NATIONAL INSTITUTE FOR HEALTH AND CARE EXCELLENCE

DIAGNOSTICS ASSESSMENT PROGRAMME

Diagnostics consultation document

Adjunctive colposcopy technologies for assessing suspected cervical abnormalities: the DYSIS colposcope with DYSISmap and the Zedscan I

The National Institute for Health and Care Excellence (NICE) is producing guidance on using adjunctive colposcopy technologies in the NHS in England. The diagnostics advisory committee has considered the evidence base and the views of clinical and patient experts.

This document has been prepared for public consultation. It summarises the evidence and views that have been considered, and sets out the draft recommendations made by the committee. NICE invites comments from registered stakeholders, healthcare professionals and the public. This document should be read along with the evidence base (the diagnostics assessment report and the diagnostics assessment report addendum).

The advisory committee is interested in receiving comments on the following:

- Has all of the relevant evidence been taken into account?
- Are the summaries of clinical and cost effectiveness reasonable interpretations of the evidence?
- Are the provisional recommendations sound, and a suitable basis for guidance to the NHS?

Equality issues

NICE is committed to promoting equality of opportunity, eliminating unlawful discrimination and fostering good relations between people with particular protected characteristics and others. Please let us know if you think that the preliminary recommendations may need changing in order to meet these aims. In particular, please tell us if the preliminary recommendations:

- could have a different effect on people protected by the equality legislation than on the wider population, for example by making it more difficult in practice for a specific group to access the technology
- could have any adverse effect on people with a particular disability or disabilities.

Please provide any relevant information or data you have regarding such effects and how they could be avoided or reduced.

Note that this document is not NICE's final guidance on adjunctive colposcopy technologies. The recommendations in section 1 may change after consultation.

After consultation, the committee will meet again to consider the evidence, this document and comments from the consultation. After considering these comments, the committee will prepare its final recommendations, which will be the basis for NICE's guidance on the use of the technology in the NHS in England.

For further details, see the Diagnostics Assessment Programme manual.

Key dates:

Closing date for comments: 16 November 2017

Third diagnostics advisory committee meeting: 10 January 2018

1 Draft recommendations

1.1 The Dynamic Spectral Imaging System [DYSIS] colposcope with DYSISmap shows promise and is recommended for use in assessing suspected cervical abnormalities in people referred for colposcopy. Centres using the technology should audit their outcomes (see section 5.16).

1.2 Further research on the effects of using the DYSIS colposcope with DYSISmap on clinical and patient outcomes, particularly when used in a human papilloma virus primary screening setting, and on patient experience (see sections 6.1 to 6.3) is also recommended.

1.3 The ZedScan I shows promise when used in assessing suspected cervical abnormalities, but there is currently not enough evidence to

recommend its routine adoption. Further research (see sections 6.1 to 6.3) on the effects of using the technology on clinical and patient outcomes is recommended. Colposcopy services currently using the ZedScan I are encouraged to collect data to produce more evidence. Colposcopy services not currently using the ZedScan I should only use it as part of a research study.

2 Clinical need and practice

The problem addressed

2.1 The Dynamic Spectral Imaging System (DYSIS) colposcope with DYSISmap and the ZedScan I adjunctive colposcopy technologies are intended to be used with colposcopy to help identify cervical intraepithelial neoplasia (CIN) during a colposcopy examination. Assessment using conventional colposcopy is subjective and can be associated with both inter- and intra-observer variability, particularly with lower-grade abnormalities. Conventional colposcopy is usually done using a binocular colposcope, unless the clinic has a DYSIS colposcope which incorporates a digital (video) colposcope.

2.2 The adjunctive colposcopy technologies aim to give an objective evaluation of cellular changes, known as CIN, using methods such as optical or electrical impedance spectroscopy to assess the characteristics of cervical cells. CIN is a term that is used to describe precancerous changes in cells in the surface layer of the cervix (the cervical epithelium). Most cellular changes arise in an area of the cervix known as the transformation zone, where the endocervical canal (the internal canal of the cervix) meets the external part of the cervix. This is the area of the cervix that is examined during a conventional colposcopy examination, and from which a sample is taken for a cervical screening test. Less often, abnormalities occur on the inside of the cervical canal instead of

the surface, and these changes are known as cervical glandular intraepithelial neoplasia (CGIN).

2.3 The results provided by the technologies can help a colposcopist to determine whether further treatment or biopsies are needed, by guiding them to areas that are most likely to be abnormal. When the results did not suggest any areas of abnormality, and the conventional colposcopy examination was normal, the colposcopist can be more confident that high-grade disease is unlikely to be present. It is claimed that using the devices may result in more accurate detection of cervical abnormalities and identification of the correct sites for biopsy.

2.4 The purpose of this assessment is to evaluate the clinical and cost effectiveness of the DYSIS colposcope with DYSISmap and the ZedScan I. It is a full update of the NICE diagnostics guidance on the DYSIS colposcope with DYSISmap and the Niris Imaging System which was published in 2012. NICE's original guidance concluded that DYSIS was a clinically and cost-effective option compared with standard colposcopy. Since the publication of the original guidance there have been changes to the care pathway (see sections 2.9 and 2.10) and changes to the CE-marked products. In addition, the Niris Imaging System is no longer available to the NHS.

The condition

Cervical intraepithelial neoplasia and cervical cancer

2.5 Cervical cancer is one of the less common cancers in the UK, largely because of the NHS cervical screening programme (NHSCSP). In 2013 there were 3,200 cases of cervical cancer (Cancer Research UK) in the UK, which accounted for less than 1% of all new cases of cancer. In 2014 there were 890 deaths from cervical cancer in the UK (Cancer Research UK). The main cause

of cervical cancer is persistent infection with high-risk genotypes of human papilloma virus (HPV; hereafter referred to as high-risk HPV), which causes changes in the cervical cells leading to abnormalities that can progress to cervical cancer if not treated.

2.6 CIN can be classified using a grading scale, which ranges from CIN 1 (low-grade) to CIN 3 (high-grade). CIN classification is based on the depth of abnormal cells within the surface layer of the cervix, seen on a diagnostic or excisional (treatment) biopsy:

- CIN 1 – one third
- CIN 2 – two thirds
- CIN 3 – full thickness.

Grades 2 and 3, often referred to as high-grade, are usually treated to prevent possible progression into cervical cancer. But expert advice suggests that CIN 2 may be managed more conservatively in people who have smaller lesions and who have not completed their family.

The diagnostics and care pathways

Diagnosis

2.7 Precancerous changes to cells in the cervix are detected by cervical screening. People aged 25 to 64 are invited, through the NHSCSP, to have a cervical screening test; every 3 years for those aged 25 to 49, and every 5 years for those aged 50 to 64. Cervical screening involves a sample of cells being taken from the cervix, usually the transformation zone (see section 2.2), using a specially designed brush. The cells are preserved using liquid-based cytology kits, which include vials containing a preservative fluid, and are sent to a cytology laboratory where they are examined under a microscope.

2.8 The criteria used for reporting cervical cytology and the corresponding management protocols for results are outlined in the NHSCSP Achievable standards, benchmarks for reporting, and criteria for evaluating cervical cytopathology (commonly known as ABC3; 2013). Samples are graded depending on the degree of abnormality, known as dyskaryosis (changes to the nucleus of a cell), seen under the microscope. Finding dyskaryotic cells suggests the presence of CIN.

2.9 The current management protocols for cervical cytology are described in the third edition of the NHSCSP's colposcopy and programme management (2016) guidelines (publication number 20). Currently, people with samples that show high-grade dyskaryosis or worse are referred for colposcopy. If low-grade dyskaryosis is seen, the residual cellular material collected during the cervical screen is used for high-risk HPV testing to determine whether a colposcopy referral is needed. This is part of the management protocol referred to as HPV triage. The use of the HPV test helps to identify people who are at the greatest risk of having abnormalities that may need further investigation and treatment. If low-grade dyskaryosis is seen but HPV is not detected, the risk of having underlying abnormalities is low and the cellular changes are likely to resolve without further investigation or treatment.

