referral from the screening programme, data on people referred for colposcopy for other reasons (such as clinical symptoms) will be excluded from the review wherever possible.

Interventions

Studies using DYSIS with DYSISmap (DYSIS Medical) or Zedscan I (Zilico Ltd) for the diagnosis of CIN or cervical cancer will be eligible for inclusion. All versions of these tools will be considered.

Comparators

Standard colposcopy alone. However papers need not report data for standard colposcopy to be eligible. Both binocular and video colposcopy will be considered.

Reference standard

Histopathology, used to differentiate between the three grades of CIN and cervical cancer. Where the colposcopy examination is normal, it may not be considered ethical to take biopsies to confirm absence of disease. Therefore, studies that do not report histology results for people with no suspected high-grade lesion will also be included. The limitations of these studies will be accounted for in the interpretation of the results.

Outcomes

The following outcomes will be included:

- diagnostic accuracy, including sensitivity and specificity, predictive values, or sufficient data to calculate estimates of diagnostic accuracy
- 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 treats'
- duration of colposcopy examination
- number of people discharged from colposcopy

For the diagnostic accuracy review, studies should report results from both the diagnostic test and the reference standard. As a minimum, results should be classified as CIN, differentiating between mild dysplasia or less (CIN1 or less, i.e. negative diagnostic result) and moderate dysplasia or worse (CIN 2 or greater, i.e. positive diagnostic result).

For biopsies, excisions and other treatments, the differentiation between necessary interventions and unnecessary interventions will be considered, where possible.

In addition, the following clinical outcomes will be included:

- morbidity and mortality associated with treatment and biopsies conducted as part of the colposcopy examination (these include 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
- 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 (e.g. infection, infertility, miscarriage)

Outcomes related to the implementation of the interventions of interest and related practical issues will be included:

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

Study designs

Diagnostic accuracy

Prospective cohort studies in which index test and reference standard test are done independently in the same group of people, and that report sufficient data to calculate diagnostic accuracy (sensitivity, specificity etc.), will be included.

Clinical effectiveness/implementation

Any experimental or observational study where DYSIS with DYSISmap and/or Zedscan testing was used and that reports relevant clinical outcomes as listed above. Ideally this will include studies that included a control group that underwent standard colposcopy alone. If no comparative studies are identified for all eligible outcomes, studies that only recruit people who have received adjunctive colposcopy will be included, providing they report relevant clinical outcomes for this assessment.

We will also include relevant publications reporting issues related to implementation of, or practical advice relating to the index tests of interest. This may include experimental or observational studies, reviews or cost-effectiveness analyses.

The following types of report will be excluded: editorials and opinions; case reports; reports focusing only on technical aspects of the adjunctive colposcopy technologies (such as technical descriptions of the testing process or specifications of machinery). We will select the most recent or most complete report in cases of multiple reports for a given study or when we cannot exclude the possibility of overlapping populations.

Data extraction

Data relating to both study characteristics and results will be extracted by one reviewer using a standardised data extraction form and independently checked for accuracy by a second reviewer. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary. If time constraints allow, attempts will be made where possible to contact authors and/or manufacturers for missing data. Data from relevant studies with multiple publications will be extracted and reported as a single study.

To avoid unnecessary duplication of work, where possible, relevant data presented in previous NICE diagnostic assessment reports (including DG4)[7] may be extracted (and then checked for any transcription errors); additional data may also be extracted where appropriate.

Patient characteristics will be extracted, including: age, ethnicity, results of last cytology/smear test, indication for colposcopy (e.g. abnormal cytology, follow-up CIN1-2), presence and type of high-risk HPV. Data on study intervention will be extracted (e.g. characteristics of colposcopy technologies used, colposcopist experience, diagnostic cut-off and thresholds) and data on exclusions from study/analysis with reasons (e.g. unsatisfactory colposcopy, no histology) will be recorded.

