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

1. Title of the project:

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

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

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

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

Eldon Spackman Research Fellow Centre for Health Economics
University of York, Heslington, York
YO10 5DD
Tel: (01904) 321422
Fax: (01904) 321402
Email: eldon.spackman@york.ac.uk

3. Plain English summary

2,828 women were diagnosed with cervical cancer in the UK in 2007, making it the eleventh most common cancer in women, and accounting for around 2% of all cancers among women. Women will develop changes in the cervix many years before any progression to cancer. These pre-malignant changes are called high grade cervical intraepithelial neoplasia (CIN). Women may also get low grade CIN which is not precancerous but can cause changes at cervical screening.

Women in England between the ages of 25 and 64 are invited for regular cervical screening every three to five years under the NHS Cervical Screening Programme in order to detect abnormalities of the cervical cells. Screening is conducted using liquid based cytology (LBC) where a sample of cells is brushed from the cervix. If the test identifies abnormal cells they are described as 'dyskaryosis'. These abnormalities can range from borderline changes to severe dyskaryosis.

Women with an abnormal result from their LBC test, or repeated inadequate or borderline results, are referred for a colposcopy examination. With the introduction of HPV triage guidelines in 2011/2012, patients with borderline or mild abnormalities who also test positive for high risk human papillomavirus (HPV) should be referred for colposcopy, whilst those who test negative for high risk HPV should be returned to routine recall for cervical screening.

A colposcope (a binocular with a bright light) enables the cervix to be magnified and clearly seen; any abnormal area can be biopsied for histological analysis to diagnose CIN or invasive cervical cancer. There were 155,414 referrals for colposcopy in 2009–2010 in England; 78.6% of these were as a result of cervical screening and 17.5% were referred with symptoms, 3.9% were referred for reasons not otherwise specified. There were 453,947 appointments at colposcopy clinics in England in 2009–2010.

Colposcopy involves a significant amount of subjective assessment. The DySIS digital video colposcope (DySIS Medical), the LuViva Advanced Cervical Scan (Guided Therapeutics), the Niris Imaging System (Imalux Corporation) and the APX 100 device (Zilico Ltd) have been developed for use as an adjunct to colposcopy to improve its accuracy.

The DySIS system maps the whitening effect following application of acetic acid (aceto-whitening) to the cervix, to assist the clinician in selecting areas for biopsy and treatment. Aceto-whitening is highly correlated with the altered structure and functionality of abnormal cervical epithelium. The LuViva Advanced Cervical Scan has been designed to detect changes in cervical cells by shining light on the cervix and measuring the patterns of light reflected. The Niris Imaging System directs near infra-red light at the cervix; the intensity of light reflected back is a function of tissue structure and content, allowing differentiation of normal and abnormal tissue. The APX 100 device has been designed to measure the resistivity of cervical cells to distinguish between normal and abnormal tissue.

The main purpose of this project is to assess the benefits, adverse effects and cost-effectiveness of the DySIS digital video colposcope (DySIS Medical), the LuViva Advanced Cervical Scan (Guided Therapeutics), the Niris Imaging System (Imalux Corporation) and the APX 100 device (Zilico Ltd) used as an adjunct to colposcopy for patients referred for colposcopy through the NHS Cervical Screening Programme.

4. Decision problem

4.1. Objectives

The aim of the project is to determine the clinical and cost-effectiveness of adjunctive colposcopy technologies for examination of the uterine cervix for patients referred for colposcopy through the NHS Cervical Screening Programme; the technologies under consideration are DySIS, LuViva Advanced Cervical Scan, Niris Imaging System and APX 100. The clinical outcomes to be considered are diagnostic test accuracy outcomes (e.g. sensitivity and specificity), adverse effects and patient experience.

4.2. Interventions

DySIS (developed by DySIS Medical)

The Dynamic Spectral Imaging System (DySIS) or Dynamic Spectral Imaging colposcope, is a digital image analysing system, for detecting cancerous and precancerous cervical tissue. DySIS maps the whitening effect following application of acetic acid (aceto-whitening) on the epithelium of the cervix, to assist the clinician in selecting areas for biopsy and treatment. It does this by producing a quantitative measurement of the rate, extent, and duration of aceto-whitening, which is highly correlated with the altered structure and functionality of abnormal epithelial cells of the cervix. The dynamic map produced can be overlaid on a colour image to assist in determining the presence and grade of any neoplastic lesion. DySIS is designed to work in conjunction with a bespoke DySIS speculum.