2.10 In July 2016, the Department of Health announced its decision to roll out HPV primary screening through the NHSCSP. In HPV primary screening, the same sample is taken but is first tested for high-risk HPV. When the results are positive, a cytology test is routinely done on the residual sample. Those people with either low- or high-grade abnormalities are referred for colposcopy. Those whose cytology results are negative are asked to come back in 12 months. HPV primary screening has now been adopted as the

standard of care in several sites in England where it was piloted. At the time of writing, full roll out of this pathway is expected by 2019.

Treatment

2.11 Treatment for CIN aims to remove the cells either by excision or ablation. Treatment for CGIN often needs deeper excisions than for CIN.

2.12 The management protocols for colposcopy services in England are described in the NHSCSP's colposcopy and programme management (2016) guidelines. Of the 188,179 people referred for colposcopy in England between 2015 and 2016, 61% had a treatment or procedure at their first appointment. The most common procedure was diagnostic biopsy (47%), followed by an excision (12%). The most common excision was a large-loop excision of the transformation zone (LLETZ; NHS Digital 2016).

2.13 Management is guided by a colposcopist's opinion of the extent of any abnormalities seen during the colposcopy examination. If an abnormality is found, the colposcopist may take a diagnostic biopsy (punch biopsy). Or they may opt to treat an abnormality during the first clinic appointment ('see and treat') by excising the area of abnormal cells if they believe that high-grade changes are present. The NHSCSP's colposcopy and programme management guidelines (2016) recommend that treatment should not be offered at a person's first visit to a colposcopy clinic after referral for borderline or low-grade dyskaryosis. Ablative treatments should only be done after a diagnostic punch biopsy has been taken and the results have been checked.

2.14 Biopsies are examined by a histopathologist and the results of the biopsy are used to help the colposcopist decide whether treatment is needed. Typically, areas of CIN 2 or worse would need treatment. Treatment can be done either by excising the area of

abnormal cells or by destroying them in situ (ablation). During an excision treatment, cells are usually removed using a thin electrically-heated looped wire in the LLETZ procedure. The excised tissue is sent to histopathology to confirm the extent of the abnormality and to guide further management. LLETZ is usually done in the colposcopy clinic using local anaesthetic.

2.15 Unlike excisional treatments, ablative treatments are not examined by a histopathologist because the destruction of the cells in situ mean that no tissue samples are available for histopathology. Ablative treatments include laser ablation, cryocautery and cold coagulation.

2.16 If cervical cancer is identified, depending on the stage, conservative treatment could be offered. Treatment options for cervical cancer include cone biopsy for very early stage disease, trachelectomy, hysterectomy, radiotherapy and chemotherapy. The treatment and management of cervical cancer is described in more detail in the NICE interactive flowchart on cervical cancer and in the SIGN guideline on the management of cervical cancer.

3 The diagnostic tests

Two interventions and 1 comparator were included in this assessment.

The interventions

Dynamic Spectral Imaging System (DYSIS) colposcope with DYSISmap (DYSIS Medical)

3.1 The DYSIS colposcope is a CE-marked digital video colposcope. It uses spectral imaging technology and an inbuilt algorithm to produce an adjunctive map of the cervical epithelium, known as the DYSISmap (or pseudo-colour imaging). The DYSISmap is intended

to be used as an adjunct to colposcopy to help detect cervical intraepithelial neoplasia (CIN).

3.2 The system comprises:

- a high-resolution digital colposcope, which incorporates an inbuilt display console and monitor for the clinician
- an optional additional monitor that allows the patient to view the images
- single-use or reusable specula
- an acetic acid applicator
- software
- a patient database (the patient management system) that stores images and videos from a colposcopy examination and can be used to record biopsy site locations.

3.3 The device can be used as a standard digital video colposcope, but the spectral imaging technology used by the DYSIS colposcope also measures the speed, intensity and duration of aceto-whitening. These parameters are used to produce dynamic curves that plot intensity against time and an inbuilt algorithm assigns each area of the cervix a colour on the DYSISmap.

3.4 The DYSISmap is displayed on the screen, overlaid on a live image of the cervix, and can be used by the colposcopist to select areas for biopsy. The colour spectrum shown on the DYSISmap 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 takes 3 minutes, but the colposcopist can stop it manually. However the company recommends that the

system needs at least 125 seconds of imaging to allow it to calculate and display the DYSISmap.

ZedScan I

3.5 The ZedScan I is a CE-marked electrical impedance spectroscopy (EIS) system, which is designed to be used as an adjunct to colposcopy to help detect high-grade CIN. The system comprises

- a portable handset, which takes EIS readings and displays the results to the user on an inbuilt interface
- a docking station
- single-use EIS sensors that are placed over the snout of the handset
- a software application, which incorporates a database to store results and can be installed onto a PC.

3.6 The device uses EIS to differentiate normal, precancerous and cancerous tissue by measuring the electrical properties of the cervical epithelial cells. 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 device can be used in a scanning mode or in a single-point mode. During scanning mode, and after acetic acid has been applied, the single-use EIS sensors take readings from between 10 and 12 sites on the cervical transformation zone. The readings are processed by the handset using an inbuilt algorithm, which quantifies the degree of abnormality (dysplasia) at each reading site and compares it to a reference value to give the user a semi-quantitative result. Results are displayed to the colposcopist on the inbuilt user interface. The results show the likelihood of high-grade CIN being present at each of the scanned sites.

3.7 The results provided by the device are intended to be used to guide a colposcopist to areas that need to be biopsied when used in

conjunction with standard colposcopy. It is estimated that the device takes 2 to 3 minutes to scan the cervix and display the results. The results from the ZedScan I handset are automatically uploaded to the system's database through the docking station.

The comparator

Colposcopy

3.8 During a colposcopy examination the cervix is assessed by a colposcopist using a colposcope, which is a low-powered microscope. The aim of the colposcopy examination in the NHS cervical screening programme (NHSCSP) is to confirm whether a potential abnormality identified by the cervical screening test is present, and if so to assess the likely extent and grade of the abnormal cells. Colposcopy is a subjective test that may be influenced by both intra- and inter-observer variation. Binocular colposcopy is most often used method in the NHS.

3.9 The NHSCSP's colposcopy and management guidelines (2016) state that when an adequate colposcopy has been done, that is where the transformation zone has been fully visualised, the colposcopic diagnosis should have a positive predictive value of 65% for a high-grade lesion (CIN 2 or worse).

4 Evidence

The diagnostics advisory committee (section 9) considered evidence on the DYSIS colposcope with DYSISmap (hereafter referred to as DYSIS) and the ZedScan I for detecting cervical intraepithelial neoplasia (CIN) from several sources. Full details of all the evidence are in the committee papers.

4.1 For the diagnostic accuracy review, studies were included if they reported a prospective cohort in which the index test or their prototypes (DYSIS or ZedScan I done in addition to colposcopy)

and reference standard (histopathology) were done independently, and contained enough data to allow diagnostic accuracy estimates to be calculated. For the effectiveness and implementation reviews, studies were included if they reported an observational or experimental study in which DYSIS or ZedScan I, or their prototypes, were used in addition to colposcopy. All studies included in the diagnostic accuracy review were appraised using the QUADAS-2 tool and studies in the implementation review were appraised using guidance from Burns et al. (2008) and the Centre for Evidence Based Management (2014).

4.2 In total, 12 studies were included: 11 in the diagnostic accuracy review, 3 in the review of clinical outcomes, and 5 in the review of implementation. Some studies reported outcomes that were relevant to more than 1 review. Most studies were reported in more than 1 paper or abstract.

Diagnostic accuracy

4.3 Of the 11 studies included in the diagnostic accuracy review, 9 reported data for DYSIS and 2 reported data for ZedScan; 1 for ZedScan I and 1 for a prototype. All studies were done in hospital-based colposcopy clinics, and 6 were multi-centre studies. Five studies included at least 1 centre in England. Most of the participants in the studies were referred for colposcopy because of an abnormal screening result.

4.4 Of the 9 DYSIS studies, 1 was considered to be at a low risk of bias and the other 8 at a high risk of bias. Both ZedScan studies (1 on ZedScan I and 1 on a prototype) were considered to be at a high risk of bias. The main source of bias in the studies was verification bias, which arose because biopsies were not taken to confirm the absence of disease when the colposcopist did not identify any abnormalities because this is not generally considered to be good

clinical practice. Concerns about generalisability of the results of the ZedScan studies were highlighted because most of the participants in the studies were examined a single centre.