Diagnostic accuracy data will be extracted in terms of numbers of people. Data will be extracted at a level of detail that is sufficient and relevant to inform diagnostic accuracy analyses and the economic model (e.g. normal, CIN1, CIN2, CIN3 or cancer). If numbers of people are not presented estimates of sensitivity and specificity (with confidence intervals) will be extracted. For other clinical outcomes data will be extracted either as numbers of events, means or standard deviations, or as summaries such as risks or odds, depending on reporting.

For outcomes related to implementation that do not present numerical data we will perform a qualitative synthesis. For this we will extract summary information on the findings of included studies that relate to the implementation outcomes, the conclusions of these studies, and consequences for colposcopy, recommendations for practice and suggested needs for further research.

Quality assessment strategy

The quality of the included studies of diagnostic accuracy will be assessed using the Quality Assessment tool of Diagnostic Accuracy Studies (QUADAS-2 tool) adapted as necessary to incorporate topic-specific quality issues. The Cochrane risk of bias tool for randomised studies and the Cochrane ACROBAT-NSRI tool for non-randomised studies will be used and adapted as appropriate for studies reporting other eligible clinical outcomes. The risk of bias assessments will be performed by one reviewer, and independently checked by a second. Disagreements will be resolved through consensus, and if necessary, a third reviewer will be consulted.

The results of the quality assessment will be tabulated and the more important methodological problems will be discussed in terms of their potential effect on the results of the included studies.

The external validity of the included studies (including population characteristics and intervention setting) will also be evaluated and discussed by using and modifying existing tools as appropriate.[29]

Synthesis

In the initial synthesis, the results of data extraction will be presented in structured tables and as a narrative summary, grouped by participant and intervention characteristics. Where sufficient clinically and statistically homogenous data are available, data will be pooled using appropriate meta-analytic techniques.

Statistical analysis

Using extracted diagnostic accuracy data from the 2 x 2 tables, estimates of sensitivity and specificity will be calculated and presented on forest plots and in the receiver operating characteristic (ROC) space to examine the variability in diagnostic test accuracy within and between studies. Positive and negative predictive values will also be calculated and presented in figures and tables. Where three or more studies are available which use equivalent clinical thresholds to diagnose CIN/cancer the hierarchical bivariate model described by Reitsma et al.[30] will be fitted which calculates summary estimates of sensitivity and specificity and the associated 95% confidence intervals (CIs). The hierarchical summary ROC (HSROC) model will also be fitted to produce summary ROC curves.[31] Results of both models will be presented in ROC plots.

Other eligible clinical or implementation outcomes will be pooled if at least two studies report on the same outcome, and if data are reported consistently enough for analysis to be feasible. Otherwise, results will be synthesised narratively. Where meta-analyses are performed, data will be pooled using standard random-effects DerSimonian-Laird meta-analyses.

If sufficient data are available statistical models (such as simulation studies) will be generated to assess the impact of adjunctive colposcopy on the numbers of biopsies and excisions performed, and on morbidity and mortality and other longer-term outcomes.

Analyses will be conducted in R and/or Stata software, as appropriate.

Investigation of heterogeneity and subgroup analyses

For diagnostic accuracy data, we will initially visually inspect the forest plots and ROC space to check for heterogeneity between study results. To investigate sources of heterogeneity, we will incorporate relevant covariates in the bivariate and HSROC models. Subgroup analyses will be conducted, by performing separate bivariate and HSROC models in defined subgroups of studies.

For other clinical outcomes, where possible, heterogeneity will be assessed using I^2 and visual inspection of forest plots. Subgroup analyses and meta-regression will be used where feasible. Possible sources of heterogeneity will be discussed and accounted for in the interpretation of the results.

Where possible, for diagnostic accuracy data and clinical outcomes reviews, we will consider the following factors as potential sources of heterogeneity:

- people with HPV genotype 16 vs. other hr-HPV
- low grade dyskaryosis or less vs. high-grade dyskaryosis (moderate) or worse
- people with a recent CIN diagnosis (such that they would be in the “test of cure” pathway in the UK)

Sensitivity analyses

We will carry out sensitivity analyses to explore the robustness of the results according to study quality based on QUADAS domain results (for example, by excluding studies with high risk of verification bias) for diagnostic accuracy studies, and based on results from the Cochrane risk of bias tool and ACROBAT-NSRI, and study date (to reflect improvements in technology).