DySIS consists of an optical head with a white light-emitting diode for uniform illumination, magnification optics coupled to a digital colour charged-coupled device camera for image capture, and a computer and control electronics unit with a thin film transistor monitor for image and data display. Linear polarisers are used in both the imaging and illumination pathways to reduce surface reflection (which might obscure the acetowhitening effect). The optical head does not come into contact with the tissue and magnifies images between 10 and 27 times.[1] It is mounted on a mechanical arm to position and stabilise it, and locked onto an extension shaft attached to the speculum, to ensure a stable field-of-view during image acquisition. For this reason, the speculum used with DySIS is different from the standard specula used in colposcopy and gynaecology practice.

DySIS has a CE mark and the cost in the UK ranges from £18,000 to £22,000. This is around twice the cost of a standard colposcope. Costs for specula are £3.50 per examination.[2]

LuViva Advanced Cervical Scan (developed by Guided Therapeutics)

LuViva distinguishes between normal and diseased tissue by detecting biochemical and morphological changes at the cellular level. This is done using optical spectroscopy; light is directed at the cervix and the resulting fluorescence and reflectance spectra are collected and analysed. LuViva consists of a base unit with a results display, and a single-use guide which is placed on the surface of the cervix.[3]

LuViva costs £11,500 and the single-use guide costs £17.25 per patient.[2] It is expected to receive a CE mark by the end of 2011 and should be available in the UK in early 2012.

Niris Imaging System (developed by Imalux Corporation)

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

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

Niris probes have a limited useful life of around 200 patient procedures but can be processed for re-use. A probe sheath is used to provide physical stability and help prevent cross-contamination.

The Niris Imaging System costs $49,500 (around £31,000) plus taxes and shipping. The probe costs $2,700 (around £1700) and a disposable sheath costs $30 (around £19).[2] The device is expected to receive a CE mark and become available in the UK in October, 2011.

APX 100 (developed by Zilico Ltd)

The APX 100 handset device, designed to work in conjunction with a standard speculum, measures the resistivity (via electrical impedance spectroscopy) of cervical epithelial cells to distinguish between normal and abnormal tissue. The degree of impedance seen is related to tissue structure; normal, pre-cancerous, and cancerous cervical tissue has different structures.

The handset takes readings by direct contact (using a disposable sleeve) with the cervix. A base station charges the handset and collects data (which can then be transferred to a computer). Results from each reading site are compared with reference spectra, derived from models of different cervical tissues, to calculate the probability of high grade neoplasia. The exact location for biopsy is determined by using the device in a second, single-point, operating mode. In this mode the device will immediately

indicate when it has been placed onto high-grade CIN and a biopsy can be taken or the patient offered immediate treatment.[2]

Zilico aim to use data from a recent trial to obtain a CE mark and expects to launch the APX 100 by the end of 2011. The device costs £2000 and single-use, disposable sleeves cost £20.[2]

4.3. Comparator technologies

Standard colposcopy, with directed biopsy/treatment when necessary, is the current usual management for women referred with abnormal cytology results. A colposcope is a binocular field microscope used to examine the cervix following sequential application of saline, 3–5% acetic acid, and sometimes Lugol's iodine to identify any epithelial changes or capillary vessel patterns suggestive of disease. Histological examination of any biopsied tissue, which is the gold standard for diagnosis of cervical intraepithelial neoplasia (CIN) or invasive cervical cancer, is then undertaken. The initial outcome of colposcopy is classified as being adequate, where the whole of the transformation zone (and any lesions) can be viewed, or inadequate, where full visualisation is not possible, and where further investigation may be required. The skills of the colposcopist relate to training, experience, and the volume of patients seen. Colposcopy involves a significant amount of subjective assessment – results from the same patient may vary when assessed by different colposcopists.[4] Details of referral cytology results, other clinical information, the type of management available, and the number of biopsies taken are also relevant when interpreting the results of colposcopy.

A meta-analysis of nine studies published in 1998 estimated the sensitivity and specificity of colposcopy as being 96% and 48% respectively in detecting CIN2+, and 85% and 69% respectively when differentiating between normal/low-grade CIN and high-grade CIN/cancer,[5] although most studies appeared to be subject to bias.[6] More recently, better quality studies have reported a sensitivity of around 57% for detecting CIN2+[7] and around 56% for detecting CIN3+.[8]

A standard colposcope costs between £6000–£12,000 and a disposable speculum costs £2.[2]

4.4. Population and relevant subgroups

2,828 women were diagnosed with cervical cancer in the UK in 2007, making it the eleventh most common cancer in women, and accounting for around 2% of all cancers among women. Cervical cancer is the most common cancer in females aged under 35; 702 women aged under 35 were diagnosed with cervical cancer in the UK in 2007.[9] Women will develop changes in the cervix many years before any progression to cancer. These pre-malignant changes are high grade CIN. Women may also get low grade CIN, which is not precancerous, but can cause changes at cervical screening.

Infection with certain genotypes of human papillomavirus (HPV), in particular HPV 16 and HPV 18, have been shown to be associated with the development of cervical cancer and CIN; almost all cervical cancers contain high risk HPV DNA. However, most HPV infections will not progress to CIN; the cell changes associated with HPV will regress to normal. Certain risk factors are associated with the progression of HPV infection to CIN, including the HPV genotype, early age at first intercourse, long duration of the most recent sexual relationship and cigarette smoking.[9]

Women in England between the ages of 25 and 64 are invited for regular cervical screening every three years (if aged between 25 and 49 years) or every five years (if aged between 50 and 64 years) under the NHS Cervical Screening Programme.[10] Most screening is conducted using liquid based cytology; a sample of exfoliated cells is brushed from the transformation zone of the cervix for assessment in a pathology laboratory. Cytological assessment is performed to detect nuclear abnormalities, which are described as dyskaryotic. The degree of dyskaryosis can range from mild to severe, or borderline changes may be seen.

Just under 3.3 million women aged between 25 and 64 attended for cervical screening in 2009–2010; the percentage of eligible women who were recorded as screened at least once in the previous 5 years was

78.9%. Approximately 3.7 million samples were examined in 2009–2010, of which 3.4 million (92.9%) were submitted by GPs and NHS community clinics (suggesting that they were part of the NHS Cervical Screening Programme).[11]

2.9% of tests did not have a result, owing to an inadequate sample. This figure has dropped significantly (from approximately 9%) since the introduction of liquid based cytology. Women with an inadequate sample should be recalled for a repeat test; if women have three consecutive inadequate results, they should be referred for colposcopy.

The table below presents a summary of cytology test results and management options for patients with an adequate test result, submitted by GPs and NHS community clinics. However, the management of patients will change with the introduction of new guidelines for HPV triage, due to be implemented in 2011/2012.[12] These are discussed further below.

Result	Definition	Action*	Proportion (2009–2010)**
Negative	No nuclear abnormalities	Place on routine recall	93.2%
Borderline changes	Nuclear changes that are not normal are present. Unsure whether the changes are dyskaryosis	Repeat the test in 6 months. Most will have reverted to normal. After 3 consecutive normal results, return to normal recall. If abnormality persists (3 times) or worsens, refer for colposcopy. If in a ten year period there are 3 borderline or more severe results, refer for colposcopy	3.8%
Mild dyskaryosis	Nuclear abnormalities that are indicative of low grade CIN	Refer for colposcopy (although it remains acceptable to repeat the test in 6 months instead – most will have reverted to normal after 6 months). Refer to colposcopy if changes persist on 2 occasions	1.9%
Moderate dyskaryosis	Nuclear abnormalities reflecting probable CIN2	Refer for colposcopy	0.5%
Severe dyskaryosis	Nuclear abnormalities reflecting probable CIN3	Refer for colposcopy	0.6%

*Recommendations taken from Colposcopy and Programme Management[10]

**Figures taken from Cervical Screening Programme England 2009–10[11]

There were 155,414 referrals for colposcopy in 2009–2010; 78.6% of these were as a result of screening and 17.5% were clinically indicated, 3.9% were referred for reasons not otherwise specified. Of women referred for colposcopy via the NHS Cervical Screening Programme, 58.8% were referred for borderline changes or mild dyskaryosis; 12.3% were referred for moderate dyskaryosis and 15.8% were referred for severe dyskaryosis or worse. There were a total of 453,947 appointments at colposcopy clinics in 2009–2010; 41.9% of which were new appointments, 7.9% were return appointments for treatment and 50.2% were follow-up appointments.[11]

27% of appointments were not attended; 2.6% were cancelled by the patient on the day, 10.2% were cancelled in advance, 10.5% were not attended with no advance warning and 3.7% were cancelled by the clinic.[11]

Overall, 63.5% of women attending for colposcopy had some treatment or procedure at their first attendance, the most common treatment or procedure at first attendance was diagnostic biopsy, carried out at 45.5% of first attendances. The most common procedure at first attendance for women referred for low-grade abnormalities was diagnostic biopsy, whilst the most common procedure at first attendance for women referred for high-grade abnormalities was excision. The majority of those women presenting with

high-grade abnormalities who had either no treatment, or only diagnostic biopsy at first attendance, are likely to have received therapeutic treatment at a subsequent attendance.[11]

New guidelines due to be implemented in 2011/2012 state that samples from women with low grade abnormalities (borderline changes or mild dyskaryosis on cytology) should be tested for high risk HPV for triage for referral for colposcopy.[12] The test is performed on the liquid based cytology sample already obtained as part of the NHS Cervical Screening Programme. Women who test positive for high risk HPV should be referred for colposcopy, whilst women who test negative for high risk HPV should be returned to routine recall.

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

4.5. Place of the intervention in the care pathway

Women with an abnormal cytology result, or repeated inadequate or borderline cytology results, are referred for colposcopy. According to the new HPV triage guidelines due to be implemented in 2011/2012 women with a borderline or mild dyskaryosis result should only be referred for colposcopy if they also test positive for high risk HPV. Colposcopy is used to visualise the cervix; if any abnormal area is identified a biopsy is taken and sent for histological analysis. Colposcopy clinics are usually located within gynaecology or genitourinary medicine departments of general hospitals, although some colposcopy may take place in primary care in the future.

DySIS, LuViva Advanced Cervical Scan, Niris Imaging System and APX 100 are used as an adjunct to standard colposcopy.

5. Report methods for assessing the outcomes arising from the use of the interventions

A systematic review of the evidence on the adjunctive colposcopy technologies; DySIS, LuViva Advanced Cervical Scan, Niris Imaging System and APX 100, compared with standard colposcopy will be conducted. The review will be conducted following the general principles recommended in CRD's guidance[13] and the PRISMA statement.[14]

Inclusion and exclusion criteria

The titles and abstracts of records identified by the search strategy will be examined for relevance by two reviewers independently. Full papers of any potentially relevant records will be obtained where possible and screened by two reviewers independently. The relevance of each study to the review and the decision to include/exclude studies will be made according to the inclusion criteria detailed below. Any disagreements will be resolved by consensus.

Participants

Studies of women referred for colposcopy because of an abnormal cytology result will be eligible for inclusion. Studies that also include women referred for colposcopy because of symptoms indicative of cervical cancer (e.g. post-coital bleeding) or women referred for colposcopy for follow-up of CIN will be eligible for inclusion. Studies that only include women referred for colposcopy because of symptoms indicative of cervical cancer or for follow-up of CIN will be excluded.

Interventions/comparators

Studies comparing DySIS (DySIS Medical), LuViva Advanced Cervical Scan (Guided Therapeutics), Niris Imaging System (Imalux Corporation) or APX 100 (Zilico Ltd) with standard colposcopy will be eligible for inclusion. Comparisons of any of these interventions plus colposcopy compared with colposcopy alone are also eligible for inclusion.

Outcomes

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

Study designs

Comparative studies will be eligible for inclusion, including diagnostic test accuracy studies and controlled trials.

Literature searching

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

Extensive searches of the literature relating to the specified technologies (DySIS, LuViva Advanced Cervical Scan, Niris Imaging System and APX 100).

Additional supplementary searches will be carried out as necessary. Searches for studies for cost and quality of life data will also be included, as determined by the model.

Electronic sources will be searched for primary studies. These sources will include MEDLINE, EMBASE, CINAHL, HMIC, ISI Science Citation Index and the Cochrane Library (including the Cochrane Database of Systematic Reviews (CDSR), the Database of Abstracts of Reviews of Effects (DARE), the Health Technology Assessment (HTA) Database, the NHS Economic Evaluation Database (NHS EED) and CENTRAL).

Ongoing and unpublished studies will be searched for using appropriate sources, including controlled trials.com and other web-based resources.

Where necessary, relevant reviews and guidelines will be identified through searching additional resources, including Clinical Evidence, National Institute for Health and Clinical Excellence (NICE) website, NHS Evidence – National Library of Guidelines, SIGN Guidelines, the Guidelines International Network website.

The searches will combine terms for cervix with terms for the technologies being assessed. For the technologies we will use both generic terms (e.g. colposcopy) and terms for specific products (e.g. DySIS).

Search terms will be identified by scanning key papers identified during the review, through discussion with the review team and clinical experts, and by using database thesauri. Reference lists of included papers will be assessed and the abstracts of relevant conferences will be searched, where possible, for additional relevant studies. Searches will be limited by date, according to the date of development of the new technologies. No limits relating to language or study design will be applied to the searches.

Data extraction strategy

Data relating to both study characteristics and results will be extracted by one reviewer using a standardised data extraction form and independently checked by another. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary. If time constraints allow, attempts will be made to contact authors for any missing data. Data from multiple publications of the same study will be extracted as a single study.

Quality assessment strategy

The quality of the included studies will be assessed using standard checklists[13] adapted as necessary to incorporate topic-specific quality issues. The methodological quality of diagnostic test accuracy studies will be assessed using the QUADAS tool.[15]

The assessment will be performed by one reviewer, and independently checked by another. Discrepancies will be resolved by discussion, with involvement of a third reviewer when necessary.

The results of the quality assessment will be tabulated and the more important methodological problems will be discussed in terms of their potential effect on the results of the included studies. In addition, if data allow, quality components will be used in sensitivity analyses.

Methods of analysis/synthesis

In the initial analysis/synthesis of data, the results of data extraction will be presented in structured tables and as a narrative summary, grouped by participant and intervention characteristics. Where possible, data will be presented separately for the specific subgroups of interest (participants with borderline changes, or mild or moderate dyskaryosis), and/or other relevant participant characteristics (e.g. women known to be more challenging in colposcopy such as pregnant women or post-menopausal women). Where sufficient clinically and statistically homogenous data are available, data will be pooled using appropriate meta-analytic techniques. Clinical, methodological and statistical heterogeneity will be investigated.

6. Report methods for synthesising evidence of cost-effectiveness

6.1. Identifying and systematically reviewing published cost-effectiveness studies

Searches for economic evaluations will be undertaken in the databases listed in section 5. These sources will be used to identify any studies of the cost-effectiveness of DySIS (DySIS Medical), LuViva Advanced Cervical Scan (Guided Technologies), Niris Imaging System (Imalux Corporation) or APX 100 (Zilico Ltd), against colposcopy or each other. A broad range of study designs will be considered in the assessment of cost-effectiveness including economic evaluations conducted alongside randomised or non randomised trials, modelling studies and analyses of administrative data sets. The review will focus on full economic evaluations that compare two or more options and consider both costs and consequences (including cost-effectiveness and cost–benefit analyses). To gain an insight into the modelling methods we will also consider cost-effectiveness studies examining screening for cervical cancer. These studies will not be subject to a formal assessment but will be used, if necessary, to assist in the overall development of a new analytical model with the aim of identifying important structural assumptions, parameter estimates and highlighting key areas of uncertainty.

The quality of the studies identified will be assessed according to the criteria for economic evaluation detailed in the methodological guidance developed by NICE.[16] This information will be tabulated and summarised within the report. In particular, information will be extracted on the comparators, study population, main analytic approaches, primary outcome measures, quality of life estimates, costs, estimates of incremental cost-effectiveness and approaches to quantifying decision uncertainty.

In a brief review of the literature no cost-effectiveness modelling has been undertaken on diagnostics that identify CIN. Multiple modelling efforts have been undertaken to determine the cost-effectiveness of screening or HPV vaccination in the UK.[17–21] Since both screening and vaccination occur upstream from diagnosis of CIN much of the previously published model structure and many of the inputs may be useful in our current modelling efforts. It is possible that a previously developed model can be adapted for the current study. The usefulness of previous models will be judged based on:

1. appropriateness for the decision problem being considered in this assessment
2. relevance of outputs for decision making (i.e. need to be able to estimate long-term NHS costs and QALYs)
3. ability to reproduce the model or to collaborate with model developers.

6.2. Evaluation of costs, quality of life and cost-effectiveness

A decision model will be developed (as above, probably based on an existing model) to estimate the cost-effectiveness of DySIS, LuViva Advanced Cervical Scan, Niris Imaging System, APX 100 and standard colposcopy for patients referred for colposcopy through the NHS Cervical Screening Programme. The perspective will be that of the NHS and Personal Social Services (PSS), health outcomes will be expressed in terms of quality-adjusted life years (QALYs) and both costs and health outcomes will be discounted at a rate of 3.5% per annum in accordance with methodological guidance developed by NICE.[16]

DySIS, LuViva Advanced Cervical Scan, Niris Imaging System and APX 100 aim to improve the accuracy of colposcopy, resulting in the improved identification of cancerous and precancerous cervical tissue.

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

Resource utilisation and costs will be estimated for DySIS, LuViva Advanced Cervical Scan, Niris Imaging System, APX 100 and standard colposcopy. These costs will include the costs of the diagnostic tests which will be dependent on capital costs of the equipment, consumables, annual maintenance costs and staff costs (including any training costs) as well as the costs of procedures occurring as a result of the tests, for example biopsies and excisions. It will be important to consider patient throughput and its impact on the cost per patient for the diagnostic tests. The diagnostic test's accuracy will also influence throughput as a large number of false positives will unnecessarily increase follow-up. Data for the cost analysis will be drawn from routine NHS sources[22] and discussions with individual hospitals and manufacturers of the technologies considered.

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

- sensitivity and specificity of the different technologies
- resource utilisation and costs for the different technologies
- links to long-term outcomes
- adherence to colposcopy and follow-up
- 'see and treat' rates,

The specific objectives of the cost-effectiveness analysis are:

- To use an economic model to estimate the cost-effectiveness of DySIS, LuViva Advanced Cervical Scan, Niris Imaging System, APX 100 and standard colposcopy for diagnosis of patients referred for colposcopy through the NHS Cervical Screening Programme. Health outcomes will be in terms of QALYs and the perspective taken will be the NHS and PSS.
- To populate the model using the most appropriate data identified from published literature and other sources.
- To characterise the uncertainty in the data used to populate the model and present the resulting uncertainty in the results to decision makers. A probabilistic model will be developed which requires that, where possible, uncertainty in inputs are reflected through the use of appropriate distributions.

Using Monte Carlo simulation, this parameter uncertainty will be translated into uncertainty in the overall results. This will be presented graphically using cost-effectiveness acceptability curves which show the probability that an intervention is cost-effective for a given cost-effectiveness threshold (cost per QALY).

- To use sensitivity analyses to examine alternative assumptions in the data and to see how sensitive the results are to different assumptions.

7. Handling information from the companies

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

8. Competing interests of authors

None of the authors has any conflicts of interest.

9. Timetable/milestones

Milestone	Date to be completed
Submission of final protocol	19/09/11
Submission of progress report	14/11/11
Submission of draft Diagnostic Assessment Report	11/01/12
Submission of Diagnostic Assessment Report	08/02/12

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