4.5 Meta-analyses were done for the diagnostic accuracy of DYSIS, which included 6 studies. Two studies were excluded from these analyses because they only reported data for subgroups and 1 was included in a narrative analysis only. The analyses assume that the DYSIS video colposcopy (without the DYSISmap), the comparator in the DYSIS studies, is equivalent in diagnostic accuracy, to binocular colposcopy (used in the ZedScan studies and in routine NHS practice). The threshold used to determine a positive result was CIN 2+. No meta-analysis was done for the ZedScan studies.

DYSIS

4.6 The pooled results from the meta-analyses are summarised in table 1. In addition to sensitivity and specificity, a pooled positive predictive value of 55.78% (95% confidence interval [CI] 47.54% to 64.03%) for colposcopy and 43.60% (95% CI 33.12% to 54.07%) for DYSISmap with colposcopy was calculated. The corresponding negative predictive values were 86.70% (95% CI 80.17% to 93.22%) for colposcopy, and 92.20% (95% CI 88.06% to 96.34%) for DYSISmap with colposcopy. A sensitivity analysis was done with a logistic regression model, which excluded Roensbo et al. (2015) because this study did not assess DYSIS in addition to colposcopy directly but recorded whether a colposcopist agreed or disagreed with the DYSISmap. To examine the effect of verification bias, results were also stratified by the number of biopsies taken in the studies when both DYSIS and colposcopy did not identify any areas of abnormality.

4.7 The results of the meta-analyses suggest that compared with colposcopy alone, DYSIS in addition to colposcopy improves

sensitivity for detecting CIN 2+, although this is associated with a reduction in specificity. However, the results of the logistic regression model show a significant difference in specificity between DYSIS and colposcopy (difference in log odds 1.33, p<0.0001), but no significant difference in diagnostic odds ratio (difference in log odds 0.04; p=0.84). This suggests that DYSIS increases the number of biopsies taken but may not improve the ability to discriminate between lesions with and without CIN 2+ when compared with colposcopy. The results of the sensitivity analyses designed to explore verification bias in people with negative DYSIS and colposcopy examinations suggested that sensitivity and specificity estimates decline as the number of random biopsies taken increases.

4.8 An additional 5 studies were included in a separate narrative analysis, which confirmed the results of the meta-analyses, that is DYSIS improves sensitivity but reduces specificity when compared with colposcopy. There was no clear evidence that DYSIS improved the detection of cervical cancer.

Table 1 Diagnostic accuracy of DYSIS

Analysis	**Technology (number of studies)**	**Summary estimates**	
		Sensitivity (95% CI)	**Specificity (95%CI)**
Forest plots of diagnostic accuracy	Colposcopy (6 studies)[a]	58.40% (50.31% to 66.50%)	86.46% (81.26% to 91.66%)
	DYSISmap alone (3 studies)[b]	59.18% (33.10% to 85.26%)	81.64% (71.25% to 92.04%)
	DYSISmap plus colposcopy (6 studies)[a]	81.21% (77.35% to 85.07%)	70.06% (60.31% to 79.82%)
Hierarchical bivariate analysis	Colposcopy (6 studies)[a]	57.74% (49.7% to 63.4%)	87.34% (79.7% to 92.4%)
	DYSISmap plus colposcopy (6 studies)[a]	80.97% (76.0% to 85.1%)	70.90% (60.8% to 79.3%)

Logistic regression model	Colposcopy (6 studies)[a]	57.91% (47.2% to 67.9%)	87.41% (81.7% to 91.5%)
	DYSISmap plus colposcopy (6 studies)[a]	81.25% (72.2 to 87.9%)	70.40% (59.4% to 79.5%)
Sensitivity analyses			
Logistic regression model (excluding Roensbo et al. 2015)	Colposcopy (5 studies)[c]	56.4% (47.5% to 64.9%)	90.2% (86.3 to 93.1%)
	DYSISmap plus colposcopy (5 studies)[c]	82.9% (75.0% to 88.7%)	72.9% (63.3% to 80.7%)
Studies with no biopsies in negative examinations	Colposcopy (3 studies)[d]	66.11% (40.89% to 83.33%)	92.18% 90.23% to 94.13%)
	DYSISmap plus colposcopy (3 studies)[d]	86.11% (79.6% to 92.7%)	73.61% (50.0% to 97.2%)
Studies with 1 random biopsy in negative examinations	Colposcopy (Louwers et al. 2011, Soutter et al. 2009)	50.27% (43.0% to 57.5%)	86.22% (79.1% to 93.3%)
	DYSISmap plus colposcopy (Louwers et al. 2011, Soutter et al. 2009)	78.7% (72.6% to 85.6%)	70.02% 57.9% to 82.2%)
Studies with multiple random biopsies in negative examinations	Colposcopy (Roensbo et al. 2015)	67.65% (56.5% to 78.8%)	67.25% 60.2% to 74.3%)
	DYSISmap plus colposcopy (Roensbo et al. 2015)	75.0% (64.7% to 85.3%)	57.31% (49.9% to 64.7%)
Abbreviations: 95% CI, 95% confidence interval; NPV, negative predictive value; PPV, positive predictive value.			
References: [a] Budithi et al. (in press), Coronado et al. (2016), Louwers et al.(2011), Roensbo et al. (2015), Salter et al. (2016) and Soutter et al. (2009) [b] Coronado et al. (2016), Louwers et al. (2011) and Roensbo et al. (2015) [c] Budithi et al. (in press), Coronado et al. (2016), Louwers et al.(2011), Salter et al. (2016) and Soutter et al. (2009) [d] Budithi et al. (in press), Coronado et al. (2016) and Salter et al. (2016).			

ZedScan I

4.9 Two studies were included in a narrative analysis, 1 included the current version (ZedScan I) and the other a third-generation prototype. The results are shown in table 2. Tidy et al. (in press), which was available to the committee as academic in confidence, provides results for the current version of the device in a human

papilloma virus (HPV) primary screening setting, but did not show data for colposcopy alone. The results of this study were confidential at the time of writing. The results of the studies suggest that the ZedScan device, when used in addition to colposcopy, may have better sensitivity or specificity than colposcopy alone depending on the threshold used (which is set by the manufacturer). But when a regression model was fitted to the results from Tidy et al. (2013), the improvement in diagnostic accuracy was not quite statistically significant (difference in log diagnostic accuracy 0.488, p=0.078).

4.10 Further data on the ZedScan I were available in 2 sub-studies of Tidy et al. (in press). A conference abstract (Tidy et al. 2016) reported that the performance of the technology varied across colposcopy clinics in England, Ireland and Germany, with sensitivity ranging from 73.1% to 100% and specificity from 25.7% to 58.1%. McDonald et al. (2017) evaluated the accuracy of ZedScan I in patients with known high-risk HPV genotypes and compared its performance between those with HPV 16 and those with other high-risk genotypes. The sensitivity of ZedScan I was high (100%) regardless of genotype but the sensitivity of standard colposcopy was higher in the HPV 16 group (86.9%) than in the other high-risk genotypes group (79.7%).

Table 2 Diagnostic accuracy of ZedScan prototype

Study	Colposcopy cut-off	Colposcopy alone		ZedScan cut-off	ZedScan plus Colposcopy	
		Sensitivity (95% CI)	Specificity (95% CI)		Sensitivity (95% CI)	Specificity (95% CI)
Tidy et al. (2013) – prototype device	Colposcopic impression	73.6% (64.3% to 82.8%)	83.5% (76.5% to 90.5%)	1.321	73.6% (64.3% to 82.8%)	90.8% (85.4% to 96.2%)
				1.083	78.2% (69.5% to 86.8%)	83.5% (76.5% to 90.5%)
				1.568	62.1% (51.9% to 72.3%)	95.4% (91.5% to 99.3%)
	Disease present	88.5% (81.8% to 95.2%)	38.5% (29.4% to 47.7%)	0.768	88.5% (81.8% to 95.2%)	65.2% (56.2% to 74.1%)
				0.390	96.6% (92.7% to 100%)	38.5% (29.4% to 47.7%)
				0.568	92.0% (86.2% to 97.7%)	51.4% (42% to 60.8%)

Disease present = colposcopy was considered positive if at least 1 measurement point was suggested for biopsy; colposcopic impression = colposcopy was considered positive if it was judged that high-grade CIN was present.