Where possible, the impact of excluding studies that only performed biopsies in patients with suspected high-grade lesions (rather than in all patients) will be explored.

Where participants from several studies are recruited from the same cohorts and significant overlap is suspected, data from only one study with the most reliable reporting will be included in the main analyses. The impact of studies where substantial overlap is suspected, or where only a composite outcome is reported, will be explored by including/excluding them from the main analyses.

Implementation outcomes, narrative and qualitative synthesis

For outcomes related to implementation that do not present numerical data we will perform a qualitative synthesis. For this we will extract summary information on the findings of included studies that relate to the implementation outcomes, the conclusions of these studies, and consequences for colposcopy, recommendations for practice and suggested needs for further research. These results will be tabulated and summarised.

Narrative summaries will be used for any outcomes where meta-analyses or other statistical analyses are not feasible. This will include tabulating or plotting results as reported in studies, and narratively describing and comparing these results.

Systematic review of cost-effectiveness evidence and development of decision model

Relevant cost-effectiveness evidence of adjunctive colposcopy technologies (DYSIS with DYSISmap and ZedScan I) will be systematically identified, appraised for quality and summarised. This review will be used to identify key issues associated with adapting existing decision model structures to address the current decision problem and to inform the subsequent development of a new decision model drawing on the issues identified in the clinical and cost-effectiveness review.

Systematic review of cost-effectiveness studies

The results of the searches carried out for the systematic review of clinical effectiveness will be used to identify any relevant studies of the cost-effectiveness of DYSIS with DYSISmap or ZedScan I (Zilico Ltd) for assessing suspected cervical abnormalities in people who are referred for colposcopy.

A broad range of studies will be considered in the assessment of cost-effectiveness including economic evaluations conducted alongside trials, modelling studies and analyses of administrative databases. Only full economic evaluations that compare two or more options and consider both costs and consequences (including cost-effectiveness, cost-utility and cost-benefit analyses) will be included in the review of economic literature.

The main findings of existing economic evaluations will be narratively summarised and tabulated for comparison. In particular, information will be extracted on the comparators, study population, main analytic approaches (e.g. patient-level analysis/decision-analytic modelling), primary outcome specified for the economic analysis, details of adjustment for quality-of life, direct costs and indirect costs, estimates of incremental cost-effectiveness and approaches to quantifying decision uncertainty (e.g. deterministic/probabilistic sensitivity analysis).

The review will examine existing decision-analytic models in detail, with the aim of identifying important structural assumptions, highlighting key areas of uncertainty and outlining the potential issues of generalising from the results of existing models. This review will be used to identify the central issues associated with adapting existing decision models to address the specific research question posed and to assist in the development of a new decision model drawing on the issues identified in the clinical and cost-effectiveness review.

To further inform the development of the new decision model, we will also undertake a targeted literature search to identify cost-effectiveness studies evaluating screening (including cytology based programmes and HPV primary screening) for cervical cancer in the UK. Since screening occurs upstream from diagnosis of CIN, the model structures, inputs and assumptions in these studies may be important to consider as part of the conceptualisation and development of the new decision model. These studies will not be subject to a formal assessment but will be used, if necessary, to assist in the overall development of a new analytical model with the aim of identifying important structural assumptions, parameter estimates and highlighting key areas of uncertainty.

The cost-effectiveness model developed for the previous assessment (DG4) combined a decision tree to model the diagnostic and treatment pathways for people referred to colposcopy from the NHS Cervical Screening Programme with a Markov model to simulate the natural history of patients

including future cytological screening and referrals to colposcopy. The Markov model was adapted from a model made available to the EAG by researchers at the School of Health and Related Research (ScHARR) at the University of Sheffield, henceforth referred to as the Sheffield model. The Sheffield model was based on two previous models: (i) a cost-effectiveness model for the use of LBC in England[32] and (ii) and a colposcopy capacity model [33].