Abbreviation: CI, confidence interval; CIN, cervical intraepithelial neoplasia.

Test positive rates

4.11 Test positive rates ranged from 21.22% to 55.51% for DYSIS and from 13.77% to 42.68% for colposcopy alone in 6 DYSIS studies (Budithi et al. in press, Coronado et al. 2016, Louwers et al. 2011, Roensbo et al. 2015, Salter et al. 2016 and Soutter et al. 2009). In each study the test positive rate was always higher for DYSIS than for colposcopy alone.

4.12 Test positive rates ranged from 30.20% to 77.04%, depending on the cut-off used in the 2 ZedScan studies (Tidy et al. 2013, Tidy et al. in press). Test positive rates for colposcopy were 41.84% when

colposcopic impression was used as a cut-off and 73.47% when disease present was used as a cut-off (Tidy et al. 2013).

Test failure rates

4.13 Test failure rates with DYSIS were reported in 6 studies and ranged from 2.9% to 31.4%. The highest failure rate was reported by Soutter et al. (2009), which included a prototype version of the system and had problems with unsatisfactory view and faulty acetic acid applicators. Failure rates for ZedScan were reported in 2 studies, 5.6% (Zedscan I) and 13.6% (prototype; Tidy et al. in press and Tidy et al. 2013).

Biopsy rates

4.14 All diagnostic accuracy studies included in the external assessment group's (EAG's) analysis reported some data on the number of diagnostic and treatment biopsies taken, but there were not enough details to assess whether the adjunctive technologies had a substantial effect on this.

4.15 Two pre-publication manuscripts by Cholkeri-Singh et al. (2017) and DeNardis et al. (2017), which both reported additional data from the IMPROVE-COLPO trial, were submitted to the committee during consultation. The IMPROVE-COLPO trial was an observational study done in 39 colposcopy clinics across the US.

4.16 Cholkeri-Singh et al. (2017) reported results of a 2-arm observational study in which participants who were prospectively assessed using DYSIS were compared with a historical control arm, in which patients were assessed with standard colposcopy. The yield of CIN 2+ (defined as the proportion of participants with at least 1 biopsy showing CIN 2+) was higher in the prospective arm (9.48% compared with 7.21%; p=0.014). The yield of CIN 3+ was also higher in this arm (3.23% compared with 2.07%; p=0.031). The number of people having biopsies between the arms

was similar (71.6% compared with 71.5%), but the average number of biopsies per person was higher for the DYSIS cohort (1.26 compared with 1.03).

4.17 DeNardis et al. (2017) reported results of a cross-sectional observational study in which DYSIS was used after an initial assessment with standard colposcopy to identify further sites for biopsies. Standard colposcopy directed biopsies identified 78 participants with CIN 2+; DYSIS assisted biopsies identified a further 34 people with CIN 2+. In addition, standard colposcopy directed biopsies identified 30 participants with CIN 3+; DYSIS assisted biopsies identified a further 15 people with CIN 3+. The positive predictive value of standard directed biopsies was 13.24% compared with 16.16% for DYSIS assisted biopsies.

Subgroup analyses

4.18 When data were reported for referrals for low-grade (CIN 1) and high-grade (CIN 2 and 3) cytology, colposcopy seemed to be less sensitive for detecting CIN 2 or worse in low-grade cytology referrals. No differences in sensitivity were seen for DYSIS and ZedScan I.

4.19 There were not enough data to determine whether the accuracy of any of the technologies differed between people with and without high-risk HPV.

4.20 Founta et al. (unpublished) reported data from a test of cure population for which the EAG calculated 95% confidence intervals. This showed a sensitivity of 0% (95% CI 0% to 53%) and a specificity of 94.0% (95% CI 89.35% to 98.65%) for colposcopy, and a sensitivity of 80.0% (95% CI 44.94% to 100%) and a specificity of 64.0% (95% CI 54.59% to 73.41%) for DYSIS in a test of cure population. The accuracy of colposcopy is substantially

different in this study compared with the summary estimates provided in the meta-analyses for all colposcopy referrals.

Clinical effectiveness

4.21 Four studies reported data on adverse events. In a ZedScan prototype study, 1 patient felt unwell after the examination and 2 patients experienced issues with bleeding after biopsies were taken. It is uncertain whether these events were related to using the ZedScan. Three DYSIS studies reported no adverse events.

4.22 No data were found for morbidity and mortality associated with treatment and biopsies done during colposcopy, or for health-related quality of life. There were insufficient data to determine whether the increase detection of CIN 2 was associated with a reduction in cervical cancer.

4.23 Two systematic reviews of adverse outcomes of CIN treatment were found. Kyrgiou et al. (2015) focused on fertility and early pregnancy outcomes (less than 24 weeks' gestation) and reported that people who had treatment for CIN were at increased risk of miscarriage in the second trimester of pregnancy (relative risk 2.60, 95%CI 1.45 to 4.67). Kyrgiou et al. (2016) focused on obstetric (more than 24 weeks' gestation) and neonatal outcomes and reported that patients who had treatment with a large-loop excision of the transformation zone (LLETZ) were at increased risk of giving birth prematurely (relative risk 1.56, 95%CI 1.36 to 1.79), with the risk increasing as the depth of the excision increases.

Implementation

4.24 Five studies were included in the implementation review. Of these, 3 were based in the UK (Lowe et al. 2016, Palmer et al. 2016 and Budithi et al. in press), 1 in Spain (Coronado et al. 2014) and 1 in

the Netherlands (Louwers et al. 2015). None of the studies used validated questionnaires.

Patient and clinician satisfaction

4.25 Lowe et al. (2016) surveyed 763 patients in 4 NHS hospitals that were using DYSIS. Two questionnaires were available: 1 for patients having their first colposcopy and 1 for people who had previously had a colposcopy; the number of respondents per questionnaire was not reported in the conference abstract available to the EAG. Participants reported that the examination did not take longer than their previous smear test or colposcopy and that anxiety was reduced during and after DYSIS examinations compared with during previous examinations.

4.26 Louwers et al. (2015) gave a patient satisfaction questionnaire to 239 people who had a DYSIS examination. Results showed that 93.9% of participants agreed or strongly agreed to have colposcopy with DYSIS if it helped locate CIN, 29.5% agreed or strongly agreed that DYSIS was less comfortable than a cervical smear; 16.5% reported that DYSIS made them feel nervous during the examination, and 6.5% thought that an examination with DYSIS took too long.

4.27 Budithi et al. (2017) gave questionnaires to both patients and colposcopists in 5 colposcopy clinics in Wales; 68 patients responded and 45 colposcopist responses were received (number of colposcopists unknown). Results from patients showed that 86% agreed or strongly agreed that the DYSIS images helped their understanding and were reassuring, 52% believed DYSIS to be more accurate than their previous colposcopy, 4% thought that DYSIS lasted too long compared with previous colposcopies, and 13% found it less comfortable. Of the colposcopists who filled in the questionnaire, 96% agreed or strongly agreed that they were

confident about colposcopy and their decision-making in selecting biopsy sites, but only 48% went on to agree that DYSISmap affected their decisions in selecting biopsy sites, 58% said they were able to identify additional sites with DYSISmap and 55% agreed or strongly agreed that DYSISmap improved their colposcopic examination.

Training requirements

4.28 Coronado et al. (2014) surveyed 63 colposcopists with different levels of experience. A retrospective review of 50 colposcopy and DYSISmap images was also done. This found that correct diagnosis (either normal, low-grade lesion, high-grade lesion or cancer) was more frequent with DYSIS than with conventional colposcopy for colposcopists with low and medium levels of experience. There was no difference for highly experienced colposcopists. All groups agreed that DYSIS is better at directing diagnosis and provides more information than conventional colposcopy. The survey also reported that using DYSISmap improved detection of CIN 2+ by colposcopists across all the different experience levels; however the EAG noted that this was based on a small subgroup analysis of the retrospective review of stored images.

Cost effectiveness

Review of economic evidence

4.29 Two relevant economic evaluations were identified; 1 (Wade et al. 2013) provided results for DYSIS compared with colposcopy over a life-time time horizon and another (Whyte et al. 2013) provided results for a ZedScan prototype compared with colposcopy over a 3-year time horizon. Wade et al. (2013) was produced for NICE's diagnostics guidance on adjunctive colposcopy technologies and found that DYSIS dominated colposcopy (that is, DYSIS cost less

and was more effective than colposcopy). Whyte et al. (2013) reported lower costs associated with the use of a prototype ZedScan device per person with CIN 2 or 3 treated, because it was reduced both rates of overtreatment and the number of follow-up appointments needed for people with CIN 1. However, this was associated with a reduction in the number of CIN 2 or 3 lesions treated and a consequent reduction in the number of cancers detected. Neither of the studies fully addressed the decision problem.

Modelling approach

4.30 The EAG developed a de novo economic model designed to assess the cost effectiveness of DYSIS and ZedScan I, used in addition to colposcopy, in both an HPV triage and an HPV primary screening setting. The analyses took the perspective of the NHS and personal social services and had a 60-year (life-time) time horizon. All costs and effects were discounted at a rate of 3.5%.

Model structure

4.31 A patient-level state-transition model with a 6-month cycle time was constructed using TreeAge Pro (2016) software. The model included 500,000 simulations to ensure that first-order uncertainty was adequately captured, that is, variability in the simulated experiences between identical patients. The model incorporated both screening and treatment pathways: a submodel that simulated the natural history of CIN and cervical cancer, and a submodel for people who had treatment for CIN which simulated adverse obstetric outcomes. The adverse obstetric outcome model captured the costs and quality-adjusted life year (QALY) decrements associated with initial management and the increased probability of neonatal mortality and QALY decrements associated with higher risks of disability among infants born pre-term. The natural history

model was adapted from Kulasingam et al. (2013) with invasive cancer parameters taken from Campos et al. (2014).

4.32 At the beginning of the first cycle each patient is referred for colposcopy and has treatment if needed, before entering the natural history model. In subsequent cycles, the patient can follow 1 of 4 screening and treatment pathways: no screening, colposcopy referral, routine screening, or a follow-up pathway for those who had previous treatment, unless they died in the previous cycle. Every pathway ends with the patient entering the natural history model.

4.33 The model was implemented using a random walk and for each patient it simulated the occurrence of the following uncertain events: disease progression, diagnostic results or treatment outcomes. The characteristics which determined the associated events and transitions for each individual in the model were as follows:

- age
- health state (clear, HPV, CIN 1, CIN 2 or 3, cancer)
- reason for referral for colposcopy (high-grade or low grade cytology)
- next scheduled screening (routine call, 6-month cytology, 6-month colposcopy, test of cure, CIN 1 follow-up)
- time elapsed since last screening
- type of clinic visited ('see and treat' or 'watchful waiting').

Identical patients were run through each treatment strategy and random numbers were maintained across all runs of the model.

4.34 Two base cases were modelled: HPV triage and HPV primary screening. The modelled pathways for HPV triage were based on those outlined in the NHS cervical screening programme's

(NHSCSP) colposcopy and programme management (2016) guidelines and for HPV primary screening on the testing algorithms used in the NHSCSP's pilot sites.

Model inputs

Diagnostic accuracy estimates

4.35 The diagnostic accuracy estimates used in the model for DYSIS, and colposcopy are shown in table 3. The accuracy of ZedScan I was taken from Tidy et al. (in press). These data are confidential at the time of writing but available to the EAG and committee as academic in confidence.

Table 3 Accuracy estimates used in the model

Technology (source)	Sensitivity (95% CI)	Specificity (95%CI)
Colposcopy alone (regression model)	57.91% (47.2% to 67.9%)	87.41% (81.7% to 91.5%)
DYSIS (regression model)	81.25% (72.2% to 87.9%)	70.40% (59.4% to 79.5%)
Abbreviation: CI, confidence interval.		

4.36 The performance of cytology was modelled using data from Hadwin et al. (2008) and from the NHSCSP statistical bulletin (2015/16). This was applied to cytology in both the HPV triage and HPV primary screening scenarios. The diagnostic accuracy of HPV testing in HPV triage was modelled using data from the TOMBOLA study (Cotton et al. 2010) and in HPV primary screening from the ARTISTIC study (Kitchener et al. 2014).

Underlying health states and reasons for referral

4.37 In the model, people referred for colposcopy have 2 initial characteristics; a true underlying health state (clear, HPV, CIN 1, CIN 2 or 3, or cancer) and a reason for referral (low-grade or high-

grade lesions). These joint distributions were taken from the NHSCSP statistical bulletin (2015/16) for HPV triage and unpublished data provided by the NHSCSP pilot sites for HPV primary screening, and were influenced by disease prevalence and the accuracy of screening.

Treatment probabilities

4.38 Heterogeneity in treatment decisions after a positive colposcopy was modelled using 2 different types of clinic; a 'watchful waiting' clinic or a 'see and treat' clinic. The probability of treatment failure after an excisional biopsy was taken from Ghaem-Maghami et al. (2011) and ranged from 4.9% for CIN 1 to 10.3% for CIN 3. The probability of adverse obstetric outcomes after treatment was estimated by applying the relative risk of pre-term birth (1.56) from Kyrgiou et al. (2016) to the probability of pre-term birth for people with untreated lesions as reported in NICE's guideline on preterm labour and birth (7.3%). This gave an excess risk of pre-term birth after LLETZ treatment of 4.09%.

Costs

4.39 The average cost per patient of using the technologies was calculated using information from companies and clinical experts. The costs include the capital cost of the technologies (annuitised over 15 years for a colposcope and 5 years for DYSIS and ZedScan I), annual maintenance costs and consumable costs. To calculate the average cost per procedure, and be consistent with Wade et al. (2013), it was assumed that 1,229 patients per year were seen. The following costs per patient were assumed:

- colposcopy: £3.75
- DYSIS: £9.24
- ZedScan I: £30.52.

4.40 Biopsy and treatment costs were taken from NHS reference costs and the cost of a cytology and HPV test were taken from the TOMBOLA study and inflated to 2016 prices. The values used in the model for screening events are shown in table 4.

Table 4 Costs of screening events

Treatment	Device	Cost per treatment
Colposcopy examination only	Colposcopy	£175
	DYSIS	£180.49
	ZedScan I	£205.52
Diagnostic biopsy		£47
LLETZ		£63
Cytology test		£37.19
HPV test		£29.66
Abbreviations: HPV, human papilloma virus; LLETZ, large-loop excision of the transformation zone.		

4.41 Cancer treatment costs were taken from Martin-Hirsch et al. (2007), and costs associated with adverse obstetric outcomes were taken from Lomas et al. (2016) and inflated to 2016 prices. It was assumed that a pre-term birth costs £24,610, which takes into account initial inpatient neonatal care and ongoing costs over the first 18 years of life.

Health-related quality of life and QALY decrements

4.42 Health-related quality-of-life estimates were taken from the published literature. The disutilities associated with screening, diagnosis and treatment of CIN were taken from Simonella and Canfell (2014) and are shown in table 5. Age- and gender-specific utilities from Kind et al. (1999) were applied to the HPV, CIN 1 and CIN 2 or 3 asymptomatic health states. Disutilities associated with cervical cancer were taken from Goldie et al. (2004) and a QALY decrement of 1.3 was applied for pre-term birth (Lomas et al. 2016).

Table 5 Disutilities for screening, diagnosis and treatment of CIN

Screening event	QALY decrement
Negative cytology or HPV	0.0062
False positive referral for colposcopy	0.0276
Diagnosed CIN 1	0.0276
Treatment of CIN	0.0296
Abbreviations: CIN, cervical intraepithelial neoplasia; HPV, human papilloma virus; QALY, quality-adjusted life year.	

Base-case results

4.43 The following assumptions were applied in the base-case analysis:

- Diagnostic accuracy estimates for both colposcopy and the adjunctive technologies were based on a cut-off of CIN 2 or worse.
- The probability of a positive colposcopy result was:
  - identical for people with clear, HPV or CIN 1 results
  - identical for people with CIN 2 or 3 or invasive cancer.
- The choice between a 'see and treat' clinic and a 'watchful waiting' clinic was independent from diagnostic accuracy.
- Biopsy and histopathology (the reference standard) were 100% accurate.
- Excision at first colposcopy appointment was only possible for referrals for high-grade lesions with a positive colposcopy result.
- For low-grade lesion referrals, CIN 2 was confirmed by diagnostic biopsy before treatment.
- CIN 1 lesions were not treated and patients had a 12-month follow-up screening in the community.
- People whose lesions were treated for CIN remained at risk of pre-term birth (birth before 37 weeks' gestation) for each year after treatment up to the age of 45.
- When cancer was detected, treatment was given appropriate to the stage and an excess risk of mortality was applied for 5 years and decreased according to time since diagnosis.