We will assess the feasibility and appropriateness of adapting previously developed screening models for the purposes of the current study assessed based on:

i) Appropriateness for the decision problem being considered in this assessment.
ii) Relevance of outputs for decision making (i.e. to estimate long-term NHS costs and QALYs based on morbidity and mortality associated with treatment and biopsies conducted as part of the colposcopy examination and with cervical cancer).
iii) Flexibility to address referrals 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).
iv) Ability to reproduce the model or to collaborate with model developers.

Evaluation of costs and cost effectiveness

Following the review of existing cost-effectiveness, a decision model will be 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 algorithm (including test of cure). The model will be populated using results from the systematic clinical effectiveness review, other focused reviews to inform key parameters (e.g. utilities), routine sources of cost data, and if necessary additional study specific cost estimates provided by experts and/or relevant investigators.

Costs will be considered from an NHS and Personal Social Services perspective and depending on data availability will include:

- Costs of the adjunctive colposcopy technologies including the cost of the devices, software and any consumables
- Costs of staff and associated training
- Medical costs arising from testing including ongoing care and follow up and histopathology costs
- Medical costs arising from adverse events including those associated with false test results and inappropriate treatment.

It will be important to consider patient throughput and its impact on the cost per patient for the diagnostic tests. The diagnostic test's accuracy will also influence throughput; for instance, a large number of false positive results from colposcopy will unnecessarily increase the number of people undergoing treatment and follow-up care. Data for the cost-analysis will be drawn from routine NHS sources and discussions with manufacturers of the technologies considered.

The model will attempt to establish a link between diagnostic test accuracy and final health outcomes. This will involve consideration of how each technology impacts on the identification of cancerous and precancerous cervical tissue and linking this identification to treatment or monitoring options and their effect on disease progression. The model will also include the impact of the technologies on unnecessary biopsies and excisions which may increase the risk of preterm labour, pain, bleeding and discharge.

Further details of the model structure and data to be used to populate it will have to await the findings of the systematic searches of the literature. However, it is expected that particular consideration will be given to the following key variables:

- Sensitivity and specificity of the different technologies
- Resource utilisation and costs for the different technologies
- Links to long-term outcomes including morbidity and mortality associated with treatment and biopsies conducted as part of the colposcopy examination and with cervical cancer
- Adherence to colposcopy and follow-up
- 'See and treat' rates

The specific objectives of the cost-effectiveness analysis are:

- To structure an appropriate decision model to characterise existing care pathways and the subsequent impact of adjunctive colposcopy technologies (DYSIS with DYSISmap and ZedScan I), compared to conventional colposcopy alone, for people who are referred for colposcopy through the NHS Cervical Screening Programme.
- To incorporate sufficient flexibility within the model structure (or to develop separate structures) to reflect referral for colposcopy through the NHS Cervical Screening Programme based on HPV triage (including test of cure) or the HPV primary screening algorithm (including test of cure).
- To populate this model using the most appropriate data. This is likely to be identified systematically from published literature, routine data sources and potentially using data elicited from relevant clinical experts and manufacturers.
- To relate intermediate outcome measures, such as diagnostic accuracy and number of biopsies taken and diagnostic yield to final health outcomes including: morbidity and mortality associated with treatment and biopsies and cervical cancer. Final health outcomes will be 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.
- To estimate the incremental cost-effectiveness of adjunctive colposcopy technologies (DYSIS with DYSISmap and ZedScan I), compared to conventional colposcopy alone, based on an assessment of long-term NHS and Personal Social Service costs and quality-adjusted survival. The time horizon of the model will be sufficient to capture both the short-term and longer-term outcomes. The final specification of the model will be determined during the review and model conceptualisation stage.