- Examinations with DYSIS or ZedScan I were equivalent in duration to a standard colposcopy examination.
- ZedScan I was used for diagnostic colposcopies only.

4.44 There were 2 base cases: 1 for HPV triage and 1 for HPV primary screening. In a 'see and treat' clinic, treatment was done at the first visit for patients who had a referral for high-grade lesion according to cytology and a colposcopy examination graded as CIN 2+. In a 'watchful waiting' clinic, treatment was done at the second visit when the results of any diagnostic biopsies showed CIN 2+.

4.45 The results of the HPV-triage base case showed that both technologies dominate standard colposcopy in 'see and treat' clinics (that is, they cost less and are more effective). In 'watchful waiting' clinics, DYSIS dominated standard colposcopy for low-grade lesion referrals and for all referrals combined, but had an incremental cost-effectiveness ratio (ICER) of £675 per QALY gained for high-grade lesion referrals. ZedScan I had an ICER of £272 per QALY gained for low-grade lesion referrals and £4,070 per QALY gained for high-grade lesion referrals. For all referrals, it had an ICER of £418 per QALY gained. Indirect comparisons suggest that ZedScan I always costs more but is more effective than DYSIS in both 'see and treat' and 'watchful waiting' clinics. The results of the HPV primary screening base case were similar to the HPV-triage base case.

4.46 The number of treatments, biopsies and missed disease in each of the base cases is shown in table 6. This shows that because of their increased sensitivity, the adjunctive technologies are associated with less missed disease and so less cancers. However, they also have reduced specificity and result in more unnecessary diagnostic biopsies and treatments (except in 'watchful waiting' clinics).

Table 6 Secondary outcomes per 1,000 people referred for colposcopy (60-year time horizon)

Clinic	Strategy	Missed CIN 2+	Cancers	LLETZ	Unnecessary LLETZ	Unnecessary diagnostic biopsy
HPV triage						
'See and treat'	Colposcopy	69	43	466	27	139
	DYSIS	30	34	501	61	229
	ZedScan I	3	29	524	82	291
'Watchful waiting'	Colposcopy	69	44	449	0	137
	DYSIS	30	37	465	0	260
	ZedScan I	3	32	477	0	347
HPV primary screening						
'See and treat'	Colposcopy	82	33	446	22	164
	DYSIS	34	25	478	50	296
	ZedScan I	4	20	498	68	386
'Watchful waiting'	Colposcopy	82	34	432	0	172
	DYSIS	34	27	450	0	316
	ZedScan I	4	22	460	0	417
Abbreviations: CIN 2+, cervical intraepithelial neoplasia grade 2 or worse; HPV, human papilloma virus; LLETZ, large-loop excision of the transformation zone.						

Scenario analyses

4.47 The following scenario analyses were done to explore the effect of alternative structural assumptions:

- time horizon restricted to 1 screening interval (3 years)
- adverse obstetric outcomes excluded
- ZedScan I used in both diagnostic and treatment colposcopies.

4.48 When the time horizon was restricted to 3 years, colposcopy dominated (that is, it cost less and was more effective) both DYSIS and ZedScan I in most scenarios except for high-grade lesion referrals in HPV triage 'see and treat' clinics. In this scenario, DYSIS had an ICER of £236,692 saved per QALY lost and ZedScan I had an ICER of £84,045 saved per QALY lost. For HPV primary screening, the respective ICERs were £250,587 saved per

QALY lost for DYSIS and £110,371 saved per QALY lost for ZedScan I. Colposcopy generally dominated because its higher specificity resulted in fewer treatments, and because people with untreated CIN (false negatives) did not go on to develop cancer within the 3-year time horizon. The results of the model did not change substantially in the other scenario analyses.

Sensitivity analyses

4.49 The following inputs were changed in sensitivity analyses to explore the effect of parameter uncertainty:

- diagnostic accuracy
- costs of technologies
- costs of treatment and biopsies
- characteristics of the population referred for colposcopy under HPV primary screening.

4.50 When the accuracy of colposcopy relative to ZedScan I was taken from Tidy et al. (2013), the incremental costs associated with ZedScan I compared with colposcopy increased, whereas the QALYs decreased. Under these assumptions ZedScan I became less cost effective than in the base case and it no longer dominated colposcopy in 'see and treat' clinics. Its highest ICER was £24,686 per QALY gained for high-grade lesion referrals in HPV primary screening 'watchful waiting' clinics.

4.51 The DYSIS results were sensitive to assumptions around reduced throughput and a consequent increase in cost per test because of its higher purchase price. When it was assumed that only 614 patients per year were seen, it no longer dominated colposcopy in HPV primary screening 'watchful waiting' clinics and had an ICER

of £270 per QALY gained for all referrals. None of the other sensitivity analyses changed the results substantially.

4.52 The ZedScan I results were sensitive to changes in the cost of diagnostic and treatment biopsies because of its increased sensitivity and lower specificity compared with colposcopy. When the cost of a diagnostic biopsy was increased to £102.72 and a treatment biopsy (LLETZ) to £490.89, ZedScan I no longer dominated colposcopy for low-grade lesion referrals and all referrals combined. Under these assumptions, its highest ICER was £6,709 for high-grade referrals to an HPV primary screening 'watchful waiting' clinic. None of the other sensitivity analyses changed the results substantially.

5 Committee discussion

Current practice

5.1 The committee discussed current practice for assessing suspected cervical abnormalities in a colposcopy clinic. It heard from clinical experts that clinics in the NHS most often use binocular colposcopy, which allows a colposcopist to examine a cervix and take both diagnostic and treatment biopsies under direct visualisation. Acetic acid is used to highlight areas of abnormality. It further noted that colposcopy is associated with both intra- and inter-observer variability because it is a visual examination that is highly dependent on the expertise of the colposcopist. The committee considered the role of the adjunctive colposcopy technologies and was advised by clinical experts that the technologies could provide less subjective results and help colposcopists to select areas for biopsies.

5.2 The committee noted that a series of changes are being made to the screening pathways used in the NHS cervical screening

programme (NHSCSP); human papilloma virus (HPV) triage was fully implemented across England in April 2014, and HPV primary screening is currently being done in several pilot sites, with full implementation across England expected in 2019. These changes could affect referrals to colposcopy clinics and consequently the prevalence of high-grade disease, particularly when people with a HPV-positive cytology-negative screening result are seen in colposcopy. The committee concluded that there had been substantial changes to the care pathways since NICE's first diagnostics assessment of the DYSIS colposcope with DYSISmap in 2012.

Diagnostic accuracy and clinical effectiveness

5.3 The committee discussed the critical appraisal of the included diagnostic accuracy studies done by the external assessment group (EAG). It noted that the greatest risk of bias in the studies occurred because not all patients had the reference standard test (colposcopically directed biopsies and histopathology). In most studies, people who had a negative colposcopy did not have biopsies taken. The committee heard from clinical experts that it was not considered good clinical practice to take biopsies when there was no clinical indication. But it noted that the EAG's sensitivity analyses to investigate the effect of verification bias showed that the more random biopsies that were taken, the lower the estimates of both sensitivity and specificity. The committee concluded that the diagnostic accuracy estimates provided by the included studies were likely to have been influenced by this, and highlighted that future studies should aim to minimise verification bias when possible.

5.4 The committee considered the applicability of the diagnostic accuracy studies that were done outside the UK. It heard from clinical experts that the quality assurance measures for colposcopy

carried out elsewhere were different to those in the UK, and that this was likely to influence the accuracy of colposcopy. It further noted that the NHSCSP recommends that a satisfactory colposcopy should have a 65% positive predictive value for CIN 2+. The committee considered that although the measure of positive predictive value was likely to be influenced by several confounding factors, video colposcopy in the DYSIS studies did not achieve this benchmark, with a pooled positive predictive value of 55.78%. The clinical experts also noted that the pooled sensitivity of colposcopy in the DYSIS studies was lower than what they would expect to see in the UK. They also noted that the ZedScan I study, which was done in the UK and used binocular colposcopy, reported a higher sensitivity for colposcopy. The committee concluded that because of differences in colposcopy practice, such as fewer quality assurance measures and the use of video colposcopy, the accuracy data from non-UK studies may not be generalisable to the NHSCSP.

5.5 The committee considered the potential for the adjunctive colposcopy technologies to reduce both intra- and inter-observer variability. The committee heard from the companies that both technologies reduce the subjectivity of the colposcopy examination by providing more objective results, but noted that no data on the reproducibility of the tests had been presented for the assessment. However, the committee also noted that published data were available which suggested that clinicians felt that the DYSISmap improved their confidence when selecting biopsy sites. The committee concluded that the technologies had the potential to help standardise colposcopy examinations, but that insufficient data were available at present to determine whether this benefit would be realised in clinical practice across the NHS.

5.6 The committee discussed the results of the diagnostic accuracy analyses for both the DYSIS colposcope with DYSISmap and the ZedScan I. It noted that although there was considerable diversity in accuracy estimates for colposcopy alone in both the DYSIS and ZedScan studies, the available estimates suggested that the technologies were more sensitive but less specific than colposcopy alone. It considered that in practice this would result in a reduced false negative rate with more people being diagnosed with CIN 2 or worse (CIN 2+), but this could be at the expense of a higher false positive rate with more people having unnecessary diagnostic biopsies and treatment. The committee further noted that the diagnostic odds ratios, which had been calculated by the EAG for the DYSIS colposcope with DYSISmap studies, suggested that there was no difference between the accuracy of DYSIS colposcopy alone compared with DYSIS colposcopy with DYSISmap. The committee concluded that the results of the diagnostic accuracy studies suggest that it is plausible that the adjunctive colposcopy technologies may change the test threshold so that more people have biopsies, but without improving colposcopists' ability to differentiate between high- and low-grade disease.

5.7 The committee discussed the Cholkeri-Singh et al. (2017) and DeNardis et al. (2017) studies, both submitted to the committee as pre-publication manuscripts during consultation, which report data from the IMPROVE-COLPO study. It acknowledged that these studies provide real world outcome data on the number of biopsies taken and supplement the diagnostic accuracy data found by the EAG in their systematic review. It noted that the results of the Cholkeri-Singh et al. study indicate that DYSIS with DYSISmap detects additional cases of both CIN 2 and CIN 3, relative to standard colposcopy, without increasing the number of patients having biopsies. The committee considered the design of this study

and noted a lack of detail on the methods used to ensure that controls in the retrospective arm were comparable to the cases in the prospective arm. The committee also considered analyses provided at consultation based on KC65 data (from the NHSCSP in England between 2012/13 and 2015/16). The committee noted that the data generally showed no increase in biopsy rates in centres after adoption of DYSIS; but it acknowledged that DYSIS may not be used for every colposcopy in these centres. The committee concluded that despite these papers having methodological limitations, combined with the KC65 data they provided some reassurance that the increase in biopsies implied by the results of the diagnostic accuracy studies alone may not be realised in practice in centres using DYSIS colposcopy with DYSISmap.

5.8 The committee heard from a patient expert that referral for a colposcopy examination can often cause substantial anxiety, which may not be reduced even when the colposcopy examination is normal. Patients having a colposcopy may be anxious because of the examination itself and because they have already had a screening result informing them that an abnormality has been detected. It heard from clinical experts that it can often be difficult to reduce anxiety in people who have a negative colposcopy examination, but who were referred with an HPV-positive result, because no treatment can be offered. The committee noted evidence from the systematic review and also anecdotal evidence from clinical and patient experts, which suggested that the adjunctive colposcopy technologies could reduce anxiety because patients can be shown the objective information to explain that no abnormality has been detected. The committee concluded that although the additional information provided by the adjunctive colposcopy technologies has the potential to help clinicians provide reassurance and reduce anxiety for patients, there are currently

insufficient data to conclude that they have a significant effect on this.

Cost effectiveness

5.9 The committee discussed the assumption made in the cost-effectiveness model that video colposcopy and binocular colposcopy are equivalent in terms of diagnostic accuracy. The committee heard from clinical experts that there was no consensus among experts about their equivalence and that the sensitivity estimates for video colposcopy obtained in the DYSIS studies were lower than would be expected for binocular colposcopy in the NHS. It also heard from clinical experts that the estimates for the sensitivity of binocular colposcopy in the ZedScan studies were higher, and more representative of NHS practice, but noted that the estimates used in the cost-effectiveness model for colposcopy alone were taken from the meta-analyses of DYSIS colposcopy. Therefore, the committee concluded that the relative benefits of the adjunctive colposcopy technologies could have been overestimated in the modelling.

5.10 The committee discussed both modelled base cases and noted that the increased sensitivity of the adjunctive colposcopy technologies led to less cervical cancers developing over the 60-year time horizon. It heard from clinical experts that the additional high-grade lesions detected using the adjunctive colposcopy technologies could in fact be low-volume CIN 2 disease, which could regress without treatment. The committee questioned whether data were available that explained the natural history of low-volume CIN 2 but heard that these were not yet available. Anecdotal evidence, and results of a British Society for Colposcopy and Cervical Pathology survey, suggest that some clinicians are now using use either ablative techniques or 'watchful waiting' management strategies for low-volume CIN 2 in some circumstances. It also noted that when

the time horizon of the model was reduced to 3 years, and the longer-term outcomes associated with increased sensitivity were removed, colposcopy alone dominated; that is, it was more effective and less expensive than the adjunctive colposcopy technologies. The committee concluded that, in the absence of clinical-outcome data, or data on the natural history of low-volume CIN 2, there was currently uncertainty about the longer-term outcomes associated with the increased sensitivity of the adjunctive colposcopy technologies and wished to encourage further data collection to resolve this.

5.11 The committee discussed the effect of the lower specificity associated with the adjunctive colposcopy technologies on longer-term outcomes in the model. In the shorter term, the model showed that reduced specificity is associated with an increase in unnecessary biopsies and treatments. The committee questioned whether this would be realised in practice and heard from the EAG that the assumptions made in the model about when biopsies would be taken were based on the NHSCSP's colposcopy and programme management (2016) guidelines (publication number 20). It heard from clinical experts that these guidelines may not always be followed, and colposcopists may take biopsies for reassurance that high-grade disease is not present. The committee also noted its previous conclusion (see section 5.7) that results from the Cholkeri-Singh et al. (2017) study and the KC65 data (from the NHSCSP in England between 2012/13 and 2015/16) showed no increase in biopsy rates in centres after adoption of DYSIS. It also noted that Cholkeri-Singh et al. reported that the use of DYSIS was associated with an increased yield of CIN 2+ which, combined with the data on biopsy rates, suggests that using DYSIS helps colposcopists to target the areas chosen for biopsy. The committee concluded that there is some real world evidence that suggests that using DYSIS does not increase the biopsy rate to the

extent predicted by the model, and noted that equivalent data were not yet available for ZedScan.

5.12 The committee discussed whether reduced specificity is associated with an increased risk of adverse obstetric outcomes in the longer term. It heard from clinical experts that the relationship between biopsies, treatment and adverse obstetric outcomes was not well understood, but that it was generally acknowledged that the smaller the excisional treatment the lower the risk of adverse outcomes. It noted that the base case assumed an excess risk of pre-term delivery of 0.04, which was reduced to 0 in a scenario analysis with no substantial effect on the results. The committee concluded that although they were an important clinical consideration in practice, the longer-term effects of reduced specificity did not seem to be a key driver in the model.

5.13 The committee questioned the cost savings attributed to the adjunctive colposcopy technologies in the model. It heard from the EAG that the cost savings seen in the model were driven by increased sensitivity, which led to a reduction in costs associated with both cancer treatment and follow-up appointments. It heard from clinical experts that technologies which improve the negative predictive value of colposcopy may become more important after HPV primary screening is fully rolled out and people with HPV-positive cytology-negative results are referred for colposcopy. It further noted that the base case for HPV primary screening was based on preliminary data only, but acknowledged that improvements in sensitivity may become increasingly important in the future. The committee concluded that because of the absence of data on the natural history of low-volume disease, it was uncertain whether the adjunctive colposcopy technologies would increase detection of disease that would progress to cancer if not

treated. Therefore, the cost savings in the model may not be robust.