- To characterise the uncertainty in the data used to populate the model and present the resulting uncertainty in the results to decision makers. A probabilistic model will be developed which requires that, where possible, uncertainty in inputs are reflected through the use of appropriate distributions. Using Monte Carlo simulation, this parameter uncertainty will be translated into uncertainty in the overall results. This will be presented graphically using cost-effectiveness acceptability curves which show the probability that an intervention is cost-effective for a given cost-effectiveness threshold (cost per QALY).
- Sensitivity and scenario analyses will be undertaken explore the robustness of the cost-effectiveness results to changes in the parameter inputs (e.g. impact of increasing/decreasing sensitivity and specificity) structural assumptions of the model and the time horizon.
- Heterogeneity in the cost-effectiveness estimates will be assessed based on the findings of the clinical effectiveness review.

It is anticipated that the model will be developed in either Microsoft Excel or the statistical programming language of R; the choice of software will have to await the final conceptualisation of the model. However, due to the potential complexities of reflecting referral for colposcopy through the NHS Cervical Screening Programme based on HPV triage (including test of cure) or the HPV primary screening algorithm (including test of cure), it may be necessary to use discrete event simulation (DES) as opposed to a more conventional state-transition modelling approach. If a DES approach is considered more appropriate then the feasibility of developing this in standard software packages (e.g. Microsoft Excel, R, TreeAge Pro) will be assessed. Should a non-standard standard software package (e.g. SIMUL8) be required, then this will be discussed and with Assessment subgroup and permission sought.

Handling information from the companies

Any 'commercial in confidence' data provided by the manufacturers (DySIS Medical and Zilico Ltd) and specified as such will be highlighted in blue and underlined in the assessment report. Any 'academic in confidence' data provided by the manufacturers will be highlighted in yellow and underlined in the assessment report.

If confidential information is included in economic models then a version using dummy data or publically available data in place of confidential data will be provided.

Competing interests of authors

None of the authors have any conflicts of interest.

Timetable/milestones

Milestone	Date to be completed
Submission of final protocol	23/12/2016
Submission of progress report	27/03/2017
Submission of draft Diagnostic Assessment Report	25/05/2017
Submission of final Diagnostic Assessment Report	23/06/2017

References

1. Etherington IJ, Luesley DM, Shafi MI, Dunn J, Hiller L, Jordan JA. Observer variability among colposcopists from the West Midlands region. *British Journal of Obstetrics and Gynaecology* 1997;**104**:1380-4.
2. Hopman EH, Voorhorst FJ, Kenemans P, Meyer CJ, Helmerhorst TJ. Observer agreement on interpreting colposcopic images of CIN. *Gynecol Oncol* 1995;**58**:206-9. http://dx.doi.org/10.1006/gyno.1995.1212
3. National Institute for Health and Care Excellence. *The ZedScan as an adjunct to colposcopy in women with suspected cervical intra‐epithelial neoplasia. Medtech innovation briefing [MIB20]*. NICE; 2015. URL: https://www.nice.org.uk/advice/mib20/chapter/Technology-overview (Accessed 24th November, 2016).
4. Ferris DG, Litaker M, Group A. Interobserver agreement for colposcopy quality control using digitized colposcopic images during the ALTS trial. *Journal of Lower Genital Tract Disease* 2005;**9**:29-35.
5. Ferris DG, Litaker MS. Cervical biopsy sampling variability in ALTS. *Journal of Lower Genital Tract Disease* 2011;**15**:163-8.
6. Zuchna C, Hager M, Tringler B, Georgoulopoulos A, Ciresa-Koenig A, Volgger B*, et al.* Diagnostic accuracy of guided cervical biopsies: a prospective multicenter study comparing the histopathology of simultaneous biopsy and cone specimen. *American Journal of Obstetrics & Gynecology* 2010;**203**:321.e1-6.
7. Wade R, Spackman E, Corbett M, Walker S, Light K, Naik R*, et al.* 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 Technology Assessment* 2013;**17**:1-240.
8. *Cervical cancer incidence statistics*. Cancer Research UK. URL: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/cervical-cancer/incidence (Accessed 24th November, 2016).
9. *Cervical cancer statistics*. Cancer Research UK. URL: http://www.cancerresearchuk.org/health-professional/cancer-statistics/statistics-by-cancer-type/cervical-cancer (Accessed 24th November, 2016).
10. International Agency for Research on Cancer. *IARC monographs on the evaluation of carcinogenic risks to humans. Agents classified by the IARC monographs, volumes 1-117*. Lyon: IARC; 2016. URL: http://monographs.iarc.fr/ENG/Classification/index.php (Accessed 29th November, 2016).
11. Bosch FX, Burchell AN, Schiffman M, Giuliano AR, de Sanjose S, Bruni L*, et al.* Epidemiology and natural history of human papillomavirus infections and type-specific implications in cervical neoplasia. *Vaccine* 2008;**26 Suppl 10**:K1-16. http://dx.doi.org/10.1016/j.vaccine.2008.05.064
12. Cox JT, Schiffman M, Solomon D. Prospective follow-up suggests similar risk of subsequent cervical intraepithelial neoplasia grade 2 or 3 among women with cervical intraepithelial neoplasia grade 1 or negative colposcopy and directed biopsy. *American journal of obstetrics and gynecology* 2003;**188**:1406-12.
13. Goldie SJ, Kohli M, Grima D, Weinstein MC, Wright TC, Bosch FX*, et al.* Projected clinical benefits and cost-effectiveness of a human papillomavirus 16/18 vaccine. *Journal of the National Cancer Institute* 2004;**96**:604-15.
14. Insinga RP, Dasbach EJ, Elbasha EH. Epidemiologic natural history and clinical management of Human Papillomavirus (HPV) Disease: a critical and systematic review of the literature in the development of an HPV dynamic transmission model. *BMC Infectious diseases* 2009;**9**:1.
15. Castle PE, Schiffman M, Wheeler CM, Solomon D. Evidence for frequent regression of cervical intraepithelial neoplasia-grade 2. *Obstetrics and gynecology* 2009;**113**:18.

16. Jeronimo J, Massad LS, Schiffman M. Visual appearance of the uterine cervix: correlation with human papillomavirus detection and type. *American Journal of Obstetrics and Gynecology* 2007;**197**:47 e1-8.
17. *NHS cervical screening programme. Colposcopy and programme management. NHSCSP publication number 20*. London: Public Health England; 2016.
18. *Achievable standards, benchmarks for reporting, and criteria for evaluating cervical cytopathology. Third edition including revised performance indicators. NHSCSP Publication no 1*. Sheffield: NHS Cervical Screening Programmes; 2013.
19. Solomon D, Nayar R. *The Bethesda system for reporting cervical cytology*. New York: Springer-Verlag; 2004.
20. Health and Social Care Information Centre. *Cervical screening programme, England statistics 2014-15*. Leeds: Health and Social Care Information Centre; 2015.
21. *Changes to cervical cancer screening*. Department of Health; 2016. URL: https://www.gov.uk/government/news/changes-to-cervical-cancer-screening (Accessed 24th November, 2016).
22. Moss S, Gibney A. *HPV primary screening pilots: evaluation report to the National Screening Committee* London: Centre for Cancer Prevention, Wolfson Instititue, Queen Mary University of London; 2015.
23. Kitchener HC, Almonte M, Thomson C, Wheeler P, Sargent A, Stoykova B*, et al.* HPV testing in combination with liquid-based cytology in primary cervical screening (ARTISTIC): a randomised controlled trial. *Lancet Oncol* 2009;**10**:672-82. http://dx.doi.org/10.1016/s1470-2045(09)70156-1
24. Public Health England. *HPV primary screening pilot protocol algorithm*: Public Health England; 2016.
25. Scottish Intercollegiate Guidelines Network. *Management of cervical cancer. A national clinical guideline*. Edinburgh: SIGN; 2008.
26. *HPV primary screening pilot. Colposcopy management recommendations algorithm*. NHS Cancer Screening Programmes, Public Health England; 2015. URL: https://www.gov.uk/government/publications/human-papillomavirus-hpv-primary-screening-colposcopy-management (Accessed 285th November, 2016).
27. Centre for Reviews and Dissemination. *Systematic reviews: CRD's guidance for undertaking reviews in health care*. York: Centre for Reviews and Dissemination; 2009.
28. Moher D, Liberati A, Tetzlaff J, Altman DG. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *Annals of internal medicine* 2009;**151**:264-9.
29. Burchett H, Umoquit M, Dobrow M. How do we know when research from one setting can be useful in another? A review of external validity, applicability and transferability frameworks. *Journal of health services research & policy* 2011;**16**:238-44.
30. Reitsma JB, Glas AS, Rutjes AW, Scholten RJ, Bossuyt PM, Zwinderman AH. Bivariate analysis of sensitivity and specificity produces informative summary measures in diagnostic reviews. *J Clin Epidemiol* 2005;**58**:982-90. http://dx.doi.org/10.1016/j.jclinepi.2005.02.022
31. Rutter CM, Gatsonis CA. A hierarchical regression approach to meta-analysis of diagnostic test accuracy evaluations. *Stat Med* 2001;**20**:2865-84.
32. Karnon J, Peters J, Platt J, Chilcott J, McGoogan E, Brewer N. Liquid-based cytology in cervical screening: an updated rapid and systematic review and economic analysis. *Health Technology Assessment* 2004;**8**:1-78.
33. Hadwin R, Eggington S, Brennan A, Walker P, Patnick J, Pilgrim H. Modelling the cost-effectiveness and capacity impact of changes to colposcopy referral guidelines for women with mild dyskaryosis in the UK Cervical Screening Programme. *BJOG: An International Journal of Obstetrics & Gynaecology* 2008;**115**:749-57.

Appendix: Proposed MEDLINE search strategy

Database: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) <1946 to Present>

1 Cervix Uteri/ (26971)
2 cervix.ti,ab. (42969)
3 cervic$.ti,ab. (207320)
4 (endocervix or endo-cervix).ti,ab. (1150)
5 (endocervic$ or endo-cervic$).ti,ab. (5114)
6 (ectocervix or ecto-cervix).ti,ab. (394)
7 (ectocervic$ or ecto-cervic$).ti,ab. (639)
8 ((squamocolumnar or squamo-columnar) adj2 junction).ti,ab. (553)
9 transformation zone$.ti,ab. (1023)
10 or/1-9 (241009)
11 Colposcopy/ (6143)
12 Colposcopes/ (190)
13 Spectrum Analysis/ (44955)
14 Dielectric Spectroscopy/ (1589)
15 (colposcop$ adj4 (adjunct$ or digital$ or DSI or computer$ or video$ or alternative$ or conventional$)).ti,ab. (215)
16 (impedance adj2 spectroscop$).ti,ab. (5168)
17 (Dielectric adj2 Spectroscop$).ti,ab. (1201)
18 (impedance adj2 spectrometr$).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$).ti,ab. (19)
23 (optical adj2 spectroscop$).ti,ab. (5003)
24 ((point or pencil or impedance) adj2 probe$).ti,ab. (528)
25 (microcolposcop$ or micro-colposcop$).ti,ab. (19)
26 (dysis or dysismap).ti,ab. (31)
27 dynamic spectral imaging.ti,ab. (16)
28 Zilico.ti,ab. (0)
29 (ZedScan or Zed Scan).ti,ab. (0)
30 (APX 100 or APX100).ti,ab. (2)
31 EIS.ti,ab. (2908)
32 epitheliometer$.ti,ab. (1)
33 MKIII.ti,ab. (32)
34 or/11-33 (63597)
35 10 and 34 (4725)
36 exp animals/ not humans/ (4669488)
37 35 not 36 (4695)
38 limit 37 to yr="2000 -Current" (2399)