5.14 The committee questioned the effect of not having a probabilistic sensitivity analysis available to quantify the overall uncertainty in the model. It heard from the EAG that it could not run a probabilistic scenario analysis because of the length of time needed to run each simulation. The EAG explained that although the mean ICER may be different from the deterministic analyses if the model was run probabilistically, there was unlikely to be a substantial difference which would change the modelling conclusions. The committee noted that the model results had been robust to changes in many parameter estimates and assumptions in the deterministic sensitivity and scenario analyses, but that the results were likely to be confounded by the lack of clinical-outcome data. The committee concluded that on this occasion the absence of a probabilistic sensitivity analysis was not critical.

5.15 The committee considered whether the adjunctive colposcopy technologies should be recommended for routine adoption. It noted its conclusions on the applicability of data from non-UK studies where the accuracy of colposcopy may differ (see section 5.4), the lack of data on the natural history of low-volume CIN 2 (see section 5.10), and the uncertainty about whether using the adjunctive colposcopy technologies would lead to a reduction in cervical cancer over the longer term (see section 5.13). Taking these factors into account, the committee considered that there was uncertainty over the clinical and cost effectiveness of the adjunctive colposcopy technologies because only diagnostic accuracy data were available for these technologies. It noted, however, that further data (Cholkeri-Singh et al. 2017 and DeNardis et al. 2017) which had been provided at consultation showed that DYSIS was able detect more CIN 3 lesions compared with

standard colposcopy, without increasing the number of people having biopsies. The committee therefore concluded that there was enough evidence that colposcopy using DYSIS with DYSISmap can detect additional clinically important lesions, compared with colposcopy alone, to recommend its continued adoption. It also noted that the additional data provided at consultation were from a US study and wished to encourage centres using DYSIS to audit their outcomes and confirm that the expected benefits are achieved in the NHS (see section 5.16). Further, the committee concluded that there was too much uncertainty over the clinical and cost effectiveness of the ZedScan I to recommend its routine adoption at present, and recommended that further research was needed.

Research considerations

5.16 The committee noted their previous conclusion (see section 5.15) that the available clinical-outcome data that support using DYSIS with DYSISmap were from a US study. The committee therefore recommended that centres using this technology should audit their clinical outcomes and confirm that the expected benefits are achieved in the NHS. Outcomes that should be audited include, but are not limited to, rates of CIN 2+ detection, CIN 3+ detection and biopsy.

5.17 The committee heard from the clinical experts that all colposcopy clinics complete a quarterly data return for Public Health England, the KC65. This is used for comparison and assessment against the standards outlined in NHSCSP's colposcopy and programme management 2016 guidelines. The committee considered whether this data could be studied to see if biopsy and detection rates of CIN 2+ had increased in centres that had already adopted DYSIS colposcopy with DYSISmap or the ZedScan I. The committee heard from clinical experts that the device used in each colposcopy is not currently recorded and it is not known whether centres with

an adjunctive colposcopy technology use it routinely. The committee wished to encourage the owners of the KC65 dataset to consider whether it could be adapted and used to support further data collection for the adjunctive colposcopy technologies, and whether papers based on the data could be published and used for updates of this guidance.

6 Draft recommendations for further research

6.1 The committee recommended that further studies should be done in a human papilloma virus (HPV) primary screening setting. These studies should incorporate clinical-outcome data and be designed to minimise verification bias. Future studies should consider measuring variability and should also take into account HPV genotyping status where possible, so that the difference in accuracy in a population vaccinated against HPV types 16 and 18 can be better understood.

6.2 The committee noted that there were no data to show how the adjunctive colposcopy technologies affect clinical decision-making in the UK, when all colposcopy is done by accredited colposcopists. It therefore recommended that data should be collected to show how the results of the technologies affect decision-making, including biopsy decisions and decisions to discharge people with a negative colposcopy examination back to routine screening.

6.3 The committee considered that the adjunctive colposcopy technologies had the potential to improve patient experience and reduce anxiety (see section 5.8). Further research is needed to understand the effect of having the additional information provided by the adjunctive colposcopy technologies on anxiety for people having a colposcopy, when this information is shown to a patient during the examination.

6.4 The committee recommended that further research is needed to better understand the natural history of low-volume CIN (cervical intraepithelial neoplasia) 2 lesions. The committee noted that this is not captured in the current versions of natural history models for CIN and cervical cancer (see section 5.10), but is likely to become increasingly important for colposcopy services as HPV primary screening is rolled out and vaccinated cohorts enter the screening programme.

7 Implementation

NICE will support this guidance through a range of activities to promote the recommendations for further research. The research proposed will be considered by the NICE Medical Technologies Evaluation Programme research facilitation team for the development of specific research study protocols as appropriate. NICE will also incorporate the research recommendations in section 6 into its guidance research recommendations database (available on the NICE website) and highlight these recommendations to public research bodies.

8 Review

NICE reviews the evidence 3 years after publication to ensure that any relevant new evidence is identified. However, NICE may review and update the guidance at any time if significant new evidence becomes available.

Adrian Newland
Chair, diagnostics advisory committee
October 2017

9 Diagnostics advisory committee members and NICE project team

Diagnostics advisory committee

The diagnostics advisory committee is an independent committee consisting of 22 standing members and additional specialist members. A list of the committee members who participated in this assessment appears below.

Standing committee members

Professor Adrian Newland

Chair, diagnostics advisory committee (to October 2017)

Dr Mark Kroese

Chair, diagnostics advisory committee, (from September 2017, previously Vice Chair)

Mr John Bagshaw

In-vitro Diagnostics Consultant

Professor Enitan Carrol

Chair in Paediatric Infection, University of Liverpool

Dr Sue Crawford

GP Principal, Chillington Health Centre

Dr Owen Driskell

Lead for Laboratory Medicine, National Institute for Health Research Clinical Research Network West Midlands

Dr Steve Edwards

Head of Health Technology Assessment, BMJ Evidence Centre

Dr Simon Fleming

Consultant in Clinical Biochemistry and Metabolic Medicine, Royal Cornwall Hospital

Dr James Gray

Consultant Microbiologist, Birmingham Children's Hospital

Professor Steve Halligan

Professor of Radiology, University College London

Mr John Hitchman

Lay member

Professor Chris Hyde

Professor of Public Health and Clinical Epidemiology, Peninsula Technology Assessment Group (PenTAG)

Mr Patrick McGinley

Head of Costing and Service Line Reporting, Maidstone and Tunbridge Wells NHS Trust

Dr Michael Messenger

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Mrs Alexandria Moseley

Lay member

Dr Peter Naylor

GP, Wirral

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Consultant in Clinical Biochemistry and Metabolic Medicine, Newcastle upon Tyne NHS Trust

Dr Simon Richards

Vice President Regulatory Affairs, Europe and Middle East, Alere Inc

Professor Mark Sculpher

Professor of Health Economics, Centre for Health Economics, University of York

Professor Matt Stevenson

Professor of Health Technology Assessment, School of Health and Related Research, University of Sheffield

Professor Anthony Wierzbicki

Consultant in Metabolic Medicine/Chemical Pathology, St Thomas' Hospital

Specialist committee members

Miss Fran Berry

Lay member

Mr Christopher Brewer

Consultant Obstetrician and Gynaecologist, York Teaching Hospital NHS Foundation Trust

Dr Suha Deen

Consultant Gynaecological Pathologist, Nottingham University Hospitals NHS Trust

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Professor Jane Macnaughton

Professor of Medical Humanities and Honorary Consultant in Obstetrics and Gynaecology, Durham University

Miss Hema Nosib

Consultant Gynaecologist, North West Anglia NHS Foundation Trust

NICE project team

Each diagnostics assessment is assigned to a team consisting of a technical analyst (who acts as the topic lead), a technical adviser and a project manager.

Thomas Walker

Topic Lead (from September 2017)

Rebecca Albrow

Topic Lead (to August 2017) and Technical Adviser (from September 2017)

Frances Nixon

Technical Adviser (to August 2017)

Robert Fernley

Project Manager (to August 2017)

Donna Barnes

Project Manager (from September 2017)

ISBN: