Public Health England

Protecting and improving the nation's health

NHS Cervical Screening Programme

Colposcopy and Programme Management

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Public Health England leads the NHS Screening Programmes

About Public Health England

Public Health England exists to protect and improve the nation's health and wellbeing, and reduce health inequalities. It does this through world-class science, knowledge and intelligence, advocacy, partnerships and the delivery of specialist public health services. PHE is an operationally autonomous executive agency of the Department of Health.

About Public Health England Screening

Screening identifies apparently healthy people who may be at increased risk of a disease or condition, enabling earlier treatment or better informed decisions. National population screening programmes are implemented in the NHS on the advice of the UK National Screening Committee (UK NSC), which makes independent, evidence-based recommendations to ministers in the 4 UK countries. The Screening Quality Assurance Service (SQAS) ensures programmes are safe and effective by checking that national standards are met.

Public Health England (PHE) leads the NHS Screening Programmes and hosts the UK NSC secretariat. PHE is an executive agency of the Department of Health and exists to protect and improve the nation's health and wellbeing, and reduce health inequalities.

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Glossary of terms

Term	Explanation
ACCS	Advisory Committee on Cervical Cancer Screening
AGUS	atypical glandular cells of unknown significance
ALOs	Actinomyces-like organisms
ASCUS	atypical cells of undetermined significance
ATSM	Advanced Training Skills Module
BSCCP	British Society for Colposcopy and Cervical Pathology
CDB	colposcopically directed biopsy
CGIN	cervical glandular intraepithelial neoplasia
CIN	cervical intraepithelial neoplasia
CIN1	cervical intraepithelial neoplasia grade 1
CIN2	cervical intraepithelial neoplasia grade 2
CIN2+	cervical intraepithelial neoplasia grade 2+
CIN 3	cervical intraepithelial neoplasia grade 3, sometimes called high-grade or severe dysplasia. Also called cervical squamous intraepithelial neoplasia 3 and stage 0 cervical carcinoma in situ.
CME	continued medical education
CWT	cancer waiting times
DES	diethylstilbestrol
DySIS	dynamic spectral imaging system
ECC	endocervical curettage
FGM	female genital mutilation
HG-CGIN	high-grade cervical glandular intraepithelial neoplasia
HPV	human papilloma virus
HRT	hormone replacement therapy
HR-HPV	high-risk human papillomavirus
HSV	Herpes Simplex Virus
IUD	intrauterine contraceptive device
FIGO	International Federation of Gynecology and Obstetrics
GUM	genitourinary medicine
HAART	highly active retroviral therapy
HC2	Hybrid Capture 2

Term	Explanation
LBC	liquid-based cytology
LEEP	loop electrical excision procedure
LLETZ	large loop excision of the transformation zone
LSIL	low-grade squamous intra-epithelial lesions
MDT	multi-disciplinary team
NHAIS	The National Health Applications and Infrastructure services
NHSCSP	NHS Cervical Screening Programme
NICE	National Institute for Health and Care Excellence
OCP	oral contraceptive pill
OSCE	Objective Structured Clinical Examination
PPV	positive predictive value
RCOG	Royal College of Obstetricians and Gynaecologists
SCJ	squamocolumnar junction
TOC	Test of Cure
TZ	transformation zone
VaIN	vaginal intraepithelial neoplasia

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1. Introduction

1.1 Aim of the NHS Cervical Screening Programme

The aim of the NHS Cervical Screening Programme (NHSCSP) is to reduce the incidence of and mortality from, cervical cancer through a systematic, quality assured population-based screening programme for eligible women.

Since its introduction, the screening programme has helped half the number of cervical cancer cases, and is estimated to save approximately 4,500 lives per year in England.[1] In 2014 to 2015 approximately 3.1 million women were screened in England.[2]

1.2 Cytology reporting: terminological changes

In January 2013, the third edition of NHSCSP Publication Number 1, 'Achievable standards, benchmarks for reporting, and criteria for evaluating cervical cytopathology' was published, outlining a new classification for the reporting of abnormal cervical cytology.[3] The changes, which have been agreed by the NHSCSP and the British Association for Cytopathology, are summarised in Table 1. The new terminology will be followed throughout this document.

Table 1 Terminological changes to cervical cytology reporting

Previous terminology (BSCC 1986)	**New terminology**
Borderline change	Borderline change in squamous cells
	Borderline change in endocervical cells
Mild dyskaryosis Borderline change with koilocytosis	Low-grade dyskaryosis
Moderate dyskaryosis	High-grade dyskaryosis (moderate)
Severe dyskaryosis	High-grade dyskaryosis (severe)
Severe dyskaryosis? Invasive	High-grade dyskaryosis ?Invasive squamous carcinoma
?Glandular neoplasia	?Glandular neoplasia of endocervical type
	?Glandular neoplasia (non-cervical)

1.3 Introduction of HPV triage and test of cure

A national programme of high-risk human papillomavirus (HR-HPV) triage for women with borderline or low-grade cytology results and HR-HPV test of cure now operates following the evidence from the pilot and sentinel sites. Further information is available in chapter 3.

2. Screening programme policy

2.1 Frequency of screening

2.1.1 Screening interval

The NHSCSP offers screening at different intervals, depending on a woman's age:

Age group (years)	Frequency of invitation
Under 24.5	No invitation
24.5	First invitation (to ensure that women can be screened for the first time by their 25th birthday)
25 to 49	Every 3 years
50 to 64	Every 5 years
65+	Invitation as required for women who have had recent abnormal tests. Women who have not had an adequate screening test reported since age 50 may be screened on request.

Evidence: while most experts agree that cervical screening is effective, debates continue over the most appropriate screening interval. The recommendations outlined in the table above were based on an audit of UK screening histories by Sasieni et al.[4] Their research examined the screening histories (mostly based on conventional cytology) of 1,305 women aged 20 to 69 years diagnosed with invasive cervical cancer, and 2,532 age-matched controls. The researchers concluded that while screening offered additional protection to all women aged from 25 to 65, implementing a uniform screening interval across all age groups was undesirable:

- in women aged 55 to 69, a negative screening result in the previous five years offers considerable protection (83%) against invasive cervical cancer, with annual screening adding only modest additional protection (87%)
- women aged 40 to 54 need to have a negative screening result in the previous three years to achieve a similar level of protection (84%). A negative result in the previous five years confers a lower level of protection (73%). Annual screening in this age group offers only modest additional protection (88%) over three-yearly screening
- for women aged 20 to 39 years, screening confers less protection. Even annual screening is not as effective (76%) as three-yearly screening is for older women. Three

years after screening, cancer rates are similar to those found in unscreened women, suggesting that three-yearly screening intervals are most suitable for this age group
- the screening of women aged 25 to 64 is discussed in section 2.2

Several national and international guidelines have changed to become more similar to the English programme.[5,6,7]

2.1.2 Invitations for routine screening

A woman's first invitation for routine screening must be sent out 6 months before her 25th birthday, ie at the age of 24 and a half. This ensures that the woman can be screened by her 25th birthday. The NHAIS system has been adapted to support these advance invitations.

All subsequent invitations to screening must be sent around 6 weeks before the woman's test due date:

- women aged from 24 and a half to 49 should receive a routine invitation 34.5 months after a previous test
- women aged 50 to 64 should receive a routine invitation 58.5 months after a previous test

Evidence: there is evidence that a delay of several months may occur between the issuing of invitations to women and the date of their screening test. Sending invitations before test dates reduces possible delays.[8]

2.1.3 Monitoring the screening interval

The actual screening intervals should be monitored by PHE quality assurance teams.

Evidence: good practice. The number of women screened in the previous three and five years does not correspond with the number regularly screened at intervals of three and five years, because a proportion of women will not be screened in every screening round.

NHSCSP returns can provide data on the proportion of the population screened at different intervals, but more detailed research is required to explore the effect of different patterns of screening attendance on cervical cancer incidence and mortality. Data on a small random sample of women is published in the national 'Audit of invasive cervical cancers'.[9]

2.2 Age at starting screening

Women should be invited for their first screening test at the age of 24 and a half years. Women under this age who have symptoms, are concerned about their sexual health, or are worried

about their risk of developing cervical cancer, should contact their GP or the local genitourinary medicine (GUM) clinic.

2.2.1 Policy development

The optimum age for starting routine cervical screening has been a matter of national debate for some time. In 2003 the Advisory Committee on Cervical Cancer Screening (ACCS), advised the Department of Health (DH) to raise the starting age for cervical screening from 20 to 25.[10] In March 2009, the ACCS held an extraordinary meeting to review the evidence relating to risks and benefits of cervical screening in younger women. Members voted to keep the starting age for screening at 25. The International Agency for Research on Cancer also recommends that women should not commence cervical screening before the age of 25.[11]

2.2.2 Clinical evidence

For women under 25, the prevalence of HPV infection after coitarche is high, with the result that sexually active women in this age group are quite likely to have HPV-associated cellular changes.[12]

Because HPV infection is less likely to persist in younger women, the majority of low-grade abnormalities detected in cytology samples taken from women under the age of 25 will regress spontaneously with time.[13] The incidence of cervical cancer in this age group is very low.[4,14,15]

Screening women under the age of 25 is therefore likely to result in a large number of referrals to colposcopy for further investigation. This is associated with heightened levels of anxiety for these women. Additionally, if treatment is administered by the colposcopist for abnormalities that are likely to resolve without intervention, there may be negative consequences for the woman's subsequent ability to carry a child to term.[16,17,18,19,20,21] Counter-evidence has been presented questioning this, including a recent study that suggests the risk of preterm delivery in women treated by colposcopy within the NHS in England is substantially lower than that reported in studies from other countries.[22,23]

Screening has not been shown to reduce the incidence of, or mortality from, cervical cancer in women under the age of 25.[14] There is no published report showing an association between cervical screening in women under the age of 25 and either lower rates of cervical cancer in women under the age of 25, or lower rates of cervical cancer mortality in women under the age of 30. There is, however, ample evidence that screening in women aged 20 to 24 leads to the detection of large numbers of cytological abnormalities (the majority of which would resolve of their own accord) resulting in referrals to colposcopy and subsequent treatment. Most women with high-grade cervical intra-epithelial neoplasia (CIN) are treated by excision.[13] Several publications show that the benefits of cervical screening under age 25 are small (or non-existent):

- (at most) a very small percentage of women treated for CIN aged 20 to 24 would have developed cervical cancer by age 26 in the absence of treatment[24]
- women screened aged 20 to 24 are at no lower risk of cervical cancer aged 20 to 24 than are women not screened at that age[14]
- increases in rates of cervical cancer in the north-east of England in the period following the raising of the lower age limit to 25 have been no greater than the increase in Wales where the screening of women aged 20 to 24 has continued[25]
- cervical cancer in women aged 20 to 24 remains rare in England and most cases found in women aged 20 to 29 are micro-invasive (which is often treated by the same excision as is used for cervical intraepithelial neoplasia (CIN3))[26]
- evidence from other countries supports the policy of not screening under the age of 25: for example, an American study recently showed that 25% of cytology in African American and Hispanic women aged under 21 was abnormal, but none of the 8,011 study subjects developed cervical cancer before turning 21[27]

2.3 Age at finishing screening

Routine screening should end at the age of 65.

Evidence for screening in women aged 50 to 64*:* cervical screening is extremely effective in preventing cervical cancer in women aged 50 to 64. One study suggested that it may be safe to withdraw well-screened women who have 3 consecutive negative cervical samples from the screening programme at the age of 50[28], but this was not supported by another piece of research.[29] Cervical screening is less efficient at detecting CIN3 in older women, and a greater number of cervical cytology samples are required to detect a case of CIN3 after the age of 50[30], however, screening is more efficient at preventing invasive cancer in this age group.[4,14]

There is insufficient evidence to warrant stopping screening before the age of 65, although the ACCS will keep this matter under review, and will revisit the issue in the event of technological developments or new evidence.[31] To date, no study has been able to show that cervical cancer rates in women aged 60 to 70 would not rise if screening were offered only up to age 50.

Evidence for ceasing at age 65*:* the prevalence of CIN3 and invasive cancer in women over the age of 50 is low: 11/100,000 in well screened women compared with a prevalence rate of 59/100,000 women in the population as a whole. Most women diagnosed with invasive cancer after the age of 50 have not participated fully in the cervical screening programme, and it is expected that screening previously poorly screened women over the age of 65 would result in a reduction in the subsequent rate of cervical cancer.[9] The pre-existing recommendation to offer a screening test to previously unscreened women over the age of 65 is still appropriate based on the available evidence.

2.4 Unscheduled screening

Unscheduled cervical screening does **not** form part of the NHSCSP. Provided a woman has undergone screening within the recommended interval (depending on her age), she should not be re-screened:

- on taking, or starting to take, an oral contraceptive
- on insertion of an intrauterine contraceptive device (IUD)
- on taking or starting to take hormone replacement therapy (HRT)
- in association with pregnancy (antenatally or postnatally)
- on being diagnosed with genital warts or pelvic infection
- due to heavy cigarette smoking
- due to having multiple sexual partners

Women with cervical symptoms, including persistent vaginal discharge that cannot be otherwise explained (eg by an infection), should be referred in a timely manner for further evaluation of the cervix. Specific management algorithms have been published to manage women under 25 who have symptoms of cervical cancer.[32]

Evidence: in a mathematical simulation, the practice of routinely taking a second cervical cytology sample one year after a woman's first sample was reported as negative conferred no additional benefit in terms of person-years of life saved.[33] There is no evidence to suggest that social or behavioural risk factors reduce the length of the preclinical, cytologically detectable phase of cervical neoplasia[34], and the association with socio-sexual correlates is not strong enough to predict women with high-grade CIN.[35]

2.5 Cervical sampling in genitourinary medicine (GUM) clinics

The indications for performing cervical cytology in GUM clinics are no different to those for the rest of the NHSCSP. Cervical samples taken for screening purposes in GUM clinics should be restricted to women who have not been screened in the previous routine screening interval, with the exception of HIV positive women. Further information on the screening and management of HIV positive women can be found in section 12.8. Cervical screening sample takers in GUM clinics should be able to demonstrate appropriate competencies.[36] The criteria for referral to a designated colposcopy clinic for women requiring further assessment remain the same as for the rest of the NHSCSP.

The specificity and sensitivity of cervical cytology for the identification of sexually transmitted infections by cervical cytology is not high enough to permit this test to be used as a diagnostic tool.

Evidence: a case-control study of women attending GUM clinics across the UK suggested that they were as likely to participate in the NHSCSP as women in the general population.[37] Higher

rates of cytological abnormality have been observed in cervical samples from GUM clinics, a finding confirmed in data from clinics dealing with sexually transmitted infections.[38,39] This is mainly due to a large number of samples containing low-grade abnormalities. Audits of cervical screening in GUM clinics suggest that a greater proportion of samples are reported as inadequate or exhibit inflammatory changes owing to the presence of infection.[40,41,42] Inflammatory changes in cervical samples are not a reliable indicator of other types of genital infection, and further tests must be conducted where infection is suspected.[43,44,45]

2.6 Withdrawal from screening

2.6.1 Voluntary withdrawal

Women can withdraw from the programme by written request. Reasons for voluntary withdrawal may include:

- women at low risk of cervical cancer, for example women who have never had intimate contact with another person (male or female)
- women with a physical or learning disability of a nature that makes taking a sample very difficult or distressing, who do not wish to receive further invitations
- women who may not benefit from screening, for example those who are terminally ill
- women who for any reason, for example, female genital mutilation (FGM), are unable to give an adequate sample – alternative options such as gynaecological referral should be discussed and agreed with the woman
- women who do not want to participate at any point

Health professionals must ensure that all women who express a wish to withdraw are provided with sufficient and accurate information to make an informed decision. Such women should never be ceased without their informed consent to withdraw. In all cases, the woman should be offered an appointment with an appropriate health professional to discuss their withdrawal.

2.6.2 ‘Best interests’ decisions

Rarely, a woman may be unable to make either an informed choice to accept a screening invitation or to withdraw from the screening programme permanently. Under the Mental Capacity Act (2005), decisions can be made on behalf of such women by a legally authorised representative.

A ‘best interests’ decision must be the least restrictive of all possible options and so, in most cases, it is preferable to continue with regular invitations at routine intervals, which can be accepted or declined individually.

2.6.3 Medical reasons for ceasing a woman

Women should be ceased from the programme where they do not have a cervix due to:

- having undergone total hysterectomy (women with a subtotal hysterectomy remain at risk and should remain in the programme)
- congenital absence of the cervix
- being a male-to-female transsexual
- having undergone a radical trachelectomy for cervical cancer

2.6.4 Radiotherapy

It is difficult to accurately report samples from women who have undergone radiotherapy for cervical, bladder, rectal and other pelvic cancers. This group should be ceased from the programme, and provided with gynaecological follow-up.

All cases should be considered individually, and women who are unsuitable for screening can be ceased from the programme.

2.6.5 Cervical stenosis

It may not be possible to obtain a cytology sample that represents the entire transformation zone from women who have severe cervical stenosis (often a result of previous surgery). Cervical dilatation should be considered in all such cases, but for women with a history of high-grade dyskaryosis or cervical glandular intraepithelial neoplasia (CGIN), hysterectomy can also be considered. Involvement of the colposcopy multi-disciplinary team (MDT) may be useful when making this decision. Where neither cervical dilatation nor hysterectomy are appropriate, the lead colposcopist should consult with the woman and a joint decision may be reached to withdraw her from the NHSCSP. Where the woman declines withdrawal, she should continue to receive invitations to screening and the situation re-evaluated at each subsequent screening episode.

2.6.6 Automatic ceasing

Women will be automatically ceased from the programme if they meet all three of the following criteria:

- their most recent test was normal and coded ‘A’ for routine recall
- their next test due date would fall after their 65th birthday
- all of their last three screening tests (fewer if less than three in the screening history) were taken at the appropriate intervals and all reported as normal

Women who have not responded to invitations will also be ceased if their next test is due after their 65th birthday.

2.7 Summary of standards

Between the ages of 24 and a half to 49, women should be offered cervical screening every three years. Between the ages of 50 and 64, women should be offered cervical screening every five years.

3. Screening strategies

3.1 Liquid-based cytology

The current standard screening modality within the NHSCSP is liquid-based cytology (LBC).

Evidence: a 2003 review by the National Institute of Clinical Excellence (NICE) concluded that LBC represented a cost-effective alternative to Papanicolaou smears, offering improved sensitivity without any reduction in specificity, and a reduction in the number of inadequate tests reported.[46]

3.2 HPV testing

3.2.1 Background to HPV triage and test of cure: pilots and sentinel sites

In light of the evidence from the pilot and sentinel sites, national rollout of HR-HPV triage for women with borderline or low-grade cytology results and HR-HPV test of cure was completed in 2013.

Evidence: the potential benefits of introducing HR-HPV testing for triage of women with borderline and low grade dyskaryosis screening results have been extensively investigated over the last ten years.

In 2001, an original UK pilot study was conducted:

- the study reported that the incorporation of HPV triage into the NHSCSP was feasible and acceptable to women[47]
- the pilot showed that HPV triage enabled rapid diagnosis of women with abnormalities, and rapid return of women who were unlikely to have cervical abnormalities to routine recall – the consequence was a reduction in repeat cytology samples
- the pilot site experienced a transient rise in colposcopy referral rates (48%)[48]

In 2007, six sentinel sites (accounting for approximately 10% of the English NHSCSP) began to carry out HR-HPV tests on all LBC samples showing low-grade abnormalities from women aged 25 to 64 years of age undergoing routine screening. The project was designed to assess whether HPV triage and test of cure could be introduced into the programme in a safe and non-disruptive way:

- the sentinel sites demonstrated the high negative predictive value of HR-HPV testing. 16% of samples reported as showing low-grade dyskaryosis and 45% of samples reported as showing borderline changes and HR-HPV negative were

returned back to routine screening, significantly reducing the number of women invited for repeat cytology

- overall HR-HPV positivity rates were 53.7% and 83.9% for borderline and low-grade dyskaryosis samples respectively.[48] These findings are similar to results from a large meta-analysis of studies from 1991 to 2007, which found that HR-HPV positivity rates were reported as 43% for women with atypical cells of undetermined significance (ASCUS)and 76% in women with low-grade squamous intra-epithelial lesions (LSIL) [49]
- a similar transient increase in referral rates to colposcopy (64%) was observed to that witnessed in the pilot
- for those women who were referred to colposcopy, the positive predictive value for high-grade disease (CIN2+) varied from 9.1% to 30% between the six sites – satisfactory negative colposcopy examinations carried a high negative predictive value, with only 4.4% of these women diagnosed with CIN2+ over the following three years[50]

Following results from the pilot and the sentinel sites, HPV triage and test of cure was rolled out throughout England.

3.2.2 HPV triage and test of cure

Under the HR-HPV triage protocol, women whose cervical samples are reported as showing borderline changes (of squamous or endocervical type) or low-grade dyskaryosis are given a reflex HR-HPV test. Those who are HPV positive are referred to colposcopy; those who are HR-HPV negative are returned to routine recall. Women whose cervical sample is reported as high-grade dyskaryosis or worse are referred straight to colposcopy without a HR-HPV test.

Under the HR-HPV 'test of cure' protocol, after treatment for all grades of CIN women are invited for screening six months after treatment for a repeat cervical sample in the community. A woman whose sample is reported as negative, borderline change (of squamous or endocervical type), or low-grade dyskaryosis is given an HR-HPV test. If the HPV test is negative, the woman is recalled for a screening test in three years (irrespective of age) and can be returned to routine recall if the subsequent test result is cytologically negative. Those who are HR-HPV positive are referred back to colposcopy. Women whose cytology is reported as high-grade dyskaryosis or worse are referred straight to colposcopy without an HR-HPV test.

Further guidelines for referral to colposcopy are given in Chapter 4, and a summary of the HR-HPV triage and test of cure protocol is provided in appendix 1.

Evidence: HR-HPV testing using Hybrid Capture 2 (HC2) is a more sensitive screening test than either cytology or colposcopy.[48,51,52] The NHSCSP has systematically evaluated other HPV testing platforms and identified those that also meet the criteria for inclusion as an approved technology within the NHSCSP. Attendance rates for HR-HPV triage and test of cure

among the sentinel sites were high (90.2%) supporting the conclusion that HR-HPV triage is acceptable to women. Despite the increased referral rates to colposcopy, the original HR-HPV pilot study was shown to be cost effective in terms of quality and of life years saved.[53] A recent systematic review from Denmark has shown that in the management of low-grade cytological abnormalities, women prefer immediate referral to colposcopy as opposed to surveillance.[54]

3.3 HPV primary screening

Using HR-HPV as the primary screening test is an attractive option for countries with existing cervical screening programmes. HPV testing has the advantage of increased sensitivity and efficacy compared to liquid-based cytology, along with the potential for increasing the interval between screening rounds so that women need to attend less frequently if used as a primary screening test. It may also be a more appropriate screening test for vaccinated women. Following a trial, HR-HPV screening is being piloted at six sites across England to assess how this approach can be used across the programme as a whole.

Evidence: primary screening with HR-HPV testing generally detects more than 90% of all cases of CIN2, CIN3, and invasive cancer. HR-HPV testing is approximately 25% more sensitive than liquid-based cytology in detecting borderline changes or worse, though it is about 6% less specific.[55]

The ARTISTIC trial investigated 24,510 women aged 25 to 64 over two screening rounds approximately three years apart within the NHSCSP.[55] It compared the combination of HR-HPV testing and LBC triage with cytology alone. Its findings suggest that the combination of LBC and additional HR-HPV testing over two screening rounds is slightly more sensitive than cytology alone for the detection of CIN3+ or CIN2+. The ARTISTIC trial concluded that the most cost-effective way of using HPV testing in a population-based screening programme was as a primary screening method, combined with cytology triage. The conclusion that HR-HPV positive women with normal cytology are at low risk of CIN3+ was confirmed by the VUSA-screen study. The risk was 5.22% (95% CI: 3.72-7.91) compared with 42.2% (95% CI: 36.4-48.2) for HR-HPV positive women with abnormal cytology.[56]

The high negative predictive value of the HR-HPV test raises the prospect that HPV primary screening may make it possible to increase the interval between cervical screening rounds for those women who test HR-HPV negative.[56,57] The final results of a Dutch randomised controlled study (POBASCAM) comparing HPV polymerase chain reaction-based testing with conventional cytology (ie Papanicolaou smears) concluded that screening with HR-HPV testing leads to earlier detection of clinically relevant CIN2 or worse. At the second of two screening rounds, spaced five years apart, CIN3 or worse was less common in a group of women who underwent primary HR-HPV testing than in the control group who underwent conventional cytology (relative risk 0.73, 95% CI 0.55 to 0.96; p=0.023).[58]

Additionally, the US ATHENA study has investigated the performance of HR-HPV testing and HR-HPV 16/18 genotyping for screening purposes in women over 25 years of age.[59] Results showed increased sensitivity and similar positive predictive values for the detection of CIN3+ for HR-HPV testing compared to screening with liquid-based cytology alone. Research also shows that the reduced specificity of HR-HPV DNA testing can be improved if HR-HPV genotyping is also conducted. Genotype-specific differences in clearance rates at six and 18 months were revealed by the POBASCAM study: among women who did not clear their HPV infection, HPV 16 persistence was associated with increased detection rates of CIN3 or greater (normal $P<0.0001$; low-grade dyskaryosis $P=0.005$).[60] Genotyping would potentially lead to an increase in surveillance following referral of women positive for HR-HPV types 16/18, whilst allowing a more conservative approach for the follow-up of women positive for the remaining HR-HPV types.

4. Management and referral guidelines for colposcopy

4.1 Cancer waiting times: national policy

The current policy on cancer waiting times is laid out in the document Improving Outcomes: A Strategy for Cancer.[61]

4.2 Cancer wait and referral standards applicable to the NHSCSP

The standards applicable to the NHSCSP are:

1. No more than two months (62 days) should elapse between receipt of a referral from a cancer screening service to first treatment for cancer.

2. No more than one month (31 days) should elapse from diagnosis (decision to treat) to first treatment for all cancers.

3. Women should wait no longer than 18 weeks between GP referral and treatment (or discharge after cancer has been excluded).

4. No more than 1% of patients should wait longer than six weeks for a diagnostic test (colposcopy qualifies as a diagnostic test).

Waiting times are measured in calendar days, not working days, and the date of receipt of referral counts as day 0 in all calculations.

The NHSCSP also sets its own standards for the programme that are designed to ensure that all services meet these national requirements. These are outlined in the appropriate sections, below.

A summary of all waiting time standards is given in Table 2.

Table 2 Summary of referral/waiting time standards

Cytology/HPV	Wait/CWT pathway	NHSCSP standard
3 consecutive inadequate samples	18 week pathway, upgraded to 62 days if cancer subsequently suspected	Offered an appointment with a colposcopist within 6 weeks
Borderline change/ HR-HPV positive	18 week pathway, upgraded to 62 days if cancer subsequently suspected	Offered an appointment with a colposcopist within 6 weeks
Low-grade/ HR-HPV positive	18 week pathway, upgraded to 62 days if cancer subsequently suspected	Offered an appointment with a colposcopist within 6 weeks
High-grade (moderate)	62 day pathway/2 week urgent GP referral; (move to 18 week pathway if cancer excluded)	Offered an appointment with a colposcopist within 2 weeks of referral
High-grade (severe)	62 day pathway/2 week urgent GP referral (move to 18 week pathway if cancer excluded)	Offered an appointment with a colposcopist within 2 weeks of referral
?Invasive squamous carcinoma	62 day pathway (move to 18 week pathway if cancer excluded)	Offered an appointment with a colposcopist within 2 weeks of referral
?Invasive glandular neoplasia Cells of endocervical origin → referral inside NHSCSP	62 day pathway (move to 18 week pathway if cancer excluded)	Endocervical cells → Offered an appointment with a colposcopist within 2 weeks of referral
Cells of other origin → referral outside NHSCSP)		Cells of other origin → Offered an appointment with a gynaecologist within 2 weeks of referral
Abnormal cervix (outside the NHSCSP)	62 day pathway (move to 18 week pathway if cancer excluded)	Offered an appointment with a gynaecologist within 2 weeks of referral
Symptomatic (outside the NHSCSP)	62 day pathway (move to 18 week pathway if cancer excluded)	Offered an appointment with a gynaecologist within 2 weeks of referral

4.3 Cytological reports

Colposcopy is a continuation of the screening process, providing further evidence about the nature of observed changes. The colposcopists must therefore have access to the cytology report including any free text comments at the time of the examination.

4.4 Inadequate samples

4.4.1 Cytological management of inadequate samples

Where an initial LBC sample is reported as inadequate, cytology should be repeated. The repeat sample should not be taken less than three months after the previous test. In addition, a sample must be reported as inadequate if the sample-taker has not completely visualised the cervix, or if the sample has been taken in an in inappropriate manner, for example with a sampling device that has not been approved by the NHSCSP.

Samples must not be reported as inadequate if they contain any evidence of borderline change or dyskaryotic cells.

4.4.2 Referral on the basis of consecutive inadequate samples

After three consecutive inadequate samples, a woman should be referred to colposcopy. She should be seen by the colposcopist within six weeks of referral (99%).

Evidence: the referral of women to colposcopy after three consecutive inadequate samples is a good practice point. Invasive cancers may be associated with cytology samples which do not contain abnormal cells. Women with persistent inadequate smears should undergo colposcopy to exclude invasive cancer,

4.5 Negative results

Adequate samples with no abnormal cells are classified as negative. Women who receive a negative report can be safely returned to routine recall.

Evidence: there is a 61 to 84% reduction in the risk of developing cervical cancer over the three to five year interval following negative cervical cytology.[4]

4.6 Borderline change in squamous or endocervical cells

4.6.1 Cytological management of borderline change in squamous and endocervical cells

When borderline change is reported in either endocervical or squamous cells on a cytology sample, a reflex HR-HPV test is performed. Women who have borderline change of either type and who test positive for HR-HPV must be referred for colposcopy. Women who are HR-HPV negative are returned to normal recall.

If a sample is of insufficient cellularity, HR-HPV testing may be attempted, but should only be considered reliable where the result is positive, or where the validity of a negative result is confirmed by an internal control. In cases involving a scanty sample in which cytology is reported as borderline and the HR-HPV result is negative and confirmed by an internal control, the woman can be returned to routine recall. In cases where the HR-HPV test is unreliable, a further sample should be taken in six months and the woman should be managed as follows:

- if the cytology report from the second screen is negative, borderline, or low-grade dyskaryosis, an HR-HPV test should be conducted. Women who are positive for HR-HPV must be referred to colposcopy. Women who are negative for HR-HPV can be returned to routine recall
- If the second screen is reported as high-grade dyskaryosis (moderate) or worse, the woman must be referred straight to colposcopy. A HR-HPV test is not necessary.

Evidence: the evidence-base for this policy is presented in chapter 3 and in other NHSCSP guidance.[3] The recommended interval for the second sample is empirical, based on the experience of the sentinel sites.[48] HR-HPV triage applies to the second sample for the same reasons that are outlined above, ie that HR-HPV testing has been shown to be more sensitive, though slightly less specific, than cytology alone for detecting high-grade CIN.

4.6.2 Time from referral to first clinic appointment for borderline change in squamous and endocervical cells

All women who are HR-HPV positive and have borderline changes reported in their LBC cytology sample must be referred to colposcopy. They should be seen within six weeks of referral (99%).

4.7 Low-grade dyskaryosis

4.7.1 Management of low-grade dyskaryosis

When low-grade dyskaryosis is reported on a cytology sample, a reflex HR-HPV test will be performed. If the HR-HPV test is positive, the woman must be referred for colposcopy. If the HR-HPV test is negative, the woman must be returned to routine recall. Where the HPV test is inadequate or unreliable the woman must be referred for colposcopy. In cases involving a scanty sample in which cytology is reported as low-grade dyskaryosis, and the HR-HPV result is negative and confirmed by an internal control, the woman can be returned to routine recall. However, if the HR-HPV negative test result is not confirmed by an internal control in this scenario, the woman must be referred for colposcopy.

Women with a low-grade result who are HPV positive and who attend for colposcopy should be seen and assessed. To prevent possible overtreatment, however, they should not be managed on a 'see and treat' basis. For information on follow-up after treatment and on the surveillance of women who have not been treated, see chapter 10.

Evidence: the evidence-base for this policy is presented in chapter 3 and in other NHSCSP guidance.[3]

4.7.2 Referral wait time for low-grade dyskaryosis

All women who are HR-HPV positive and have low-grade dyskaryosis reported in their LBC cytology sample must be referred to colposcopy. They should be seen within six weeks of referral (99%).

4.8 High-grade dyskaryosis (moderate)

4.8.1 Management of high-grade dyskaryosis (moderate)

Women must be referred for colposcopy after one test reported as high-grade dyskaryosis (moderate). A HR-HPV test is not indicated/performed.

Evidence: a randomised trial of the management of women with a high-grade (moderate) report on cervical cytology found that 74% had CIN 2/3.[62] Case series also report a high incidence (74% to 77%) of CIN 2/3 at colposcopy.[63,64,65]

4.8.2 Referral wait time for high-grade dyskaryosis (moderate)

Women whose LBC samples are reported as high-grade dyskaryosis (moderate) are included in the 62-day standard introduced by the 'Cancer Reform Strategy'.[61] Since the clock for the 62-day period runs from receipt of the referral from the NHSCSP until the start of the first

definitive treatment (should the woman be diagnosed with cancer), prompt referral to colposcopy is necessary. If a woman is not referred directly to colposcopy, her GP must make an urgent referral through the 'two-week wait' pathway. The woman should be seen by a colposcopist within two weeks (93%).

Receipt of this referral at the acute provider is the starting point for the 18-week commitment, to which the woman should move once cancer is excluded following colposcopic examination.

4.9 High-grade dyskaryosis (severe)

4.9.1 Management of high-grade dyskaryosis (severe)

Women must be referred for colposcopy after one test is reported as high-grade dyskaryosis (severe).

Evidence: case series report a high incidence (80% to 90%) of CIN 2/3 at colposcopy.[64,66]

4.9.2 Referral wait time for high-grade dyskaryosis (severe)

Women whose liquid-based cytology samples are reported as high-grade dyskaryosis (severe) are included in the 62-day standard introduced by the Cancer Reform Strategy.[61] Since the clock for the 62-day period runs from receipt of the referral from the NHSCSP until the start of the first definitive treatment (should the woman be discovered to have cancer), prompt referral to colposcopy is necessary. If a woman is not referred directly to colposcopy, her GP must make an urgent referral through the 'two-week wait' pathway. The woman should be seen by a colposcopist within two weeks of referral (93%).

Receipt of this referral at the acute provider is the starting point for the 18-week commitment, should the woman receive a benign diagnosis.

4.10 ?Invasive squamous cell carcinoma

4.10.1 Cytological management of ?invasive squamous cell carcinoma

Women must be referred for colposcopy after one test reported as ?invasive squamous cell carcinoma.

Evidence: the correlation between a cervical cytology sample showing features of invasion and the histological diagnosis of invasive cancer is high. The PPV in one series was 56% for all cancers. [67]

4.10.2 Referral wait time for ?invasive squamous cell carcinoma

Women whose LBC samples are reported as ?invasive squamous cell carcinoma are included in the 62-day standard introduced by the 'Cancer Reform Strategy'.[61] Since the clock for the 62-day period runs from receipt of the referral from the NHSCSP until the start of the first definitive treatment (should the woman be discovered to have cancer), prompt referral to colposcopy is necessary. If a woman is not referred directly to colposcopy, her GP must make an urgent referral through the 'two-week wait' pathway. The woman should be seen by a colposcopist within two weeks of referral (93%).

Receipt of this referral at the acute provider is the starting point for the 18-week commitment, to which the woman should move once cancer is excluded following colposcopic examination.

4.11 ?Glandular neoplasia

4.11.1 Referral pathway for ?glandular neoplasia

When glandular neoplasia has been reported, the referral pathway will depend on the details provided about the source of the abnormal glandular cells:

- in cases in which the abnormal glandular cells probably originated from the endocervix, or the source is not specified, the woman must be referred for colposcopy. If a woman is not referred directly, the GP must make an urgent referral through the 'two-week wait' pathway
- in cases in which the source of the abnormal glandular cells is likely to be the endometrium or another gynaecological site, the woman should be referred to a gynaecology clinic. If a woman is not referred directly, the GP must make an urgent referral through the 'two-week wait' pathway (see table 2)

Referrals to gynaecology clinics are not part of the screening programme and may be managed according to local protocols. The following guidance should be followed to ensure appropriate management:

- the woman's individual circumstances must be considered holistically. A referral combining cervical and extra-cervical investigations may be feasible in some cases. Communication with the woman's GP may be advisable to avoid causing distress if the woman is already under treatment for the suspected condition
- a member of the consultant medical staff at the cervical cytology laboratory must ensure that communication of the result is made in a timely manner. Note that gynaecological referrals will not be covered by programme-wide failsafe systems
- arrangements must be made to inform the woman of her diagnosis of non-cervical glandular neoplasia. Such communications are particularly

sensitive, as the woman may have received a screening result letter referring to a negative, borderline, or low-grade cytological abnormality

In rare cases, a woman's cytology test may reveal the co-existence of non-cervical glandular neoplasia with cervical abnormalities. Treatment of the former falls outside the scope of the screening programme; therefore it is the latter result that is recorded and sent to The National Health Applications and Infrastructure services (NHAIS) to determine the woman's management in the screening programme. This ensures that the woman is protected by NHSCSP failsafe systems.

Evidence: the natural history of this condition remains unclear. Case series of women referred to colposcopy with a single cervical cytology sample reporting glandular neoplasia are associated with high levels of invasive (40% to 43%) and pre-invasive (20% to 28%) disease.[68,69]

4.11.2 Referral wait time for ?glandular neoplasia

Whatever the source of the abnormal glandular cells, if a woman is not referred directly to colposcopy or gynaecology services, she must be referred by her GP via the 'two-week wait' pathway.

The woman must be seen urgently, within two weeks of referral (93%).

4.12 Difficult cases

Those reporting abnormal cervical cytology samples may refer a woman for colposcopic assessment when cytological changes are difficult to interpret. In these instances, colposcopic appearances may also be non-specific, but a more accurate assessment is likely to be obtained by combining cytological review, colposcopic appearances, and histological biopsy of any abnormality seen. Ideally, such cases should be reviewed by a cytologist, colposcopist, and histopathologist at the colposcopy multi-disciplinary team meeting before future management is decided.

4.13 Benign endometrial cells in cervical samples

The significance of cytologically benign endometrial cells in cervical samples varies with the phase of the menstrual cycle, and medication, clinical history, and age of the woman, however, in a population-based cervical screening programme, some, if not most, of the information listed above is often unavailable. This should be reflected in the clinical management advice provided.

There is now a considerable body of evidence suggesting that endometrial cells in a sample from a woman under the age of 40 do not indicate significant endometrial pathology. Therefore,

normal endometrial cells found in a cervical sample from a woman of this age need not be reported.

In women over the age of 40, normal endometrial cells are significantly more likely to be found in the cervical sample up to the 12th day of the menstrual cycle than in the remainder of the cycle, and need not be specifically reported by the laboratory.

In women aged over 40, who are beyond the twelfth day of the menstrual cycle, the finding of normal endometrial cells in a cervical sample may indicate endometrial pathology ranging from benign polyps to carcinoma. The association of normal endometrial cells in a cervical sample with significant pathology (endometrial hyperplasia and neoplasia) increases with age: it has been reported that endometrial disease may be found in up to 13% of women over the age of 60 with normal endometrial cells in their sample[70], however, normal endometrial cells found beyond the twelfth day of the menstrual cycle in an individual over 40 may not indicate pathology if the woman is receiving oral contraceptives, hormone replacement therapy, or tamoxifen, or where an IUCD has been fitted.

Normal endometrial cells identified in a sample from a woman aged 40 or over should always be reported if the menstrual, drug, and contraceptive history are not known (see above). They should also be reported where they are found in any postmenopausal woman, accompanied by a comment similar to the following: ‘Endometrial cells are present in a woman aged over 40. Such cells may be associated with endometrial pathology, particularly if out-of-phase or after the menopause. Referral for a gynaecological opinion should be considered in light of the menstrual, medication, and clinical history.’

If the day of the menstrual cycle is not known, and the sample is otherwise negative, then it should be reported as negative, with a comment similar to the following: ‘Endometrial cells are present but menstrual history not stated. If there is any history of abnormal vaginal bleeding, referral for a gynaecological opinion should be considered.’

Evidence: compared with conventional cytology, LBC may be associated with a higher prevalence of normal endometrial cells, but when found these are less likely to be associated with endometrial pathology. Their prevalence may be explained by more consistent use of sampling instruments for LBC with better access to the lower uterine segment or by changing technology and improved reporting standards. Most endometrial pathology is accompanied by symptoms, implying that a relatively small number of additional cases will be found through follow-up of asymptomatic women.[71]

4.14 Abnormal cervix

Sample-takers must visualise a woman’s cervix when taking an LBC sample. If they notice abnormalities suggesting possible malignancy, the woman should be referred for gynaecological examination. These women must be seen urgently, within two weeks of referral.

4.15 Women with symptoms

4.15.1 Management of women with symptoms

The NHSCSP is a population-based screening programme, designed to reduce the incidence of, and mortality from, cervical cancer by detecting disease at an early stage of its development. Women presenting with symptoms of cervical cancer (eg postcoital bleeding, persistent vaginal discharge that cannot be explained by infection or other causes) are not suitable candidates for screening. If the common causes of these symptoms have been excluded in general practice eg infection, type of contraception usage, they must instead be referred for examination by a gynaecologist experienced in the management of cervical disease (for example a cancer lead gynaecologist). Gynaecologists may refer these women on for symptomatic colposcopic examination outside the NHSCSP if cancer is suspected.

Contact bleeding at the time of cervical sampling may occur, and is not an indication for referral to colposcopy in the absence of other symptoms.

Evidence: good practice point – case series reported a high incidence of cervical neoplasia in women with postcoital bleeding[72] however, the majority of cases of postcoital bleeding are not due to malignant disease and in younger women chlamydial infection or problems with contraception are more likely causes.

4.15.2 Referral guidelines for women with symptoms

Women with symptoms of cervical cancer must be seen urgently, within two weeks of referral.

4.16 Previous treatment for CIN and ‘test of cure’

Women who have been treated for CIN should be returned to community-based routine recall, irrespective of their excision margin status. A cervical cytology sample should be taken six months after treatment:

- where the cytology sample is reported as negative, borderline, or low-grade, a reflex HR-HPV test will be undertaken, women who are positive for HR-HPV will be referred for colposcopy, women who are negative for HR-HPV will be recalled for a repeat cytology sample in three years, irrespective of their age – the three year repeat is managed according to standard HR-HPV triage protocols
- where the cytology sample is reported as high-grade dyskaryosis or ?invasive squamous carcinoma women must be referred for colposcopy – an HR-HPV test is not necessary

If the test of cure cytology sample is performed in a hospital setting instead of the community, it should be taken in a cytology clinic, as a formal colposcopic examination is not required.

Evidence: women treated for CIN are at increased risk of developing cervical cancer.[73]

4.17 Previous treatment for CGIN

Women who undergo excision for CGIN are at risk of recurrence. If the CGIN has been completely excised, at the time of first excision or subsequent re-excision, a test of cure (TOC) sample should be taken six months after treatment. If negative for cytology (endocervical cells must be present) and negative for HR-HPV a second TOC sample is taken 12 months later (ie 18 months after treatment) – if this is also negative for cytology and HR-HPV the woman can be discharged to recall in three years. Further recall will depend on the result of this test and the age of woman. These samples can be performed in the community. If either cytology or HR-HPV, at six or 18 months after treatment, is positive the woman should be referred to colposcopy.

If the woman fails TOC at six months only because of a positive HR-HPV test and no abnormality is detected at colposcopic examination the woman should have a second TOC sample 12 months later, if this sample is negative for cytology and HR-HPV the woman can be discharged to recall in three years. Further recall will depend on the result of this test and the age of woman. If a positive cytology result is reported in either of the six or 18 months 'TOC' samples the woman must be referred to colposcopy and managed appropriately. If no colposcopic abnormality is present and re-excision is not appropriate the women should revert to ten years of cytology follow up. Women who have incompletely excised CGIN and have declined re-excision should be followed up in the colposcopy clinic. Cytology should be performed six months after treatment and if negative repeated six months later (ie at 12 months after treatment) and then annually for the subsequent nine years. Complex CGIN cases will benefit from discussion at the colposcopy MDT.

Although robust data is lacking the increased sensitivity of HR-HPV testing permits the introduction of TOC for women with completely excised GCIN.

Evidence: good practice point

4.18 Summary of standards

The following standards apply to both women undergoing HPV triage and women undergoing test of cure:

1. A woman should be referred for colposcopy after three consecutive inadequate samples. Within six weeks of referral **99% of women** must be seen.

2. A woman should be referred for colposcopy after one test is reported as borderline change (of either type) and HPV positive. Within six weeks of referral **99% of women** must be seen.

3. A woman should be referred for colposcopy after one test is reported as low-grade dyskaryosis and HPV positive. Within six weeks of referral **99% of women** must be seen.

4. A woman should be referred for colposcopy after one test is reported as high-grade dyskaryosis (moderate). No HPV test is necessary. Within two weeks of referral **93% of women** must be seen.

5. A woman should be referred for colposcopy after one test is reported as high-grade dyskaryosis (severe). No HPV test is necessary. Within two weeks of referral **93% of women** must be seen.

6. Women should be referred for colposcopy after one test is reported as ?invasive squamous cell carcinoma. No HPV test is necessary. Within two weeks of referral **93% of women** must be seen.

7. Women should be referred for colposcopy after one test is reported as ?glandular neoplasia of endocervical type or not specified. No HPV test is necessary. Within two weeks of referral **93% of women** must be seen.

8. Women should be referred for a gynaecological opinion after one test is reported as ?glandular neoplasia of non-endocervical type. No HPV test is necessary. Within two weeks of referral **93% of women** must be seen.

Evidence: Patients waiting for a diagnostic test should have been waiting less than six weeks from referral. Maximum two-week wait for first outpatient appointment for patients referred urgently with suspected cancer by a GP [74,75]

5. Quality standards for colposcopy clinics

5.1 Good working practices

5.1.1 Quality Assurance

Whether it is provided in a gynaecological or GUM clinic or in primary care, colposcopy should be organised as a quality assured service.

Local implementation of this guidance document should be documented in clinical protocols. The service must be run by a team working to the protocols and quality standards outlined in this document. Any problems arising in connection with colposcopy practice should be addressed in a confidential and supportive manner.

5.1.2 Role of lead colposcopist

Each colposcopy team must have a lead colposcopist, whose role is to ensure that good practice is followed, that protocols are observed, and that the quality standards outlined in this document are met. The lead colposcopist must also ensure that the service collects data to meet the minimum dataset of the British Society for Colposcopy and Cervical Pathology (BSCCP). This will ensure that the requisite information is available to enable the completion of KC65 (the mandatory quarterly Health and Social Care Information Centre (HSCIC) return) and audits.

5.1.3 Role of hospital-based programme co-ordinator

The hospital-based programme co-ordinator is a requirement of the programme. The hospital-based programme co-ordinator has responsibility for ensuring quality standards are met across the cervical screening programme activities. They will liaise closely with the lead colposcopist, lead cytologist. Lead histologist and others to achieve this. They have the lead role in the audit of invasive cervical cancers.

5.1.4 Audit of invasive cervical cancers

The ‘audit of invasive cervical cancers’ aims to understand why cervical cancers occur in spite of the existence of the cervical screening programme. The overall purpose of this is to identify modifications to the programme that might reduce the incidence of invasive cervical cancer. There is an educational element to the audit, since it offers an opportunity to review the original management of each case of invasive cancer, and to determine whether it was appropriate.

The ‘audit’ collates data from different sources: screening invitations, cytology results, colposcopy attendance, and histology. Since April 2013, colposcopy services participating in

the NHSCSP have been required to provide data on their performance. Any colposcopic examinations that predate the index referral by up to five years are reviewed since these examinations (and associated management) may have impacted on the development of cervical cancer. The reviewer checks whether the colposcopic management of the woman reflected the NHSCSP guidelines of the time. The aim is to improve education through assessment of potential errors, so any colposcopic examinations associated with the index referral cytology and made within 18 weeks of the subsequent diagnosis of cervical cancer does not require routine review.

In most cases, the lead colposcopist at the unit where the diagnosis of the cancer was made will undertake the review. She or he must include notes from other clinics where necessary. However, if the lead colposcopist participated in the management of the woman, another BSCCP certified colposcopist from the same unit should undertake this task.

Women who have participated in the screening programme, but who have subsequently developed invasive cervical cancer, should be offered an opportunity to review the results of their previous tests (cytology and colposcopy). The local cancer team must decide how this disclosure is managed, taking into account the principles for disclosure outlined in the 'Audit of Invasive Cervical Cancers' (NHSCSP Publication No 28).[76]

5.1.5 NHAIS

Decisions made by colposcopists directly influence a woman's management, including the interval to any follow-up tests. If follow-up tests are managed by the colposcopy service, details of the test results should be added to the woman's screening record on NHAIS to ensure that no premature or inappropriate recall invitations are produced by the failsafe system.

If follow-up tests are to be carried out in primary care, colposcopy services will need to communicate information on each woman's screening recall due date to call/recall departments to allow the NHAIS system to produce an automatic invitation at the correct interval. In practice, it is preferable for these updates to be communicated electronically in a standard format and must be sent using a secure mechanism for the transfer of information.

5.1.6 Certification

All colposcopists in the team must be certified through the BSCCP/Royal College of Obstetricians and Gynaecologists (RCOG) scheme. They must undergo the recertification process every three years in order to maintain levels of expertise and ensure that individuals are completing a sufficient caseload.

To achieve recertification, a colposcopist must pursue continued medical education (CME) to ensure that they are abreast of developments in scientific knowledge and clinical practice. Suitable CME opportunities include attendance at regional educational meetings arranged by

the screening quality assurance service, advanced colposcopy courses, and the BSCCP Annual Meeting.

Those who are actively engaged in providing colposcopic services should also be able to demonstrate, through audit activity, workload, attendance at meetings, and other educational events (such as general revalidation), that they are maintaining their knowledge base and competency.

Independent colposcopy should be conducted in the NHS only by competent practitioners. Individual colposcopy services may apply more stringent standards if thought to be of benefit.

5.1.7 Clinic staffing and facilities

Every colposcopy service requires at least one colposcopy nurse whose duties are to ensure the smooth running of the clinic and the provision of support to the woman being seen.

A second trained member of staff will be needed to assist in making the necessary preparations for cervical sampling, biopsies, and treatment. Nurse colposcopists working in a clinic must receive the same level of staff support. All clinic staff must be familiar with the treatment method(s) used (100%).

The colposcopy service requires adequate clerical and secretarial support to ensure timely communication with patients and their GPs. In addition, administrative support is needed to ensure efficient data collection, effective communication with other agencies, and robust failsafe mechanisms.

Evidence: having a dedicated, specialist team in the colposcopy unit provides continuity of care and allows women to develop confidence in individual members of staff.[77] This in turn helps reduce anxiety and improves both attendance and satisfaction with the service. The extended role of the nurse colposcopist may be of particular benefit here.[78,79]

5.1.8 Operational meetings

The colposcopy team should hold operational meetings.

Operational meetings should be arranged at least every three months to discuss clinic policy, protocol problems, the findings of audit and peer review visits, and any areas where the clinic falls short of quality standards.

5.2 Reducing anxiety for women

5.2.1 Information and communication

Effective information and communication are crucial to reducing anxiety.[80]

Each woman should be offered verbal information and sent written information before and after cervical screening, and before colposcopy (95%):

- women must be sent an appropriately worded invitation, which must contain the name of a contact at the clinic, a telephone number for the clinic, and the clinic's times
- information concerning the visit to the clinic and the results of investigations should be communicated to the patient within four weeks of her attendance (best practice 90%) and all results must be communicated within eight weeks (minimum standard 100%)
- in addition to the national information leaflets, information leaflets tailored to the needs of the local population should be available at each clinic
- counselling must be available as an integral part of colposcopy
- results and management plans should be communicated to the GP or the referrer within four weeks of the patient's attendance at the clinic (best practice 90%)
- all results must be communicated to these parties within eight weeks (minimum standard 100%)

Evidence: there is compelling evidence[77,81,82,83,84,85,86] that many women suffer significant negative psychological effects from receiving an abnormal cervical cytology result and being called for further investigation. The psychological sequelae may discourage compliance with subsequent screening and follow up. The provision of accurate and clear information reduces anxiety and improves the patient experience.

5.2.2 Black and minority ethnic groups

Culturally appropriate information should be made available for members of minority ethnic groups. Good practice dictates that patients should have their history taken and be counselled with an independent interpreter present. Friends or family members should not undertake this role.

Evidence: coverage is low in many black and minority ethnic communities. There are significant differences in awareness about cervical cancer across different groups. Promoting informed choice and effective understanding of risk in a diverse community can help to improve understanding of and participation in cancer screening.[87]

5.2.3 Information given to women having outpatient treatment

Where a woman is considering outpatient treatment, providing relevant information can reduce the risk of harmful consequences.

Women should be advised:

- to avoid using tampons for four weeks following treatment
- to abstain from vaginal intercourse for four weeks following treatment
- to avoid swimming for two weeks following treatment
- that they may drive following loop excision or local treatment, unless advised otherwise by the examining colposcopist
- that they may consume alcohol in moderation after treatment
- that other normal activities, including light exercise, may continue
- that, although there are no known health grounds for avoiding travel following treatment, overseas medical attention for complications arising from the treatment may not be covered by insurance
- that there may be a temporary change in their menstrual pattern following loop excision
- that single conisation, cervical diathermy, and loop excision measuring less than 10mm in length/depth is not associated with any increase in the incidence of preterm labour and preterm pre-labour rupture of membrane
- that single conisation, cervical diathermy, and loop excision is not associated with any increased risk of infertility but may increase the risk of mid-trimester miscarriage

Evidence: menstrual bleeding following loop excision may be heavier (19% to 48%), more sustained, and more painful (15% to 41%).[88,89] Vaginal intercourse, vaginal douches, and tampon use should be avoided for four weeks after loop electrical excision procedure (LEEP) or cryotherapy.[90] Swimming should be avoided for two weeks following loop excision.[91] Driving is acceptable immediately after minor procedures involving local analgesia without sedation (eg dental block).[92] The main risk of driving after loop excision arises from the analgesia rather than the surgery; there is no need for patients to be driven home. They can return to work the next day,[93] although some may need another day or two to recover. There are no restrictions on normal activities, other than intercourse.[94] Evidence suggests that treatment of the cervix prior to childbearing may increase the risk of preterm delivery in young women, though this is controversial.[16,17,18,19,20,21,22,23] Meta-analyses of long-term observational data suggest that cone biopsy or radical diathermy significantly increases the risks of preterm delivery and perinatal mortality.[16] Loop excision is associated with preterm delivery, but not with increased perinatal mortality.[18] A recent case control study of women attending colposcopy, within the NHSCSP, found no increase in the risk of premature labour when the length/depth of the excised specimen was 10mm or less.[95] Loop excision does not appear to be a cause of infertility but may increase the risk of mid-trimester miscarriage.[96,97]

5.2.4 'See and treat' clinics

Clinics operating a 'see and treat' policy must ensure that women who are offered treatment at their first visit have been sent adequate and appropriate information in advance of their appointment (100%).

Evidence: anxiety is greater in women attending 'see and treat' clinics if they are not adequately informed of the potential for treatment at their first visit.[78,98,99]

5.2.5 History taking

Appropriate and sensitive enquiries regarding sexual history may be made, but only under the auspices of an ethically approved study, or if the patient presents with a specific indication.

Evidence: questions regarding sexual history may cause embarrassment, resentment and distress to some women. This may result in poor compliance if the woman feels she is being judged.[90,100]

5.2.6 Clinic facilities

The clinic's facilities must include:

- a private area with changing facilities
- toilet facilities
- a permanently sited specific room for colposcopy (100%)
- refreshment facilities
- separate waiting and recovery area

Evidence: good practice point.

5.2.7 Visitors to the clinic

Women should be able to have a friend or relative present if they wish. The patient's consent should be sought prior to colposcopy if anyone not essential for its performance is to be present (eg trainees, undergraduates, or visitors).

Evidence: women may have strong negative reactions to the intrusiveness of a gynaecological examination. Those attending for colposcopy are often particularly anxious. Being sensitive to these concerns helps to improve their experience of the service.[77,85]

5.3 Equipping the colposcopy clinic

The clinic environment should be welcoming and protect the patient's dignity. Patients should be given time to discuss their care both before and after the colposcopy examination and/or treatment.

The following equipment must be available in the colposcopy clinic:

- a permanent couch and colposcope
- suitable sterile instruments and/or sterilising facilities, compliant with local and national health and safety recommendations
- adequate and immediately accessible resuscitation equipment, and staff involved in the clinical care of patients who are familiar and trained in its use
- suitable IT equipment
- software to facilitate collection of data for the BSCCP minimum data set and for submission of the statutory quarterly KC65. Where possible, television monitoring facilities should be made available for patients who wish to watch the procedure

Additionally:

- if laser or diathermy equipment is in use, adequate safety guidelines should be in place, and all staff must be trained in the operation of this equipment. Clearly written and easily accessible emergency guidelines must also be available in each clinic. These must conform with local protocols.[101]
- in units offering an exclusively diagnostic service, there must be automatic referral to a unit where treatment is available if needed

Evidence: good practice point.

5.4 Adjunctive tests in colposcopy

The dynamic spectral imaging system (DySIS) is a digital video colposcope that also uses dynamic spectral imaging to evaluate the blanching effect of applying acetic acid to the epithelium (acetowhitening). It produces a quantitative measurement of the rate, extent and duration of the acetowhitening that is summarised in a graphical display, called a DySIS map. This can be overlaid on a colour image of the tissue to help the clinician determine the presence and grade of any lesion. DySIS can be used within the NHSCSP, as long as the standard colposcopic guidelines and process are followed.

DySIS should be seen as an adjunct to standard colposcopic indicators, and additional training is required to ensure that users understand the correct use and interpretation of a DySIS map. Further information is available in the NHSCSP equipment report 1201 October 2012.[102]

Evidence: NICE has evaluated the DySIS system (DG4) and have concluded that DySIS is suitable for use as an adjunctive technology in NHS colposcopy clinics.[103]

NICE continue to evaluate further colposcopy adjunctive therapies and have issued a MIB report on ZedScan. [104] NICE propose to review their guidance (DG4) in 2016.

5.5 Non-attenders

With respect to patient non-attendance:

- there must be written protocols for the management of non-attenders
- audit should include analysis of the records of defaulters to discern any patterns that could be addressed to reduce the default rate
- the default rate should be less than 15%

Evidence: 15% of women fail to attend for their appointment, although there are wide variations across England. Their reasons may include one or more of the following: fear of cancer or the procedure; forgetting the appointment; menstruation; work or childcare commitments; transport constraints; lengthy waiting times. Wasted appointments represent an administrative cost to departments, however, if they are sent reminders, most women will eventually be seen within a year of their first non-attendance. Strategies to improve patterns of attendance should be explored.[105,106,107,108,109,110] Patient-focused booking may reduce patient default and cancellation rates in the non-colposcopy setting[111,112,113], but its role in the colposcopy clinic is unclear.

5.6 Multidisciplinary working

5.6.1 Liaison with other units

Effective liaison between units is an essential component of high-quality integrated patient care:

- colposcopy clinics within GUM clinics must have established protocols for liaison with gynaecological services[114] (100%)
- colposcopy clinics within gynaecology services should have established protocols for liaison with GUM services (100%)
- colposcopy clinics should have established protocols for liaison with cytology laboratories and the call and re-call service (100%)
- multidisciplinary audit must be an integral part of the service (100%)
- there should be well-established clinical and computer links with cytological and histological services to support multidisciplinary working
- colposcopy clinics should have protocols describing failsafe mechanisms (100%)

- colposcopy clinics should have protocols describing the notification procedure for future community based cytological recall (100%)

5.6.2 The colposcopy multidisciplinary meeting

The primary purpose of the meeting is to plan the management of patients with discordant histology, cytology and colposcopic findings:

- all meetings must be attended by a minimum of one colposcopist and one person to present and discuss the histology and cytology. Histology and cytology attendance can be in person or via video link
- all histology must be reviewed and presented by a consultant histopathologist who undertakes the reporting of colposcopic histology
- Although an extended role for the biomedical scientists in the reporting of cervical histology is currently under development this is not yet complete. Further guidance will be issued.
- cytology must be reviewed prior to the meeting and may be reviewed and presented by an AP or consultant pathologist who reports cervical cytology routinely
- all colposcopists must attend at least half the meetings
- lead cytopathologists should attend some of the meetings
- meetings must be held at least six times/year though monthly is best practice

Cases which should be discussed:

- there should be a clear local protocol – this is not an exhaustive list
- all cases where high grade cytology has not been confirmed on colposcopy and/or histology
- borderline change in endocervical cells, HPV+ with no abnormality on colposcopy and/or histology
- any case where colposcopists wish to ask for an ‘off protocol’ HPV test
- all cases of invasive cervical cancer
- there must be facilities for colposcopy, histology and cytology to add to the list any case where they have concerns they wish to discuss
- the outcome must be recorded in the patient notes and fed back to the managing clinician
- outcomes should be recorded on the cytology and colposcopy computer system or other systems allowing access to cytology/histology in the future
- regular audit is recommended

This guidance supersedes that given in NHSCSP document No.10.

Evidence: good practice point.

5.7 Training and certification of colposcopists

5.7.1 Training requirements

All practising colposcopists must be able to demonstrate that they have received an adequate training. The evidence required depends on when an individual's training began:

- for those who began training after April 1998: BSCCP/RCOG Diploma in Colposcopy
- for those who began training before April 1998 but had not completed training by April 1998: BSCCP Completion of Training Certificate
- self-certification is no longer permissible

5.7.2 Training after April 1998

The joint BSCCP/RCOG training programme is currently the only recognised colposcopy training and certification programme for colposcopists who wish to practise within the NHSCSP and commenced training after April 1998.

The training can be undertaken as an Advanced Training Skills Module (ATSM) through the RCOG, but can also be taken via the BSCCP, since not all trainees will be affiliated with the RCOG (eg nurse colposcopists).[115]

5.7.3 Training content and assessment

Training involves supervised and unsupervised colposcopic assessments, as well completion of an electronic colposcopy logbook. Attendance at histopathological and cytopathological sessions is also required. The final assessment method used is Objective Structured Clinical Examination (OSCE). This is a quality-assured examination that has been validated.[116]

5.7.4 Maintenance of clinical skill and continued medical education (CME)

Colposcopists practising within the NHSCSP must see at least 50 new referrals per year arising from the NHS CS Programme. Possession of a current BSCCP certificate does not exempt a colposcopist from achieving this standard.

All colposcopists must attend at least one BSCCP-recognised colposcopy meeting every three years. The NHSCSP considers compliance with the BSCCP recertification process to be highly desirable. Continued practice should be quality assured, with continuing personal development and regular audit. Discussion of practice should be included in colposcopists' annual general appraisals.

5.8 Summary of standards

1. **95% of women** should be offered verbal information and be sent written information before and after cervical screening and before colposcopy.
2. Counselling must be available as an integral part of colposcopy.
3. Women must be sent an appropriately worded invitation with a contact name, telephone number, and clinic times **(100%)**.
4. Information concerning the visit and results of colposcopy should be communicated to the woman within four weeks of her attendance (**best practice 90%)**. All women must receive their results within eight weeks (**100%).**
5. Results and management plans should be communicated to the referring practitioner within four weeks of the woman's attendance at the clinic **(best practice 90%).** All referring practitioners must receive results and management plans within eight weeks **(100%)**. Colposcopy clinics should have protocols describing the notification procedure for future community based cytological recall (**100**%).
6. Clinics operating a 'see and treat' policy must ensure that women who are offered treatment at their first visit have been sent adequate and appropriate information in advance of their appointment (**100%**).
7. Colposcopy clinics must have toilet facilities and a private area with changing facilities **(100%)**. Refreshments must be available for women attending the clinic and waiting and recovery areas must be separate.
8. There must be a permanently sited, dedicated room for colposcopy **(100%)** with a permanent couch and colposcope.
9. Appropriate sterilising facilities must be available in accordance with local and national health and safety recommendations.
10. In units offering a diagnostic service only, there must be automatic referral to a unit where treatment is available if required.
11. All clinic staff must be familiar with all treatment methods used (**100%**).
12. If laser or diathermy equipment is in use, all staff must be trained in its operation. Adequate safety guidelines must be in place and emergency guidelines must be available in each clinic.
13. Adequate resuscitation equipment must be immediately available in each clinic, and staff involved in the clinical care of patients must be familiar with its use.
14. IT equipment and software must be available to facilitate collection of data for the BSCCP minimum data set and for the submission of the statutory quarterly KC65.
15. All clinics must have a named colposcopist with appropriate skills who leads the service with an appropriate job description. The colposcopy unit must also have a dedicated specialist team.
16. There must be at least two trained members of staff for each clinic. Nurse colposcopists must receive the same level of staff support.
17. There must be adequate dedicated clerical support for the clinic.
18. Written protocols must be in place for the management of non-attenders. The default rate should be less than **10%**.

19. Colposcopy clinics should have established protocols for liaison with cytology laboratories and the call/recall service (100%). Colposcopy clinics in GUM must have established protocols for liaison with gynaecology services **(100%).** Colposcopy clinics within gynaecology services should have established protocols for liaison with GUM services (**100**%).
20. Multidisciplinary audit must be an integral part of the service **(100%)** and established clinical and computer links with cytological and histological services must be in place to support this. The MDT should meet once each month **(best practice)** or at least once every two months **(minimum standard**). All colposcopists must attend at least 50% of MDT meetings to ensure the timely management of difficult cases and discordant results **(minimum standard**). Attendance at MDT meetings should be recorded **(minimum standard**). MDT decisions on each case must be recorded in patients' medical records **(minimum standard).** The meetings of each meeting, including the outcome of any discussion, should be recorded and a letter describing the recommendation for future care must be sent to the colposcopist responsible for the patient **(minimum standard)**.
21. All cases of cervical cancer must be reviewed by a gynaecological cancer centre MDT **(minimum standard)**.
22. All colposcopists in the team must be certificated through the BSCCP/RCOG scheme. They must undergo the recertification process every three years in order to maintain levels of expertise and ensure that individuals are completing a sufficient caseload.
23. All colposcopists practising within the NHSCSP must see at least 50 new referrals per year arising from the NHSCSP. Possession of a BSCCP certificate does not exempt a colposcopist from achieving this standard.
24. All colposcopists must attend at least one BSCCP registered colposcopy meeting every three years.

6. Diagnostic standards for colposcopy

6.1 Cytology results

The cytology result should be available to the colposcopist before the colposcopic examination begins.

Evidence: knowledge of the cytological result improves the identification of colposcopic images of high-grade CIN.[117] When combined with colposcopic findings, the cytology result improves the sensitivity of the colposcopic impression for high-grade CIN.[118,119]

6.2 Repetition of cervical cytology

Cervical cytology should **not** be repeated at the first colposcopy following a referral for cytological abnormality. Where an initial cytology sample is inadequate, the repeat cytology sample should be taken no less than three months after the date of the first sample. HPV testing should not be repeated in a colposcopy clinic except after discussion at the colposcopy MDM.

Evidence: both prospective and retrospective observational data suggest that management may be changed in up to 9% of referrals if a 'see and treat' approach is not used at first colposcopy.[120,121,122,123,124,125,126,127] Additional cytology may detect further high-grade lesions requiring treatment, however, if cytology is repeated at an interval of less than three months[128,129,130], the sensitivity of the repeat cytology for unspecified or high-grade CIN is lower than the sensitivity of screening.[128,129] This may be because a short interval between cytology samples does not allow time for the cervical epithelium to heal, or for small dysplastic lesions to recur. Repeat cytology may also adversely affect the quality of the subsequent colposcopy. A retrospective study of 6,595 new referrals to colposcopy found that 6.4% of high-grade referrals would not have needed treatment had cytology been repeated at the time of colposcopy; while 3.7% of low-grade referrals would have been managed differently, however, 14% of high-grade disease was missed in cytological samples taken at the first colposcopic visit following referral, rising to 18% where the referral cytology was high-grade.[131] The cervical epithelium needs time to regenerate after cytology, hence the need for a more than three month interval between cytology tests.[132]

6.3 Colposcopic examination

The following data should be recorded at the colposcopic examination:

- reason for referral (100%)
- grade of cytological abnormality (100%)

- whether the examination was adequate or inadequate - for the examination to be adequate the entire cervix must be seen (100%)
- the presence or absence of vaginal and/or endocervical extension
- the colposcopic features of any lesion
- the colposcopic impression of lesion grade
- the type of transformation zone, ie type 1,2 or 3
- the site of any colposcopically directed biopsies

The IFCPC nomenclature committee revised the criteria for colposcopic examination in 2011.[133]

6.4 Invasive disease

Care must be taken not to overlook invasive disease. An excisional form of biopsy is recommended (95%) in the following circumstances:

- when most of the ectocervix is replaced with high-grade abnormality
- when low-grade colposcopic change is associated with high-grade dyskaryosis (severe) or worse
- when a lesion extends into the endocervical canal, sufficient cervical tissue should be excised to remove the entire endocervical lesion

In the situations mentioned above, punch biopsies are not considered to be reliably informative. The colposcopist should be aware of the small risk of inappropriate or inadvertent destruction of invasive or glandular lesions. These are most often encountered in association with high-grade cytological or colposcopic change (CIN3).

There may be pressing reasons for delaying biopsy, for example pregnancy. Reasons for not performing a biopsy must be recorded (100%).

Evidence: one systematic review[134] (and several subsequent retrospective reviews[135,136]) investigated 120 of cases of invasion identified through cervical screening and colposcopic examination. 56% of microinvasive and 30% of invasive lesions are missed by colposcopy.[136] The retrospective reviews[135,136] suggest that approximately two-thirds of missed cancers are due to colposcopist error, while one-third are due to the limitations of technique. A small observational study found that the likelihood of a lesion's being cancer is related to its size and to the proportion of the ectocervical transformation zone involved with a high grade abnormality: women with microinvasive cervical carcinoma had CIN3 occupying most of the surface of the transformation zone, however, comparisons of lesion size were with historic controls an indicator of who had CIN3.[137] Common cytological and colposcopic findings in cases of missed disease included one or more of the following:

- high-grade cytological abnormality

- endocervical extension of lesions, even when the upper limit of the these was thought to be visible
- large, complex lesions with raised irregular surfaces
- underevaluation of lesions by colposcopically directed biopsy.[138,139,140]

Systematic review has shown that invasive disease is more frequent when the upper limit of the lesion cannot be visualised (61% of microinvasive, 71% of invasive disease) than CIN (14% of CIN). Atypical vessels are found in 44% of microinvasive cases, and 84% of invasive cases.[134,141]

6.5 Accuracy of colposcopic diagnosis

Where an adequate colposcopic examination has been conducted and the upper extent of the lesion and squamocolumnar junction visualised, the positive predictive value of a colposcopic diagnosis should be at least **65%** for a high-grade lesion (CIN2 or worse).

Evidence: colposcopy offers an accurate way to diagnose CIN and to differentiate high-grade lesions from low-grade abnormalities[142], particularly when it is employed to assess abnormal cytology, rather than as a primary screening method.[143] A systematic review demonstrated that the PPV of a colposcopic impression of CIN3 was 78%. In this study, PPV declined as severity of CIN decreased.[134]

A variety of factors influence the precision of colposcopic diagnosis. Specific colposcopic appearances, such as acetowhite epithelium, punctuation and mosaicism, and glandular cuffing, have been related to histological findings in few studies, but any statistical analysis is unreliable.[135]

Furthermore, punctuation and mosaicism are noted in benign circumstances.[135] Scoring systems have been published, and these can be helpful in ensuring reliable assessment of abnormal cervical cytology.[144] They are particularly useful in the early phases of training, when colposcopists must learn to differentiate between high- and low-grade lesions in order to avoid missing advanced disease and to reduce overtreatment of low-grade lesions (there is a greater agreement amongst colposcopists in discriminating between these types of abnormality than in distinguishing between low-grade disease and a normal cervix).

Although it has been noted that there is considerable subjectivity and inter-observer variability in the grading of CIN by expert pathologists, this variation is markedly reduced for high-grade lesions. The histologically-confirmed presence of invasive cancer and/or high-grade CIN are therefore usually accepted as reproducible end points for significant disease when assessing the accuracy of cervical screening, including the performance of colposcopic diagnosis (colposcopic impression). There is a positive correlation between lesion size and severity of CIN, and between lesion size and the accuracy of colposcopic diagnosis in women with proven high-grade CIN.[135]

6.6 Colposcopically directed punch biopsy

Unless an excisional treatment is planned, biopsy should be carried out when the cytology indicates high-grade dyskaryosis (moderate) or worse, and always when a recognisably atypical transformation zone is present (100%). Cases occurring in pregnancy are an exception.

Low-grade cytological abnormality (low-grade dyskaryosis or less) and a low-grade or negative colposcopic examination do not require colposcopic biopsy if there is no atypical transformation zone present.

In deciding on treatment (and especially if destructive methods are being considered) associated cytological and colposcopic findings are as important as the result of directed biopsy. [139,14,145]

Evidence: a retrospective study[146] showed that in women with low grade cytological abnormalities and a normal colposcopic examination, only 7.8% had CIN2 or CIN3 on loop excision. Colposcopically directed biopsy (CDB) can only be considered as a sampling of the lesion, by convention the most atypical area, and thus can only give a provisional histological diagnosis. Systematic review[134] of studies comparing CDB with reference histology from cones or hysterectomy specimens shows a lower positive predictive value (PPV) for CIN1 and CIN2 (16%, 32%) than for CIN3 (86%). PPV for microinvasion was 59% and for invasion 83%. Additional retrospective studies show that while CDB may correctly 'overestimate' the grade of lesion compared with reference histology when the lesion is small, CDB has been shown frequently to underestimate the severity of the lesion. High-grade CIN is underestimated in 4.3% to 57.1% of cases.[147,148,149,150] Cases of early invasive disease have been underevaluated as CIN3. Subjectivity in colposcopic opinion is also reflected in selection of site for biopsy.[151,152]

6.6.1 Adequacy of biopsies

Of all biopsies taken (directed and excisional) more than 90% should be suitable for histological interpretation.

If colposcopically directed biopsy is reported as inadequate for histological interpretation, it should be repeated if there is a residual colposcopic lesion (95%).

Evidence: good practice point

6.7 Summary of standards

1. At the colposcopy examination the following data must be recorded:

- reason for referral (100%)
- grade of cytological abnormality (100%)
- whether the examination was adequate or inadequate – for the examination to be adequate the entire cervix must be seen (100%)
- the presence or absence of vaginal and/or endocervical extension
- the colposcopic features of any lesion
- the colposcopic impression of lesion grade
- the type of transformation zone, ie type 1,2 or 3
- the site of any colposcopically directed biopsies

2. An excisional form of biopsy is recommended **(95%)**:

- when most of the ectocervix is replaced with high-grade abnormality
- when low-grade colposcopic change is associated with high-grade dyskaryosis (severe) or worse
- when a lesion extends into the canal – sufficient canal must be removed with endocervical extension of the abnormality

3. Reasons for not performing a biopsy must be recorded **(100%)**.

4. All women must have had a histological diagnosis established before destructive therapy (**100%)**.

5. Unless an excisional treatment is planned, biopsy should be carried out when cytology indicates moderate dyskaryosis or worse, and always when a recognisable atypical transformation zone is present **(100%).** Pregnancy is an exception.

6. Of all biopsies taken (directed and excisional) more than **90%** should be suitable for histological interpretation.

7. If colposcopically directed biopsy is reported as inadequate for histological interpretation, it should be repeated if there is a residual colposcopic lesion **(95%).**

8. For those with an adequate colposcopic examination and the entire squamo-columnar junction and entire lesion visualised, the predictive value of a colposcopic diagnosis of a high-grade lesion (CIN2 or worse) should be at least 65%.

7. Infections, cytology, and colposcopy

7.1 Infections, cytology and colposcopy

Cervical cytology and colposcopy can identify a number of infectious agents, but appearances are not pathognomonic for any condition. For example, some colposcopic and naked-eye appearances, such as the ulcers of herpes and syphilis, are easily mistaken for squamous carcinoma. The poor sensitivity, specificity, and positive and negative predictive values of both cytology and colposcopy for infectious agents mean that neither cervical cytology nor colposcopy should be used solely for the diagnosis of infections.

7.2 Testing for infections in colposcopy clinics

To use a colposcopy visit to screen for the most common sexually transmitted infection, *Chlamydia trachomatis,* is neither-cost effective nor indicated.[153,154,155] Similarly, evidence fails to support testing for gonorrhoea in asymptomatic women when a cytology sample is taken.[156]

Evidence: the incidence of *Chlamydia* is highest in sexually active women under 25 years of age, and the NHSCSP does not screen this age group. Opportunistic screening for infections may be considered for symptomatic women attending colposcopy clinics, upon patient request, or where high-risk behaviour has been determined.

7.3 Management of infections found on cytology

The presence of some organisms on cytology may lead to variations in a woman's clinical management. Specific drug therapies will not be detailed here; instead, the issues raised by specific infections noted on cytology reporting are considered.

The following genital tract infections[157] may be noted during microscopy of a conventional cervical smear, and results from liquid-based cytology samples have been shown to be equivalent:

- *Actinomyces*-like organisms (ALOs)
- *Trichomonas vaginalis*
- *Candida* species
- *Herpes Simplex* Virus (HSV)

7.3.1 *Actinomyces*-like organisms

Actinomyces-like organisms (ALOs) are usually associated with an IUD. If the woman is symptomless, then neither removal of the device nor antibiotic treatment is indicated. If the woman has symptoms, the IUD may need to be removed (after first determining that the patient has not had sexual intercourse during the preceding five days). If the IUD is removed, the device should be sent for culture testing, and the woman prescribed a course of appropriate antibiotics. A subsequent gynaecological referral may be necessary to ensure that symptoms and/or signs resolve.[158] Alternative contraception should be arranged in the interim, as appropriate.

Due to the poor sensitivity and specificity and low positive predictive value of cervical cytology for the detection of ALOs, the prognostic significance of ALOs detected via this method is minimal in the absence of concomitant symptoms.[158]

7.3.2 *Candida* species

Microscopy of a cytology sample is not sufficiently sensitive for a diagnosis of vaginal candidiasis to be made.[159]

The presence of spores indicates the reproductive activity of the organism, but such yeasts are common in symptomless women and in such cases treatment is not indicated. Even in symptomatic women, the presence of *Candida* does not necessarily indicate that *Candida* infection is the only cause of the complaint.

7.3.3 Bacterial vaginosis

Bacterial vaginosis is associated with the presence of ‘clue cells’ (squamous cells coated with a layer of coccal bacilli along the cell membrane) and a conspicuous absence of normal lactobacilli. LBC samples offers opportunities for accurate diagnosis, with a false positive rate of less than 1% when compared to wet mount and DNA probe technologies.[160] Therefore no further testing for bacterial vaginosis is needed before treatment.

7.3.4 *Chlamydia trachomatis*

The sensitivity (31%) for the detection of chlamydial infection by cytology is low. Therefore, diagnosis of this organism by this method cannot be relied upon.[161]

The fluid used for liquid-based cytology, however, preserves the DNA of *Chlamydia trachomatis*. Many commercial tests are available to test for *Chlamydia* in this specimen type. Although not part of the cervical screening programme this could form part of clinical investigation.

7.3.5 *Neisseria gonorrhoea*

The presence of intra-cytoplasmic diplococcii is not diagnostic as other organisms (including common and non-pathogenic species of *Neisseria*) are morphologically indistinguishable. Confirmatory testing before giving the woman this diagnosis is mandatory, however, liquid-based samples preserve *Neisseria gonorrhoea* DNA. Many commercial tests are available to test for *gonorrhoea* in this specimen type. Although not part of the cervical screening programme this could form part of clinical investigation.

7.3.6 Genital herpes

LBC samples may show features that are indicative of herpes simplex virus infection. The specificity of LBC samples is high for this organism.[162]

7.4 Communicating results with the woman

It should be recognised that the potential for harming a relationship and the requirement to notify a partner of the existence of certain infections mitigate against relying on screening samples for diagnosis of sexually transmissible agents. Highly accurate testing modalities exist and should be used where there is any suspicion of infection in women attending for cytology screening and/or colposcopy. Good liaison with local GUM services is beneficial along with appropriate protocols for referral and treatment when indicated.

8. Treatment of CIN

8.1 Surgical techniques

There is no obviously superior conservative surgical technique for treating and eradicating CIN, however, ablative techniques are only suitable when:

- the entire transformation zone is visualised (100%)
- there is no evidence of glandular abnormality (100%)
- there is no evidence of invasive disease (100%)
- there is no major discrepancy between cytology and histology.

Only in exceptional circumstances should ablative treatment be considered for women over 50 years of age.

Evidence: a Cochrane review [163] of 28 randomised controlled trials comparing seven surgical techniques: knife cone biopsy, laser conisation, large loop excision of the transformation zone (LLETZ), laser ablation, cryocautery, cold coagulation, and radical diathermy. One prospective randomised trial of excision versus destruction has indicated a lower rate of moderately dyskaryotic cervical cytology samples after excision.[164] Occasionally women under 25 years of age are seen with CIN3. Management of these unusual cases should be discussed with the local lead colposcopist, preferably with the assistance of the local colposcopy MDT.

Over 50% of CIN1 lesions will regress over 22 months.[165] Follow up of women with histologically confirmed CIN1 can either be by colposcopy or community based cytology. The follow up interval should not be less than 12 months. If the lesion persists for longer than 24 months the treatment should be discussed with the patient. Treatment of CIN1 is associated with a higher test of cure failure rate when compared to treatment of CIN2/3.[48,55,166]

8.2 Local destruction

All women must have an established histological diagnosis before undergoing destructive therapy (100%).

Evidence: accepted practice dictates that the decision to perform destructive treatments should be reached only after the available cytological, colposcopic, and directed-biopsy evidence is reviewed, and it can be established with a high degree of confidence that invasion is absent. Retrospective studies of invasive disease that has presented following destructive treatment indicate that failure to exclude invasive carcinoma prior to treatment is the most important aetiological factor.[167,168] Nevertheless, a number of large observational studies looking at local destructive therapies conducted in regional centres with rigorous colposcopic assessment

indicate that high success rates are achieved, and that the risk of inadvertent or inappropriate treatment of invasive and glandular lesions is low.[169,170,171,172]

8.3 Cryocautery

Cryocautery should only be used for low-grade CIN and a double freeze-thaw-freeze technique must be used (100%).

Evidence: the rate of clearance of CIN3 is poor.[173,174] The double freeze technique has a lower incidence of residual disease compared with a single freeze technique.[175,176]

8.4 Excision

8.4.1 Removal of specimen

When excision is used, at least 80% of cases should have the specimen removed as a single sample. Removing the transformation zone in multiple fragments can increase the difficulties encountered in histopathological assessment. Furthermore, if microinvasive disease is present, it may be impossible to allocate a sub-stage or define completeness of excision in fragmented excisional specimens.

Evidence: good practice point.

8.4.2 Histology report

The histology report should record the dimensions of the specimen and the status of the resection with regard to intraepithelial or invasive disease.

8.4.3 Depth of excision

The goal of excision is to remove all the abnormal epithelium.

Type I cervical transformation zone:

- for treating ectocervical lesions, excisional techniques should remove tissue to a depth/length of more than 7mm (95%), though the aim should be to remove <10mm in women of reproductive age

Type II cervical transformation zone:

- excisional techniques should remove tissue to depth/length of 10mm to 15mm, depending on the position of the squamocolumnar junction within the endocervical canal

Type III cervical transformation zone:

- excisional techniques should remove tissue to a depth/length of 15mm to 25mm

Evidence: histological assessment of the depth of crypt involvement by CIN3 has shown a mean depth of 1mm to 2mm with a maximum of 5.22mm and a mean +3 standard deviations (99.7%) of 3.80mm.[177,178] Incomplete excision, especially of the endocervical margin, is an important adverse factor for recurrence[179,180], however, in women under the age of 35, excisions >10mm in depth are not associated with improved recurrence rates. There is, however, an increased risk of preterm delivery after loop treatments >10mm in depth. In one study loop excisions greater than 12mm in depth are associated with a threefold increase in preterm delivery,[181] however in a recent nested case control study within the NHSCSP the absolute risk of premature delivery was 8% for excisions between 10mm and 14mm, rising to 18% for excisions over 20mm in depth/length.[95]

8.5 'See and Treat' policy

Treatment at first visit to colposcopy for a referral of borderline or low-grade dyskaryosis should not be offered.

Evidence: it is inappropriate to adopt 'see and treat' if the proportion of specimens that do not show evidence of CIN is high, since many women would receive unnecessary treatment. From a randomised controlled trial studying 1,983 women aged 20 to 59 years referred with borderline change or low-grade dyskaryosis, punch biopsy and selective treatment detected as many cases of CIN2+ over three years as immediate loop excision. 60% of loop excisions contained in the immediate treatment arm had no CIN.[182]

8.6 Repeat excision

8.6.1 CIN3 extending to margins

CIN3 extending to the lateral or deep margins of excision (or uncertain margin status) results in a higher incidence of recurrence but does not justify routine repeat excision provided:

- there is no evidence of glandular abnormality
- there is no evidence of invasive disease
- the woman is under 50 years of age

Evidence: CIN extending to the resection margins of a LLETZ has been shown to be a risk factor for recurrent CIN both in the short and long term. [183,184,185] This risk appears predominantly due to the presence of CIN at the endocervical margin.[186] Despite the increased incidence of recurrence, the majority of women in the above studies had no evidence of residual disease. The increased sensitivity offered by HR-HPV testing as part of test of cure

negates any differential follow policy based on incompleteness of excision.[166] All women after treatment for CIN should be discharged from colposcopy. The TOC sample should ideally be performed in the community but may be in a hospital based cytology clinic. This guidance also applies to cases where resection margins are positive.

8.6.2 Women over the age of 50

All women over the age of 50 years who have CIN3 at the lateral or deep margins and in whom satisfactory cytology, HR-HPV typing and colposcopy cannot be guaranteed must have a repeat excision performed to try to obtain clear margins (100%).

Evidence: in a series of 3,426 LLETZ procedures, women aged 50 or over with CIN at the margins of excision constituted a minority high-risk group. It was suggested these women be offered retreatment rather than surveillance.[186]

8.7 Local excision

8.7.1 Microinvasive squamous cancer FIGO stage Ia1

Microinvasive squamous cancer International Federation of Gynaecology and Obstetrics (FIGO) stage Ia1 can be managed by local excisional techniques if:

- the excision margins are free of both CIN and invasive disease
- the gynaecological cancer centre pathologist and MDT have reviewed the histology

If the invasive lesion is excised but CIN extends to the excision margin, then a repeat excision should be performed to confirm complete excision of the CIN and to exclude further invasive disease. This should be performed even in those cases where a hysterectomy is planned to exclude an occult invasive lesion requiring radical surgery.

Evidence: several studies[187,188] have suggested that FIGO stage Ia1 disease can be managed conservatively. Variation in histological diagnosis of microinvasive disease is well recognised and all cases should be reviewed by an independent pathologist with an interest in gynaecological oncology.

8.8 Anaesthesia

Treatment should be performed with adequate pain control and should include pre-treatment counselling. Treatment should be offered with local analgesia; where this is inappropriate, general anaesthesia should be offered. Reasons for treating under general anaesthesia should be recorded in the colposcopy record. The proportion of women managed as out-patients with local analgesia should be at least 80%.

8.9 Summary of standards

1. All women needing treatment must be informed that treatment will be required, and their consent (either written or verbal) must be recorded **(100%)**.

2. All women needing treatment must have had a colposcopic assessment **(100%)**.

3. All treatment must be recorded **(100%)**.

4. All treatment must take place in properly equipped and staffed clinics **(100%)**.

5. The proportion of women treated at the first visit who have evidence of CIN2, CIN3, or CGIN on histology must be more than **90%**.

6. The proportion of women having definitive treatment for high grade CIN within four weeks of the colposcopy clinic receiving a diagnostic biopsy report should be at least **90%**.

7. All women having definitive treatment for high grade CIN must be treated within eight weeks (**100**%). Pregnant women are excepted from this. The reason for any delay must be specified.

8. The proportion of treatment associated with primary haemorrhage that requires a haemostatic technique in addition to the treatment method applied must be less than **5%**.

9. The proportion of cases admitted as in patients because of treatment complications must be less than **2%.**

10. Ablative techniques are only suitable when:

- the entire transformation zone is visualised (100%)
- there is no evidence of glandular abnormality (100%)
- there is no evidence of invasive disease (100%)

11. Cryocautery should only be used for low-grade CIN and a double freeze thaw freeze technique must be used (**100%)**.

12. When excision is used at least **80%** of cases should have the specimen removed as a single sample.

13. For ectocervical lesions, excisional techniques should remove tissue to a depth more than 7mm (**95%**).

14. When excisional treatment is used for CIN associated type 1 and type 2 TZ lesion the depth/length of the reported specimen should be 15mm or less (**85%**).

15. Treatment at first visit for a referral of borderline or mild dyskaryosis should only be used in exceptional cases, and only when audit has identified that CIN2, CIN3, or CGIN is present in at least **90%** of the excised specimens.

16. All women over the age of 50 years who have CIN3 at the lateral or deep margins and in whom satisfactory cytology and colposcopy cannot be guaranteed must have a repeat excision performed to try to obtain clear margins (**100**%).

17. Women with adenocarcinoma in situ or CGIN can be managed by local excision for those wishing to retain fertility. Incomplete excision at the lateral or deep margins requires a further excisional procedure to obtain clear margins and exclude occult invasive disease (**95**%).

18. The proportion of women managed as outpatients with local analgesia should be at least **80%**.

9. Management of glandular abnormalities

9.1 Cervical glandular epithelial abnormalities

Cervical screening with cytology can predict the presence of cervical glandular intraepithelial abnormalities.

Evidence: observational studies of women with abnormal glandular cytology with histological correlation. The data indicate that pre-malignancy and malignancy account for a variable proportion of pathology; high-grade CIN, cervical adenocarcinoma, endometrial cancer, and high-grade glandular intraepithelial neoplasia are the pathological conditions most commonly diagnosed.[68,69,189,190] Abnormal glandular samples from liquid-based cytology yield a similar pattern of diagnoses as from conventional samples. There is no clear evidence favouring an increase in diagnostic accuracy of glandular lesions with liquid-based methods, although there is some data suggesting a higher specificity is achieved.[191,192] A study that compared the diagnostic performance and inter-observer agreement of LBC and conventional smears, blinded to histological outcome, demonstrated poor agreement in the diagnosis of cervical glandular lesions. This confirmed previous impressions that the accuracy of cytology for glandular lesions remains lower than that for squamous abnormalities.[192]

9.2 Reporting of glandular abnormalities on cytology

9.2.1 Written reports

Samples should be reported as '?glandular neoplasia of endocervical type' if they show cytological features suggestive of cervical glandular intraepithelial neoplasia (CGIN) or endocervical adenocarcinoma.

9.2.2 Colposcopic assessment

Colposcopic assessment is essential when '?glandular neoplasia of endocervical type' is observed on cytology (100%).

Evidence: there is a high prevalence of invasive adenocarcinoma, CGIN, and CIN in this population.[68,193] Villous fusion, acetowhite changes proximal to the squamocolumnar junction, and characteristic vascular and surface patterns for glandular lesions have been noted by some authors.[68,194] In practice, colposcopy lacks sensitivity for the diagnosis of glandular lesions.[195] For samples showing glandular neoplasia, the negative predictive value (12.5%) and sensitivity (9.8%) of colposcopy are poor.[196] Colposcopy demonstrates concomitant CIN in 50% of cases, provides an assessment of the anatomy of the cervix and vagina, and helps to determine the most appropriate method and extent of biopsy.

9.2.3 Further investigation of '?glandular neoplasia of endocervical type'

Women with samples reported as '?glandular neoplasia of endocervical type' on cytology should be referred for colposcopic investigation within two weeks to exclude significant cervical neoplasia.

Evidence: for high-grade glandular cytological abnormality, reports suggest variations in PPV of 17% to 96% for premalignant or malignant pathology.[68,69,189,190,196,197,198] Furthermore, the predictive value of abnormal glandular cytology is compromised by the occurrence of several benign conditions which mimic cervical glandular neoplasia cytologically [199], although it should be possible to identify endocervical brush artefact which can give rise to similar problems.[200] Other non-cervical/endometrial neoplastic lesions of the genital tract and intraperitoneal organs may also present in this way. The available data support a rigorous investigative protocol for this grade of abnormality.[68,189,190,196,198,201]

9.2.4 Borderline changes in endocervical cell samples

When borderline changes are reported in endocervical cells on a cytology sample, a reflex HR-HPV test is performed. Women who have borderline changes of either type and who test positive for HR-HPV must be referred for colposcopy. Women who are HR-HPV negative are returned to normal recall.

Women referred with borderline nuclear change in glandular cells and are positive for HR-HPV should undergo colposcopy, any appropriate cervical biopsy,

Evidence: for more tentative predictions of glandular neoplasia, the borderline classification is used, however, most available studies follow the Bethesda convention[202] (which differs from the UK system in respect of glandular samples) and report atypical glandular cells of unknown significance (AGUS). While the data are somewhat unreliable, high-grade squamous intraepithelial lesions are those most commonly diagnosed, in 27% to 37% of cases[200,203], however invasive lesions have also been noted to present in this way.[204] The variability in clinical outcomes in the UK may reflect uncertainty surrounding the diagnostic criteria for this category of cytology. The limited available UK data indicate that a borderline classification of abnormal glandular cells is associated with a low, but significant, increase in the incidence of pathology, with high-grade CIN being detected in 10% to 33% of cases, and invasive disease in 1.8% to 22% of cases. Intraepithelial glandular lesions are detected in less than 10% of cases.[68,193,205,206] The above guideline conforms with the suggestions of a joint college working party which did not suggest a need for radical excision of the endocervix.[207] One study showed that when directed biopsy was compared with loop or cone biopsy, no significant advantage in diagnostic accuracy was obtained with larger biopsies.

9.2.5 Glandular neoplasia (non-cervical)

Patients should be referred to gynaecology for further investigation. They should be seen urgently, within two weeks of referral.

Evidence: normal endometrial cells in the cervical cytology of asymptomatic postmenopausal women have been reported with a low prevalence of (pre)malignant uterine disease.[208]

Diagnosis of atypical endometrial cells is clinically significant, with more than one-third of women with histological follow up having significant uterine disease. In postmenopausal women, the majority of lesions (80%) are endometrial in origin: 13% to 18% of these are endometrial carcinoma; 6% to 7% of cases are high-grade dyskaryosis and squamous carcinoma.[209,210] Asymptomatic endometrial carcinoma has been detected through the screening process, particularly following abnormal glandular cytology.[68,193]

9.2.6 Colposcopically directed/punch biopsy

Colposcopic punch biopsy is of low sensitivity for diagnosis of intraepithelial glandular lesions.[211,212,213,214] Furthermore, it has no role in precise diagnosis as it cannot exclude the presence of invasive disease.[196,197] Expert opinion indicates that a reliable diagnosis of high-grade CGIN and distinction from invasive adenocarcinoma can be achieved only in the histopathology laboratory, and an excisional biopsy including the endocervical canal is required for this purpose.

9.2.7 Endometrial biopsy

Where a woman's cervical cytology sample indicates '?glandular neoplasia of endometrial type', with or without irregular vaginal bleeding and regardless of menopausal status, she should be seen urgently for further investigations, within two weeks of referral. She should be referred for gynaecological assessment, but not to colposcopy. Repeat cervical cytology is not recommended. Although it is accepted that cervical assessment may be needed in such cases, the majority of women do not have cervical disease and should have an endometrial assessment in the first instance. For the management of women of different ages with normal endometrial cells in their sample, see section 4.13.

Evidence: good practice point.

9.2.8 Endocervical curettage in the assessment of '?glandular neoplasia of endometrial type'

There is no clear role for endocervical curettage in the assessment of '?glandular neoplasia of endometrial type'.

Evidence: endocervical curettage (ECC) is recommended by some for the assessment of atypical glandular cytology, however, when used prior to cone biopsy, it has low sensitivity for the diagnosis of CGIN, with false negative rates varying between 59% to 78%.[213,214,215] It was not possible to identify invasive disease on endocervical curettage and in this respect it is equivalent to punch biopsy. A theoretical objection to endocervical curettage prior to conisation is that it has the potential to impair histological assessment (Professional consensus).[213] The role of ECC after conisation is uncertain. In some reports, ECC performed after a cone biopsy failed to predict the presence of residual disease in 58% to 67% cases[215,216], however, one small study showed that ECC at the time of cone biopsy was a better predictor of residual disease than margin status.[217]

9.3 Clinical management of cervical glandular neoplasia

9.3.1 Management of cytology reported as '?glandular neoplasia of endometrial type'

Expert opinion supports a primary excisional procedure for initial management of all cases of high-grade atypical glandular cytology, with further management decisions based on a thorough histological assessment, including margin status. For women with suspected CGIN or early invasive adenocarcinoma, the extent of the cervical excision can be individualised. In younger women and/or women who wish to conserve their fertility who have a colposcopically visible squamocolumnar junction (SCJ), a cylindrically-shaped cervical excisional biopsy, including the whole transformation zone (TZ) and at least 1cm of endocervix above the SCJ is appropriate. In older women, or where the SCJ is not visible at colposcopy, a cylindrical biopsy should be taken that includes all of the visible TZ and 20mm to 25mm of the endocervical canal. Expert histopathological opinion favours techniques that either avoid or minimise thermal artefact to improve assessment of the excision margins. In women with high-grade atypical glandular cytology , where cervical pathology has been excluded, an endometrial biopsy, +/- pelvic imaging should be considered.

Evidence: good practice point.

9.3.2 Conservative management of confirmed HG-CGIN

High-grade cervical glandular intraepithelial neoplasia (HG-CGIN) often occurs in young women. Conservative management is recommended for those wishing to retain fertility, if the margins of the excisional specimen are negative and invasion is excluded. Women who are to be managed conservatively following cone biopsy should be counselled that the expected programme of management appears safe if careful follow up is carried out (see below).

Evidence: retrospective and prospective clinical studies[195,211,212,216,219,220,221] and histomorphometric studies[222,223] support the use of cone biopsy for the management of CGIN provided the conditions outlined above are met. Despite its origin in columnar cells, CGIN lesions are found in the TZ in 85% of cases.[220,222] TZ involvement is usually accompanied by

endocervical columnar disease. Deep clefts up to 5mm from the margin of the canal may be involved with disease.[219] While, theoretically, any site within the endocervix may be affected, multifocal disease is found in only 13% to 17% of cases; the lesion is usually unicentric, contiguous with the SCJ, and extends up the canal for a variable distance. A similar distribution of early invasive adenocarcinoma has been described. [223] 95% of CGIN extends within 25mm of the anatomical external os.[219] Further data shows a relationship between age and proximal linear extent of disease, suggesting that more limited excision of the endocervix, ie 1cm above the SCJ, may be reasonable in women aged less than 36 years. Such an approach would also allow accurate diagnosis of early invasive adenocarcinoma.[223] Glandular disease tends to be more extensive in older women. Moreover, it is well established that the SCJ retreats into the canal with increasing age so that older women require deeper excisions. Colposcopic examination may help to individualise the extent of the excisional specimen needed.

9.3.3 Management of incompletely excised CGIN

When advising expected management for CGIN, the clinician should be satisfied that the specimen submitted has been thoroughly sampled in the laboratory and that the margins of the specimen are free of disease. If the margins of an initial, conservative excision are not free, it is reasonable to offer a further attempt at conservative excision in order to confidently exclude invasion and obtain negative margins.

The colposcopy or gynaecological cancer MDT should help to guide further management.

Evidence: a meta-analysis of all adenocarcinoma in situ cases managed by conisation demonstrated a 5% to 6% risk of invasive disease associated with positive excisional margins.[224] In those conservatively managed cases with negative margins, the risk of subsequent invasive disease was 0.35% and the risk of recurrent CGIN was 2.6%. In practice, a higher proportion of women will require further surgical investigation for abnormalities detected during follow up, which is not surprising given that half of these women also have HG-CGIN. In those who were managed conservatively with positive margins, 19.4% developed recurrent in situ disease and 6% were diagnosed with invasive disease.

9.3.4 Follow-up of conservatively treated CGIN

Women who undergo excision for CGIN are at risk of recurrence. If the CGIN has been completely excised, at the time of first excision or subsequent re-excision, a test of cure (TOC) sample should be taken six months after treatment. If negative for cytology (endocervical cells must be present) and negative for HR-HPV a second TOC sample is taken 12 months later (ie 18 months after treatment) – if this is also negative for cytology and HR-HPV the woman can be discharged to recall in three years. Further recall will depend on the result of this test and the age of woman. These samples can be performed in the community. If either cytology or HR-HPV, at six or 18 months after treatment, is positive the woman should be referred to colposcopy.

If the woman fails TOC at six months only because of a positive HR-HPV test and no abnormality is detected at colposcopic examination the woman should have a second TOC sample 12 months later, if this sample is negative for cytology and HR-HPV the woman can be discharged to recall in three years. Further recall will depend on the result of this test and the age of woman. If a positive cytology result is reported in either of the six or 18 months 'TOC' samples the woman must be referred to colposcopy and managed appropriately. If no colposcopic abnormality is present and re-excision is not appropriate the women should revert to ten years of cytology follow up. Women who have incompletely excised CGIN and have declined re-excision should be followed up in the colposcopy clinic. Cytology should be performed six months after treatment and if negative repeated six months later (ie at 12 months after treatment) and then annually for the subsequent nine years. Complex CGIN cases will benefit from discussion at the colposcopy MDT.

Although robust data is lacking the increased sensitivity of HR-HPV testing permits the introduction of TOC for women with completely excised GCIN.

Evidence: Such samples can detect the presence of residual glandular lesions. There are recognised difficulties in assessing atypical glandular cells in samples after cone biopsy for CGIN. Lower segment sampling has been misinterpreted as glandular abnormality, leading to further surgical intervention.[225] The increased awareness of the possibility of glandular neoplasia introduces bias into the diagnosis with increased risks of false positive reporting as a result of benign mimics.[226] Although evidence is lacking, colposcopy may be indicated because of the need to monitor the possible recurrence of CGIN, CIN, and invasion, however, the need for some form of heightened surveillance and easy access to cytologists seems clear.

9.4 Hysterectomy for cervical glandular neoplasia

Simple hysterectomy might be considered if:

- fertility is not required[213]
- there are positive margins after an adequate excisional procedure
- treatment by cone biopsy is followed by further high grade cytological abnormality
- the patient is unwilling to undergo conservative management
- adequate cytological follow up has not been possible, eg because of cervical stenosis
- the patient has other clinical indications for the procedure
- invasive disease has been confidently excluded. (See section 8.7.1.)

9.5 Cervical screening for women exposed in utero to diethylstilbestrol

Women exposed in utero to diethylstilbestrol (DES) should have an initial colposcopic examination. In the absence of an abnormality at the first examination, only routine cervical

screening is required. For women whose initial examination shows an abnormality or stigmata of DES exposure, annual colposcopic examination of the vagina and cervix is required, possibly for life, in specialist centres. Management should be considered on an individual basis by the woman concerned and the colposcopist.

Evidence: epidemiological evidence has shown that women exposed to DES are at increased risk of clear cell carcinoma of the vagina. They appear not to be at high risk of developing other cancers. A review of 4,536 women exposed to DES revealed a twofold increased risk of developing high- grade CIN but no increase in the incidence of cervical cancer,[227] however the increased detection of CIN may have been a result of intensive follow up.

9.6 Summary of standards

1. Reporting of any ?glandular neoplasia sample must be supplemented with a written descriptive report describing where possible the site of origin of the glandular neoplasia (**100**%).

2. Colposcopic assessment is essential if a glandular abnormality is reported on cytology **(100%)**.

3. Women with ?glandular neoplasia of endometrial type in their sample must be seen urgently by a gynaecologist within two weeks of referral, irrespective of whether they have irregular vaginal bleeding and regardless of menopausal status.

10. Follow-up of women attending for colposcopy with CIN and early stage cervical cancer

10.1 Treated women

All women remain at risk following treatment and must be followed up (**100**%).

Treated women are between two and five times more likely than the general population to experience cervical cancer.[73,228] Much of this increased risk may result from poor compliance with long-term follow up; several case series demonstrate that more than 50% of cancers develop in women who are lost to follow up. Thorough compliance should be encouraged.

Evidence: several retrospective studies[184,187,229,230,231,232,233,234] of residual disease rates after LLETZ or knife cone biopsy have demonstrated that negative excision margins are associated with lower risk of residual disease and positive excision margins are associated with higher risk of residual disease. Studies have demonstrated that disease at the endocervical resection margin is associated with increased risk of residual disease compared with involved ectocervical margins.[233,235,236,237] Women aged 50 or more are particularly at risk of persistent/recurrent disease.[186,236]

10.2 Duration and frequency of follow-up after treatment for CIN under the HPV 'test of cure' protocol

Women who have been treated for CIN1, CIN2, or CIN3 should be invited six months after treatment for ‘test of cure’ repeat cytology in the community. Patient compliance with follow-up protocols should be encouraged.[238]

- women with a sample that has been reported as negative, or as showing borderline changes or low-grade dyskaryosis, and whose HR-HPV test is negative should be recalled in three years, whatever their age. Where the three-year test is negative, women over 50 can return to five-yearly routine recall
- women with a sample that has been reported as negative, or as showing borderline changes or low-grade dyskaryosis, and whose HR-HPV report is positive should be referred to colposcopy
- women with a sample that has been reported as showing high-grade dyskaryosis should be referred for colposcopy. No HR-HPV test is required
- women with a sample that has been reported as negative, or as showing borderline changes or low-grade dyskaryosis, and whose HR-HPV test result is unavailable should undergo repeat cytology at three months

- women who reach 65 must still complete the protocol and otherwise comply with national guidance
- women in annual follow up after treatment for CIN are eligible for the HPV test of cure at their next screening test unless that test is carried out at colposcopy

Evidence: women who have been treated for CIN are between two and five times more likely than the general population to develop cervical cancer.[73,228] Much of this increased risk may result from poor compliance with long term follow-up: several case series demonstrate that over 50% of cancers develop in women who are lost to follow-up.[239]

The test of cure study showed that, if both cytology and HPV testing are negative at six months, the risk of CIN2+ over the next two years is less than 0.5%.[240]

The results from the test of cure study were confirmed by data from the subsequent five year period, which showed that combining HR-HPV testing with cytology six months after treatment detects almost all subsequent cases of CIN. The rate of high-grade disease in the 917 women who completed follow-up at five years was found to be very low, while the cumulative incidence of CIN2+ in the same group was 1.72% among women who had negative cytology and who were also found to be HR-HPV negative at six months.[241]

A meta-analysis of 11 studies relating to follow-up after treatment of CIN found a sensitivity of 96% to detect treatment failure and a specificity of 81%.[242] More recently, a long-term multi-cohort study using three research projects from the Netherlands has investigated the risk of recurrent CIN after successful treatment. Among women with three consecutive cervical samples reported as negative at six, 12, and 24 months, the risk of CIN2 or higher was 2.9% (95% CI 1·2 to 7·1) within five years and 5.2% (2.1 to 12.4) within ten years. When cytology was combined with HR-HPV testing, however, the five-year risk of CIN2 or higher fell to 1.0% (95% CI 0.2 to 4.6) and the ten-year risk to 3.6% (1.1 to 10.7).[243]

Returning women to routine recall after six months prevents the need for annual cytology tests over the subsequent ten years (resulting in 350,000 fewer cytology tests per year in England[2]) and reduces anxiety for the women involved.

As the action on a positive TOC is referral to colposcopy, TOC is not offered to women still at colposcopy.

10.3 Cervical samples for follow-up cytology

Only those brush devices that have been approved by cervical screening programmes, such as the Cervex-Brush or EndoCervex Brush, should be used for liquid-based samples. Sample takers should be aware that:

- after surgical treatment, particularly excisional treatment, the squamocolumnar junction can retract into the cervical canal – care should be taken to sample the endocervical canal
- after treatment for CGIN, follow up samples must contain endocervical cells – paired samples should be taken and supplied in the same pot

10.4 Management for women following treatment for early stage cervical cancer

The treatment of early invasive cervical cancer (FIGO stage Ia1, Ia2, Ib1 and IIa1) lies outside the responsibility of the NHSCSP, however, the following guidance is provided for the sake of completeness.

10.4.1 Follow up of stage Ia1

If conservative treatment for cervical cancer has been performed, leaving a residual cervix, cytological follow up is recommended. Cervical cytology should be taken six and 12 months after treatment, followed by annual cytology for the next nine years before return to routine recall to 65 years. The NHSCSP will continue to provide recall arrangements.

The TOC utility of HPV testing has not been applied to cases of stage Ia1 and Ia2 cervical cancer. Until such evidence becomes available the current standard of annual cytology should remain.

10.4.2 Follow up of stage Ia2/Ib1

If conservative management for Ia2/Ib1 disease was by simple or radical trachelectomy, cytological follow up is determined by the management policy of the gynaecological oncologist.

If the woman has undergone hysterectomy for early stage cervical cancer, follow-up will as per the local cancer network guidelines. Women who receive pelvic radiotherapy either as primary or adjuvant treatment will be followed up according to the local cancer network guidelines.

10.5 Follow-up after a hysterectomy

Women who have had a hysterectomy with CIN present are potentially at risk of developing vaginal intraepithelial neoplasia (VaIN) and invasive vaginal disease. There is no clear evidence that colposcopy increases the detection of disease on follow-up.

Expert consensus opinion recommends that:

- for women on routine recall and with no CIN in their hysterectomy specimen, no further vaginal vault cytology is required

- women not on routine recall, and with no CIN in their hysterectomy specimen, should have vaginal vault cytology at six months following their hysterectomy and then ceased if the cytology is negative
- women who undergo hysterectomy and have completely excised CIN should have vaginal vault cytology at six and 18 months following their hysterectomy
- for women who undergo hysterectomy and have incompletely excised CIN (or uncertain excision), follow up should be as if their cervix remained in situ – CIN 1: vault cytology at six, 12 and 24 months – CIN 2/3: vault cytology at six and 12 months, followed by nine annual vault cytology samples – follow up for incompletely excised CIN continues to 65 years or until ten years after surgery (whichever is later)
- responsibility for implementing these follow up policies will rest with the treating gynaecologist and will be informed by the local lead colposcopist
- any gynaecologist discharging a patient who requires further vault cytology should ensure that the GP receives specific written guidance for follow up
- the clinician in charge (gynaecologist or GP) will be responsible for failsafe mechanisms for this small group of women
- women who undergo subtotal hysterectomy will still have their cervix in situ, and so must remain within the NHSCSP
- women who have radical trachelectomy, as part of conservative management of cervical cancer, should remain under the care and guidance of their treating gynaecologist or gynaecological oncologist. Follow up is recommended with colposcopy and cytology; owing to the limited information on outcome, however, all cases should be subject to local audit. As these women have cancer they are under the individual care of a gynaecologist and are no longer within the NHSCSP
- the role of HPV testing in the post-hysterectomy scenario has not been addressed in any trials. Given that women who have had a hysterectomy are a small proportion of the total population at risk, it seems unlikely that guidance will be based on clinical trials in the near future. While logic suggests that HPV testing would be informative in this group, cytology should continue to be performed. HPV testing in parallel is recommended as this may facilitate the development of guidance for the management of these women

Evidence: the incidence of VaIN following hysterectomy diagnosed with CIN is in the order of 1% in a series of 341 women with no subsequent cases of invasive disease.[24] In a similar series of 177 women, 4% developed VaIN with 0.6% developing subsequent invasive disease.[245] A meta-analysis of long-term results suggests that while recurrent intraepithelial disease is less common after hysterectomy for CIN than after local treatments of the cervix (522 vs. 1,587 per 100,000 woman-years), the risk of invasive recurrence is similar in both groups (57 vs. 67 per 100,000 woman-years).[239]

It is accepted that, even after hysterectomy, there is a risk of developing cancer similar to that after conisation or local destruction. It is not clear whether this is due to incomplete treatment or recurrent disease, although the latter would seem unlikely if the whole cervical transformation zone (along with the cervix) has been removed. Although supporting evidence is lacking, professional consensus suggests that if there is complete excision with no transformation zone remaining and two follow up cytology tests confirm no dyskaryosis, then the risk of developing cancer must be very small indeed and does not justify surveillance beyond the suggested 18 months.

10.6 Follow-up of untreated women

10.6.1 Women referred with high-grade dyskaryosis (moderate or severe)

Women referred with high-grade dyskaryosis (moderate or severe) on their test result are at significant risk of CIN two or three even in the presence of normal colposcopy. Biopsy should be undertaken in more than 95% of women with high-grade dyskaryosis (moderate or severe) on their test result. If treatment is not undertaken, close surveillance with colposcopy and cytology every six months is advised. If at follow up a high grade cytological abnormality persists, excisional treatment is recommended (90%).

Women referred with high-grade dyskaryosis on their test result who have a colposcopically low grade lesion, whose colposcopy is satisfactory and who are not treated should have multiple biopsies (90%). If CIN 1 or less is confirmed, colposcopic and cytological follow up at six months is advised. Cases with unexplained high-grade dyskaryosis should be discussed at multidisciplinary meetings.

Evidence: the overall specificity for distinguishing normal from abnormal tissue at colposcopy in a meta-analysis was only 48%.[246] The specificity of high grade cytology is over 90% in several studies.[247,248] This evidence suggests that high grade cytological abnormalities have a high likelihood of being associated with CIN 2 or CIN 3. Follow up studies[249,250] also support the relatively high likelihood of CIN 2 or CIN 3 in this group. Therefore the presence of persistent high grade abnormalities, even in the face of normal colposcopy, warrants treatment.

The PPV of colposcopy for distinguishing low grade from high grade lesions is only 57%.[246] As the specificity of high grade cytology is over 90%, the likelihood of an underlying high grade lesion in this situation is extremely high. If treatment is not undertaken as a result of colposcopic diagnosis of a low grade lesion, histological assessment is recommended by way of multiple directed biopsies.[248,251] If there is high grade cytology at follow up, treatment is recommended.

10.6.2 Women referred as part of HR-HPV triage

Women referred with low-grade dyskaryosis or less and HR-HPV positive that have a satisfactory and normal colposcopic examination are at low risk of developing cervical cancer. These women should be returned to community-based routine recall.

There is no new evidence, within the NHSCSP, to suggest that a colposcopically directed punch biopsy from a normal transformation zone is of any benefit following a low grade referral.

Women referred with a result of low-grade dyskaryosis or less and HPV positive that have a colposcopically low grade lesion may be followed up at 12 months in the colposcopy clinic or the community. Colposcopic biopsy at initial assessment is not essential to confirm or exclude low grade CIN. If the lesion has not resolved within two years of referral to colposcopy, at least a biopsy is warranted (more than 90%). In practice, many women are offered treatment at this point as persistent surveillance risks default.

Evidence: three studies [249,250,252] indicate that the risk of significant disease is extremely small when low grade cytology (mild dyskaryosis or less) is associated with normal colposcopy. The incidence of high grade CIN in women discharged to routine recall after a negative colposcopic examination is low [48]. The risk does not warrant intensive surveillance with its attendant costs and anxieties. In each of these studies, follow up cytology identified women with significant disease and this should form the main part of follow up.

Approximately 50% of women with a low grade cytological abnormality who are not treated at first visit will eventually revert to normal cytology and colposcopy over 24 months.[252] Prospective randomised data suggest that such a policy does not alter the number of women with high grade lesions who are treated but does reduce the number of low grade lesions treated.[201] The TOMBOLA study confirmed that the immediate treatment of women with low grade cytology results in over treatment compared with a policy of colposcopy with directed biopsy,[182] however more than one-fifth of women default from follow up. Therefore, the decision to follow up rather than treat in the presence of an apparent low grade lesion must incorporate analysis of the likelihood of default. The ongoing management decisions for this group will often be influenced by the woman's choice.

10.6.3 Management of inadequate cytology

Where cytology taken immediately prior to colposcopy remains inadequate, if the colposcopy is satisfactory and normal the patient should be invited for routine recall.

10.7 Summary of standards

1. All women remain at risk following treatment and should be followed up **(100%).** Follow up should start six months after treatment **(90%)** and should follow the test of cure protocol.

2. The proportion of women with no dyskaryosis six months after treatment should exceed **90%.**

3. The proportion of histological treatment failures should not exceed **5%** within 12 months of treatment.

4. Biopsy should be undertaken on **>95%** of women with high-grade dyskaryosis (moderate or severe).

5. If a high-grade cytological abnormality persists, excisional treatment is recommended **(90%)**.

6. Women referred with moderate dyskaryosis or worse who have a satisfactory colposcopy examination which finds a colposcopically low-grade lesion and who are not treated should have multiple biopsies **(90%)**.

11. Pregnancy, contraception, menopause, hysterectomy

11.1 Pregnant women

11.1.1 Cervical screening during pregnancy

- if a woman has been called for routine screening and she is pregnant, the test should be deferred
- a woman referred with abnormal cytology should undergo colposcopy in late first or early second trimester unless there is a clinical contraindication, however, for low-grade changes triaged to colposcopy on the basis of a positive HPV test, the woman's assessment may be delayed until after delivery
- if a previous colposcopy was abnormal and in the interim the woman becomes pregnant, then the colposcopy should not be delayed
- if a pregnant woman requires colposcopy or cytology after treatment (or follow up of untreated CIN1), her assessment may be delayed until after delivery. Unless there is an obstetric contraindication, however, assessment should not be delayed if the first appointment for follow-up cytology or colposcopy is due following treatment for CGIN. The 'test of cure' appointment should not be delayed after treatment for CIN2 or CIN3 with involved or uncertain margin status

The colposcopist may wish to perform colposcopy only at a follow-up appointment scheduled during pregnancy.

If repeat cytology is due, and the woman has missed or defaulted her appointment prior to pregnancy, cytology or colposcopy during pregnancy can be considered.

11.1.2 Colposcopy during pregnancy

A woman who meets the criteria for colposcopy should be examined in the colposcopy clinic even if she is pregnant. The primary aim of colposcopic examination of a pregnant woman is to exclude invasive disease and to defer biopsy or treatment until the woman has delivered. Women seen in early pregnancy may require a further assessment in the late second trimester at the clinician's discretion.

Evidence: the safety of delaying treatment of pregnant women has been demonstrated in a number of cohort and retrospective uncontrolled studies.[253,254,255] The incidence of invasive cervical cancer in pregnancy is low, and pregnancy itself does not have an adverse effect on the prognosis.[256] The rate of cervical cancer associated with pregnancy has declined in

countries with population-based cervical screening, with data from Sweden suggesting a reduction from 1.4% (1944 to 1957) to 0.9% (1990 to 2004).[257] Pregnant women with borderline nuclear changes or low-grade dyskaryosis rarely have high grade changes at colposcopy that require biopsy during pregnancy.[258,259]

11.1.3 Colposcopy follow up after pregnancy

If colposcopy has been performed during pregnancy, post-partum assessment of women with an abnormal cytology or biopsy-proven CIN is essential **(100%)**. Excision biopsy in pregnancy cannot be considered therapeutic and these women should be seen for post-partum colposcopy. A system must be in place to ensure women are given an appointment after delivery.

Evidence: regression rates for pre-invasive cervical disease during pregnancy and following delivery are low from retrospective uncontrolled studies and regression is not related to mode of delivery.[260,261] A retrospective study of pregnant women treated by cone biopsy for high-grade CIN and microinvasion reported high rates of disease persistence.[262]

11.1.4 Colposcopic evaluation of the pregnant woman

Colposcopic evaluation of the pregnant woman requires a high degree of skill:

- if CIN1 or less is suspected, repeat the examination three months following delivery
- if CIN2 or CIN3 is suspected, repeat colposcopy at the end of the second trimester. If the pregnancy has already advanced beyond that point, repeat three months following delivery
- if invasive disease is suspected clinically or colposcopically, a biopsy adequate to make the diagnosis is essential **(100%)**. Cone, wedge, and diathermy loop biopsies are all associated with a risk of haemorrhage and such biopsies should be taken only where appropriate facilities to deal with haemorrhage are available. Punch biopsy suggesting CIN only cannot reliably exclude invasion

Evidence: case series of biopsies taken by diathermy loop in pregnancy have shown risk of haemorrhage is in the order of 25%.[263] Case series of women with low-grade disease confirm the safety of deferring further follow-up until postpartum period.[264,265]

11.2 Use of contraceptives

11.2.1 Women with abnormal cervical screening results

Women with abnormal cervical screening results should not be advised to change from the oral contraceptive pill (OCP) if it is a successful method of contraception for them. An abnormal result should not influence the choice of contraception.

Evidence: meta-analysis indicates a small increase in the relative risk of CIN after compensating for HPV infection with long term use of the OCP.[266,267,268,269,270] The increase in cumulative risk is less marked in developed countries, however we do not have evidence that stopping OCP will alter the natural history of the disease. A large prospective UK cohort study and a review of cohort and case-control studies confirms a significant association between past or present users of OCP and cervical cancer and mortality but with very wide confidence intervals.[271] A systematic review found no significant effect for studies controlled for HPV status for up to ten years of use.[272]

11.2.2 Women with an IUD

Women with an IUD should be given clear information on the clinic's management policy regarding whether her IUD will be removed or not. She will need to know if she has to use alternative methods of contraception and if she has to schedule her treatment to coincide with the first half of her cycle. It is not necessary to remove an IUD to perform local treatment.

Evidence: good practice point

11.2.3 The use of condoms

Condom use may promote HPV clearance and CIN1 regression in conservative management, but this depends on their consistent use for at least three months.

Evidence: a small randomized trial showed higher rates of HPV clearance and CIN1 regression at two years of follow-up in women who used condoms consistently for at least three months[273], however, a meta-analysis found any effect to be inconsistent.[274]

11.3 Menopause and use of HRT

11.3.1 Post-menopausal women

The incidence of abnormal cytology and HPV positivity is low in post-menopausal women with previous normal results but HPV triage has a higher positive predictive value for high-grade CIN in older women. The use of systemic HRT is not known to alter the risk of cervical disease. Colposcopic examination and adequacy can be improved by the use of topical HRT.

Evidence: one randomized controlled trial and two case-control studies demonstrated no increase in relative risk from the use of systemic HRT.[275,276,277]

11.3.2 Post-menopausal bleeding

In an adequately screened woman, post-menopausal bleeding is not an indication to take a cervical sample. The investigation of abnormal bleeding after the menopause must include direct visual inspection of the cervix. A cervical sample is not an appropriate test for investigating PMB. All unexplained bleeding should be referred to a gynaecologist.

Evidence: good practice point

11.4 Hysterectomy

11.4.1 Women undergoing a hysterectomy for reasons other than cervical cancer

All patients in the cervical screening age range undergoing a hysterectomy for other gynaecological reasons than a diagnosis of cervical cancer should have a negative test result within the screening interval. Otherwise, a cervical sample should be taken as part of their preoperative investigations **(100%)**.

Evidence: good practice point

11.4.2 Women being considered for hysterectomy

All patients being considered for hysterectomy who have an uninvestigated abnormal test result or symptoms attributable to cervical cancer should have diagnostic colposcopy and an appropriate biopsy.[278] **(100%)**.

Evidence: professional consensus suggests that the nature and extent of cervical neoplasia is defined to avoid inadvertent non radical treatment of cervical cancer or inadvertent inadequate excision of VaIN.[278,279]

11.4.3 Hysterectomy as treatment for histologically-proven CIN

Hysterectomy is a recognised treatment for histologically proven CIN if there are co-existing conditions appropriately treated by hysterectomy.

Evidence: good practice point

11.4.4 Hysterectomy as treatment for persistent abnormal endocervical cytology

Hysterectomy is an acceptable form of treatment in cases where abnormal endocervical cytology persists despite a prior excisional biopsy of adequate size. This is provided that all measures to exclude occult invasion have been applied.

Evidence: good practice point

11.4.5 Mapping vaginal abnormalities

Patients with CIN should have any abnormality on the vagina mapped by colposcopy or Lugol's iodine at the time of surgery to ensure that any coexisting VaIN is recognised and excised at the time of the hysterectomy. [279]

Evidence: observational data.

11.4.6 Correlation of histology with cytology

The histology of the resected uterus should be correlated with prior cervical cytology as part of the quality assurance process.

Evidence: good practice point

11.4.7 Follow up after hysterectomy

After hysterectomy, follow up is advised as suggested in section 10.5.

Evidence: good practice point

11.5 Summary of standards

1. If colposcopy has been performed during pregnancy, postpartum assessment of women with an abnormal cervical sample or biopsy-proven CIN is essential **(100%)**.

2. If invasive disease is suspected clinically or colposcopically in a pregnancy women, a biopsy adequate to make the diagnosis is essential **(100%)**.

3. The investigation of abnormal bleeding after the menopause must include direct visual inspection of the cervix **(100%)**.

4. All patients in the cervical screening age range undergoing a hysterectomy for reasons other than a diagnosis of cervical disease must have a negative test result within the screening interval or as part of their preoperative investigations **(100%)**.

5. All patients being considered for hysterectomy who have an undiagnosed abnormal sample or symptoms attributable to cervical cancer should have diagnostic colposcopy and an appropriate biopsy (**100%)**.

12 Screening and management of immunosuppressed women

12.1 Definition of immunosuppression

This chapter includes guidance for the management of women on immune suppressing medication, transplant recipients of any organ, and all other forms of immunosuppression.

12.2 Women with renal failure requiring dialysis

All women aged 25 to 64 years with renal failure requiring dialysis or any other disease with a high chance of needing organ transplantation must have cervical cytology at or shortly after diagnosis. Women with an abnormal result should be referred to colposcopy as described in section 4.

All women aged 25 to 64 years about to undergo organ transplantation should have had cervical cytology performed within the previous year. Co-existing CIN should be managed according to national guidelines.

Evidence: there is a wealth of evidence demonstrating that immunosuppressed women are not only more likely to acquire a HPV infection, but are less likely to clear the infection – a risk factor for progression to CIN and cervical cancer.[280,281,282] For these reasons, screening at a more frequent interval may be beneficial to this population. There is some evidence that cervical cytology is relatively insensitive to changes in immunosuppressed women. Early recourse to colposcopy is therefore advised.[283,284]

12.3 Women taking maintenance immunosuppression medication post-transplantation

Women taking maintenance immunosuppression medication after transplantation who have no history of CIN should have cervical screening in accordance with the national guidelines for the non-immunosuppressed.

Any abnormal screening result should prompt colposcopic referral. Any woman with a previous history of CIN should have routine follow-up, in accordance with the guidelines for the immunocompetent population.

There should be effective education of both organ transplant recipients and their carers about the need to participate in the cervical screening programme, with the production of leaflets and other educational materials targeted at this group.

Evidence: there is good evidence that women who have renal failure requiring dialysis or renal transplantation are at an increased risk of CIN and cervical cancer.[285] The range of incidence of abnormal cervical cytology in the renal transplant population has been quoted as between 8.7% and 70%, a realistic figure of around 15% represents a fivefold increase compared to the normal population.[286] The risk of infection with HPV also increases, with 40% of women acquiring the virus within six months of the transplant.[282] The same risks have been found in women with stem cell transplantation.[287,288] There are insufficient data on the assessment and management of these patients long-term. Improved information resources are necessary, as uptake of cervical screening is poor among transplant recipients, despite the evidence suggesting that they are at increased risk of CIN and cervical cancer.[289] Their screening status should form part of their annual transplant review.

12.4 Women with multifocal disease

The screening and management of the immunosuppressed woman is a complex area of assessment and management. This is especially true for those with multifocal disease, which is why these patients must be managed in a centre with demonstrable skill and expertise and sufficient access to patient numbers to maintain that expertise.

There must be a compromise between the increased risk of CIN and the additional psychological and physical trauma of assessment and treatment, with due consideration paid to the co-morbidity of the underlying disease process. These patients should be assessed by cytology, HPV testing (within the context of the NHSCSP), colposcopy, vulvoscopy, and biopsy where indicated at least every six months.

Evidence: In organ transplant recipients the risk of intraepithelial disease, and therefore cancer, appears to increase with time.[290,291] The relative risk increases significantly three years after transplantation. Women who are over the age of 35 or more when they undergo transplantation also have a greater risk.[290,292]

12.5 HPV vaccination

All women who have never been sexually active prior to the diagnosis of their condition and commencement of immunosuppressive therapy should be offered HPV vaccination. After vaccination, the women should remain in the screening programme.

12.6 Women receiving cytotoxic drugs for rheumatological disorders

Women receiving cytotoxic drugs for rheumatological disorders over the long-term should have regular cytological screening according to national guidelines.

If the woman's cervical screening history is incomplete at the time she commences a course of cytotoxic drugs, then a screening test should be performed with immediate referral to colposcopy for any screening abnormality.

Evidence: there is an increased incidence of CIN in women with systemic lupus erythematous treated with long-term chemotherapy.[293,294] The data for other rheumatological disorders is lacking, but safe practice dictates adequate screening histories as a minimum requirement.

12.7 Other women who are immunosuppressed

There is no indication for increased surveillance of the following groups:

- women receiving cytotoxic chemotherapy for non-genital cancers
- women receiving long term biologic agents
- women receiving oestrogen antagonists such as tamoxifen

These women should have cytological screening according to the national guidelines for the general population.

Evidence: there is no evidence to suggest that women who receive chemotherapy with cytotoxic drugs or tamoxifen are at increased risk of CIN.[295,296,297]

12.8 Women who are HIV positive

All women newly diagnosed with HIV should have cervical surveillance performed by, or in conjunction with, the medical team managing the HIV infection. Annual cytology should be performed with an initial colposcopy if resources permit. Subsequent colposcopy for screening abnormality should follow national guidelines. The age range screened should be the same as for HIV negative women.

Despite the higher cervical treatment failure rate, high-grade CIN should be managed according to national guidelines. Lesions less severe than CIN2 should probably not be treated as these are likely to represent persistent HPV infection of the cervix which responds poorly to treatment and may clear spontaneously. Regular cytological surveillance will detect progression.

Use of highly active antiretroviral therapy (HAART) reduces HIV viral load, and may reduce HPV viral load. As a consequence, the prevalence and incidence of cervical abnormality may also be reduced, however, the evidence for this is inconsistent to date and thus there is a need for more intense surveillance of these women to detect preinvasive cervical lesions.

Close co-operation is advised between colposcopists and HIV physicians to ensure that women are not overtreated if there is a possibility of enhancing immunocompetence (eg by raising CD4 counts following compliance with antiretroviral therapy).

Women who are HIV positive can cease cervical screening at age 65 if they fulfil the criteria for ceasing.

Evidence: there is evidence that in HIV positive women there is an increased risk of false negative cytology.[298] The estimated prevalence of cervical disease in HIV seronegative women is approximately 3%.[299] By contrast a number of reports including cross sectional, case-control and cohort studies have indicated a greatly increased prevalence of squamous intraepithelial lesions, ranging between 20% to 40%[300,301,302,303], and increased incidence in HIV infected women.[304] Furthermore, regression of low-grade lesions is rare and high-grade lesions may respond poorly to standard therapies.[305,306] In one study, the recurrence rate in women with CD4 counts <200/mm^3 was 87%, compared with less than 10% in immunocompetent women.[306]

The reason for this high incidence of CIN and recurrence following treatment is thought to be the lack of immune activity against HPV. Even cohorts using highly active retroviral therapy (HAART) are at increased risk of abnormal cytology, although HAART may increase the regression of low-grade lesions. [307] Early data from a European cohort study shows a 33% prevalence of abnormal cytology, ASCUS, or worse amongst the 859 women recruited so far, although a large proportion were receiving HAART.[308]

12.9 Summary of standards

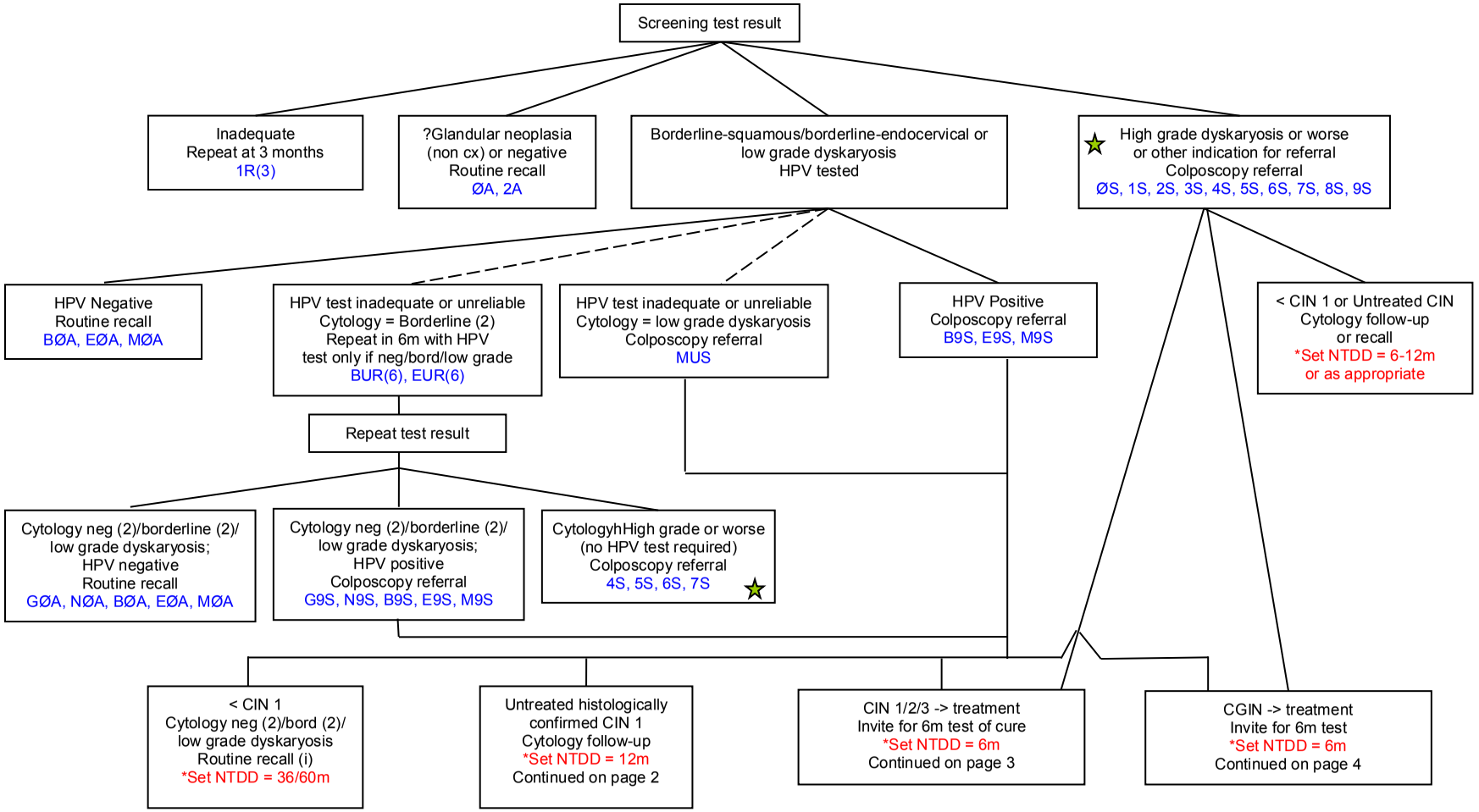
1. All patients who are immunosuppressed must be managed in a centre that has demonstrable skill and expertise and access to sufficient numbers of patients to maintain that expertise.

2. All women aged 25 to 64 with renal failure requiring dialysis, who have never been screened must have cervical cytology performed at or shortly after diagnosis.

Appendix 1:

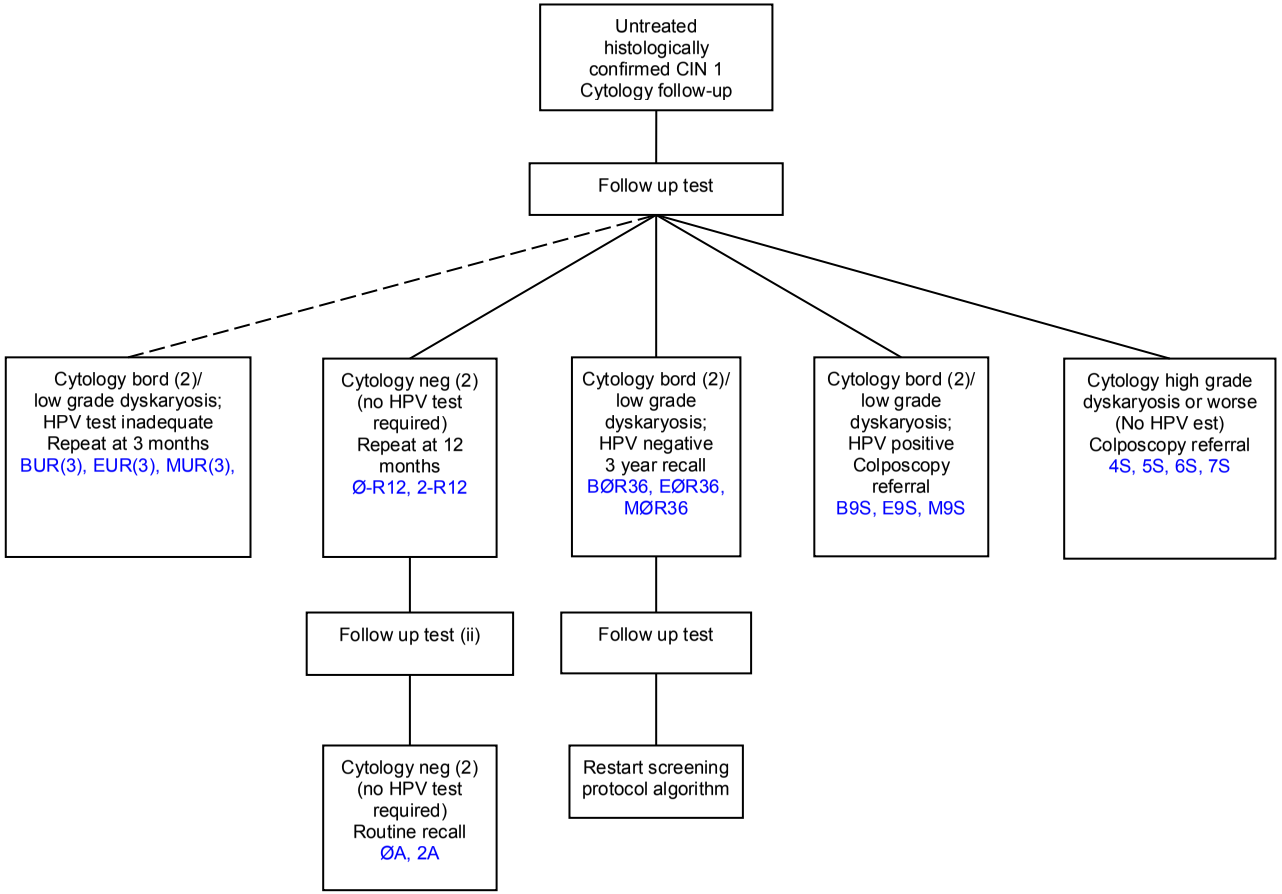
Screening Protocol Algorithm and Colposcopy Management Recommendations

Cytology with HPV Triage and TOC



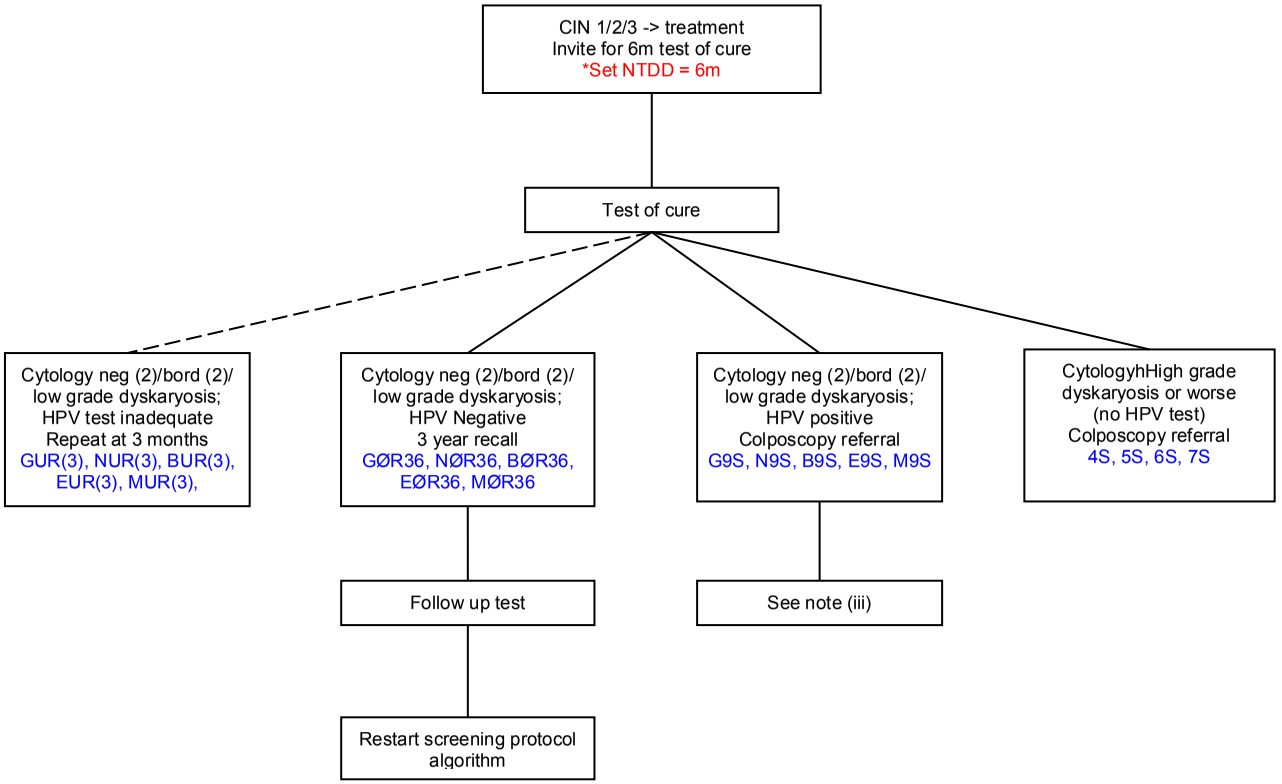
(i) Women more than 60 years who are cytology negative, HPV positive and have a satisfactory and negative colposcopy can be ceased from the programme. Women more than 60 years who are borderline/low-grade dyskaryosis, HPV positive and have a satisfactory and negative colposcopy should consider LLETZ if decline recall at 60 months.

Management of untreated histologically confirmed CIN1



(ii) The management of women with abnormal cytology at this second 12 month follow up test will mirror that at the first 12 month repeat test.

Test of cure following treatment for CIN



(iii) Women referred back to colposcopy (at TOC following treatment for CIN) due to borderline, low-grade dyskaryosis or negative cytology, who are HR-HPV positive, and who then have a satisfactory and negative colposcopy, can be recalled in three years.

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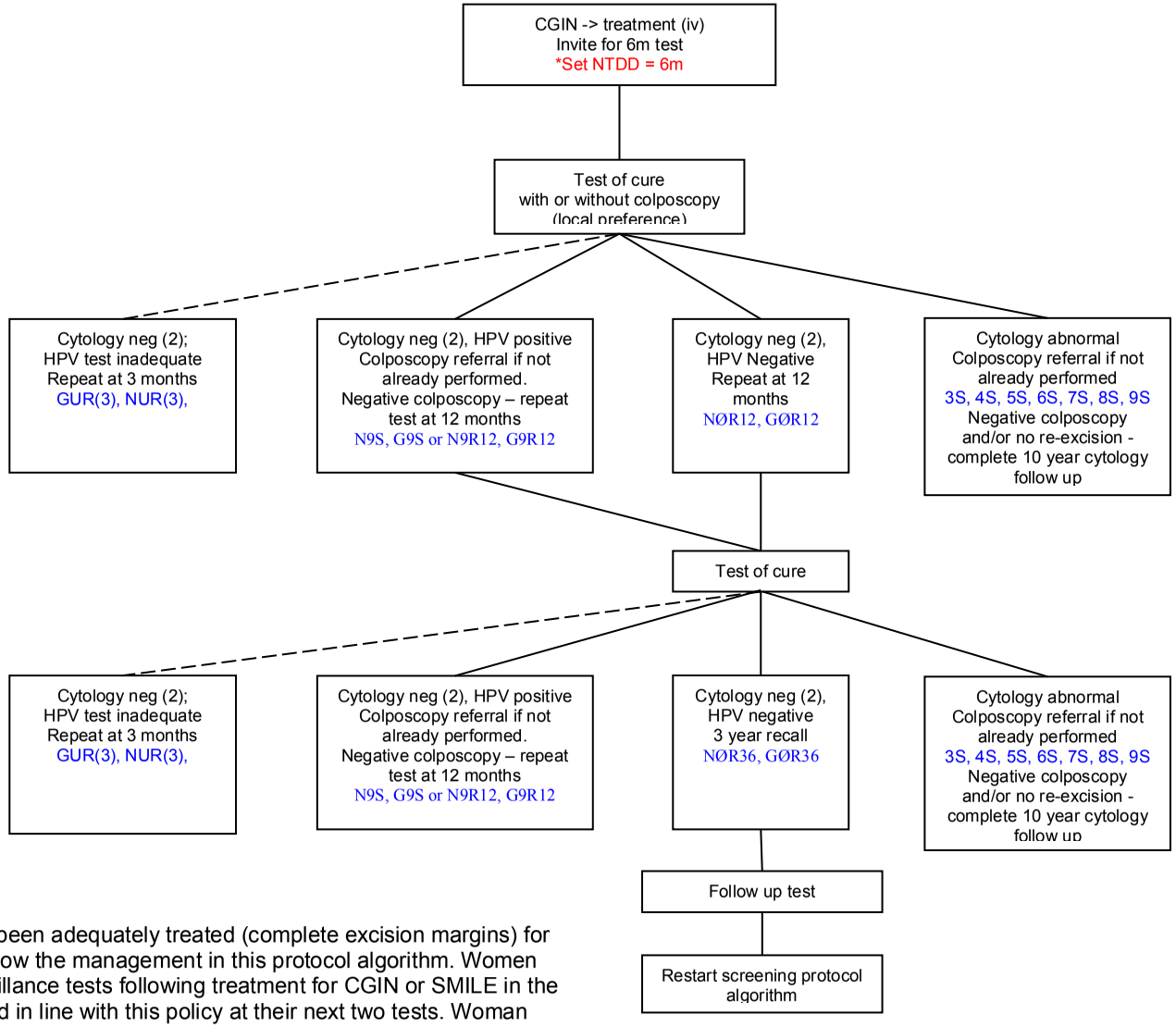
Management of women adequately treated for CGIN



(iv) Women who have been adequately treated (complete excision margins) for CGIN or SMILE will follow the management in this protocol algorithm. Women receiving annual surveillance tests following treatment for CGIN or SMILE in the past may also be tested in line with this policy at their next two tests. Woman treated for cervical cancer are excluded from this management policy.

Key to notes and abbreviations

Action codes

A	routine recall
Rm	early repeat in 'm' months
S	suspend from recall

PROVISIONAL Result codes

Ø *	?glandular neoplasia (non cervical)
G *	?glandular neoplasia (non cervical) (HPV tested)
1	inadequate
2	negative (not HPV tested)
N	negative (HPV tested)
3	low grade dyskaryosis (not HPV tested)
M	low grade dyskaryosis (HPV tested)
4	high grade dyskaryosis (severe)
5	high grade dyskaryosis ?invasive squamous carcinoma
6	?glandular neoplasia of endocervical type
7	high grade dyskaryosis (moderate)
8	borderline change in squamous cells (not HPV tested)
B	borderline change in squamous cells (HPV tested)
9	borderline change in endocervical cells
E	borderline change in endocervical cells (HPV tested)

* non-cervical neoplasia treated as negative for CSP management
(2) Used to denote both categories of negative result (negative and ?glandular neoplasia (non cervical)) or both categories of borderline result (borderline change in squamous cells and borderline change in endocervical cells.)

Infection codes

Ø (zero)	HPV negative
9 (nine)	HPV positive
U	HPV result inadequate/unreliable

Miscellaneous

NTDD Next Test Due Date

BLUE indicates codes used on NHAIS in format
Cytology result – HPV infection code – Action code
RED indicates manual action required to reset NTDD

 colposcopy referral without HPV test

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References

1. Peto J, Gilham C, Fletcher O et al. The cervical cancer epidemic that screening has prevented in the UK. *Lancet,* 2004, 364:249-56.
2. *Cervical Screening Programme, England - Statistics for 2014-15.* The Health and Social Care Information Centre, November 2015.
3. *Achievable standards, Benchmarks for reporting, and Criteria for evaluating cervical cytopathology, third edition* (NHSCSP Publication No 1). Sheffield: NHS Cancer Screening Programmes, 2013.
4. Sasieni P, Adams J, Cuzick J. Benefit of cervical screening at different ages: evidence from the UK audit of screening histories. *British Journal of Cancer,* 2003, 89(1): 88-93.
5. Cervical Screening Wales. *Changes to cervical screening age range and frequency.* Available at www.screeningservices.org.uk/csw/pub. Accessed 29 August 2013.
6. Cervical screening (press release). Available at www.scotland.gov.uk/News/Releases/2012/12/cervical-screening11122012. Accessed 29 August 2013.
7. Massad LS, Einstein MH, Warner KH et al. *2012 updated consensus guidelines for the management of abnormal cervical cancer screening tests and cancer precursors. Journal of Lower Genital Tract Disease.* 2013, 17(5):S1-S27.
8. Richardson J, Howe A, McElduff P. *Time Dependent Response to Invitation for Cervical Screening* (NHSCSP Publication No 29). Sheffield: NHS Cancer Screening Programmes, 2007.
9. *Audit of invasive cervical cancer – national report.* Sheffield: NHS Cancer Screening Programmes, annual data collection.
10. Minutes of an extraordinary meeting of the ACCS to re-examine current policy on cervical screening for women aged 20 to 24 years taking account of any new evidence and to make recommendations to the National Cancer Director and Ministers, 19 May 2009. Available at: www.cancerscreening.nhs.uk/cervical/cervical-review-minutes-20090519.pdf. Accessed 6 August 2013.
11. *IARC handbooks of cancer prevention volume 10: cervix cancer screening*. Lyon: IARC Press, 2005. Available at: www.iarc.fr/en/publications/pdfs-online/prev/handbook10/handbook10-chap8.pdf. Accessed 6 August 2013.
12. Collins S, Mazloomzadeh S, Winter H et al. High incidence of cervical human papillomavirus infection in women during their first sexual relationship. *BJOG: An International Journal of Obstetrics and Gynaecology,* 2002, 109: 96-98.
13. Sasieni P, Castanon A, Cuzick J. *Impact of cervical screening on young women: a critical review of the literature* (NHSCSP Publication No 31). Sheffield: NHS Cancer Screening Programmes, 2010.
14. Sasieni P, Castanon a, Cuzick J., Effectiveness of cervical screening with age: Population based case-control study of prospectively recorded data. *BMJ*, 2009, 339: b2968.

15. Sasieni P, Adams J. Effect of screening on cervical cancer mortality in England and Wales: analysis of trends with an age cohort model. *BMJ*, 1999, 318(7193): 1244–1245.
16. Kyrgiou M, Koliopoulous G, Martin-Hirsch P et al. Obstetric outcomes after conservative treatment for intraepithelial or early invasive cervical lesions: systematic review and meta-analysis. *Lancet,* 2006, 367(9509): 489–98.
17. Bruinsma F, Lumley J, Tan J et al. Precancerous changes in the cervix and risk of subsequent preterm birth. *BJOG*, 2007, 114: 70–80.
18. Arbyn M, Kyrgiou M, Simoens C et al. Perinatal mortality and other severe adverse pregnancy outcomes associated with treatment of cervical intraepithelial neoplasia: meta-analysis. *BMJ,* 2008, 337: a1284.
19. Jakobsson M et al. Preterm delivery after surgical treatment for cervical intraepithelial neoplasia. *Obstetrics and Gynecology,* 2007,109(2 Pt 1): 309–13.
20. Jakobsson M et al. Loop electrosurgical excision procedure and the risk for preterm birth. *Obstetrics and Gynecology,*2009, 114(3): 504–10.
21. Noehr B et al. Loop electrosurgical excision of the cervix and subsequent risk for spontaneous preterm delivery: a population-based study of singleton deliveries during a 9-year period. *American Journal of Obstetrics and Gynecology,* 2009, 201(1):33.e1-6.
22. Cruickshank M, Flannelly G, Campbell DM. Fertility and pregnancy outcome following large loop excision of the cervical transformation zone. *British Journal of Obstetrics and Gynaecology,* 1995, 102(6): 467-70.
23. Castanon A, Brocklehurts P, Evans H et al. Risk of preterm birth after treatment for cervical intraepithelial neoplasia among women attending colposcopy in England: retrospective-prospective cohort study. *BMJ,* 2012, 345:e5174.
24. Sasieni P, Castanon A, Parkin DM. How many cervical cancers are prevented by treatment of screen-detected disease in young women? *International Journal of Cancer,* 2009, 124(2):461-464.
25. Patel A, Galaal K, Burnley C et al. Cervical cancer incidence in young women: a historical and geographic controlled UK regional population study. *British Journal of Cancer,* 2012, 106:1753-1759.
26. Castanon A, Leung VMW, Landy R. Characteristics and screening history of women diagnosed with cervical cancer aged 20-29 years. *British Journal of Cancer,* 2013, 109: 35-41.
27. Saeed-Vafa, Huang Y. Should cervical cancer screening begin at 21 for everyone? A quantitative analysis in a high-risk, low-income, African American/Hispanic young-adult population. *Diagnostic Cytopathology,* 2013, forthcoming.
28. Rebolj M, van Ballegooijen M, Lynge E et al. Incidence of cervical cancer after several negative smear results by age 50: prospective observational study. *BMJ,* 2009, 338:b1354.
29. Van Wijngaarden WJ, Duncan ID. Rationale for stopping cervical screening in women over 50. *BMJ,* 1993, 306(6889): 1373.

30. Gustafsson L, Sparen P, Gustafsson M et al. Low efficiency of cytologic screening for cancer in situ of the cervix in older women. *International Journal of Cancer,* 1995, 63(6): 804-809.
31. Cuzick J, Beverley E, Ho L et al. HPV testing in primary screening of older women. *British Journal of Cancer,* 1999, 81(3): 554-558.
32. *Clinical practice guidelines for the assessment of young women aged 20-24 with abnormal vaginal bleeding.* London: Department of Health, 2010.
33. Cornelison TL, Montz FJ, Bristow RE. Decreased incidence of cervical cancer in Medicare-eligible Californian women. *Obstetrics and Gynaecology,* 2002, 100(1):79-86
34. Blomfield PI, Lancashire RJ, Woodman CBJ. Can women at risk of cervical abnormality be identified? *British Journal of Obstetrics and Gynaecology,* 1998, 105: 486-492.
35. Hakama M, Pukkala E, Saastamoinen P. Selective screening: theory and practice based on high-risk groups of cervical cancer. *Journaly of Epidemiology and Community Health,* 1979, 33:257-261.
36. *Interim good practice guidance for cervical sample takers* (NHSCSP Good Practice Guide no 2). Sheffield: NHS Cancer Screening Programmes, 2011.
37. Stedman Y, Woodman CBJ, Donnelly BJ. Is a policy of screening for all women attending a genitourinary medicine clinic justified? *Journal of Public Health Medicine,* 1979, 33: 257-261.
38. Wilson JD, Parsons W (British Co-operative Clinical Group). Cervical cytology smears in sexually transmitted infection clinics in the United Kingdom. *Sexually Transmitted Infections,* 2001, 77: 107-110.
39. Foley E, Harinda V. Cervical cytology: are national guidelines adequate for women attending genito-urinary medicine clinics? *Sexually Transmitted Infections,* 1999, 75: 349-386.
40. Edwards SK, Sonnex C. Influence of genital infection on cervical cytology. *Sexually Transmitted Infections¸ 1998, 74:271-273.*
41. Schwebke JR, Zajackowski ME. Effects of concurrent lower genital tract infections on cervical cancer screening. *Genitourinary Medicine,* 1997, 73(5): 383-386.
42. Brady M, Brook G. Influence of genital infection on cervical cytology. *Sexually Transmitted Infections,* 1998, 74:457-8 (letter).
43. Burja, IT, Shurbaji MS. Clinical impact of identifying *Trichomonas vaginalis* on cervicovaginal (Papanicolaou) smears. *Diagnostic Cytopathology,* 2000, 24(3)L 195-199.
44. Vinette-Leduc D, Yazdi HM, Jessamine P et al. Reliability of cytology to detect chlamydial infection in asymptomatic women. *Diagnostic Cytopathology,* 1997, 17(4): 258-261.
45. Dimian C, Nayagam M, Bradbeer C. The association between sexually transmitted diseases and inflammatory cervical cytology. *Genitourinary Medicine,* 1992, 68: 305-306.
46. *Guidance on the use of liquid-based cytology for cervical screening* (Technology Appraosal Guidance 69). London: NICE, 2003.

47. Moss S, Gray A, Legood R et al. Effect of testing for human papillomavirus as a triage during screening for cervical cancer: observational before and after study. *BMJ*, 2006, 332: 83–85.
48. R S Kelly, J Patnick, H C Kitchener, and S M Moss, on behalf of the NHSCSP HPV Special Interest Group. HPV testing as a triage for borderline or mild dyskaryosis on cervical cytology: results from the Sentinel Sites study. *Br J Cancer*. 2011 September 27; 105(7): 983–988.
49. Arbyn M, Martin-Hirsch P, Buntinx F, et al. Triage of women with equivocal or low-grade cervical cytology results: a meta-analysis of the HPV test positivity rate. *J Cell Mol Med*. 2009 Apr;13(4):648-59.
50. RS Kelly, P Walker, H Kitchener, SM Moss Incidence of cervical intraepithelial neoplasia grade 2 or worse in colposcopy-negative/human papillomavirus-positive women with low-grade cytological abnormalities. *BJOG: An International Journal of Obstetrics & Gynaecology* 2012 Jan: 119: 20–25.
51. Paraskevaidis E, Arbyn M, Sotiriadis A et al. The role of HPV DNA testing in the follow up period after treatment for CIN: a systematic review of the literature. Cancer Treat Rev, 2004; 30(2): 205–211.
52. Cuzick J, Arbyn M, Sankaranarayanan R, Tsu V, Ronco G, Mayrandf M, Dillner J, Meijer C. Overview of Human Papillomavirus-Based and Other Novel Options for Cervical Cancer Screening in Developed and Developing Countries Vaccine, 2008; 26(10): K29–K41.
53. Legood R, Gray A, Wolstenholme J, Moss S. Lifetime effects, costs, and cost effectiveness of testing for human papillomavirus to manage low grade cytological abnormalities: results of the NHS pilot studies. BMJ. 2006 January 14; 332(7533): 79–85.
54. Frederiksen, M., Lynge, E. and Rebolj, M, What women want. Women's preferences for the management of low-grade abnormal cervical screening tests: a systematic review. BJOG: An International Journal of Obstetrics & Gynaecology 2012 Jan; 119: 7–19.
55. Kitchener HC, Almonte M, Thomson C et al. HPV testing in combination with liquid-based cytology in primary cervical screening (ARTISTIC): a randomised controlled trial. Lancet Oncol, 2009, 10(7): 672–682.
56. Rijkaart DC, Berkhof J, van Kemenade FJ, Coupe VM, Rozendaal L, Heideman DA, Verheijen RH, Bulk S, Verweij W, Snijders PJ, Meijer CJ. HPV DNA testing in population-based cervical screening (VUSA-Screen stdy): results and implications. *Br J Cancer*, 2012, 106: 975-81.
57. Kitchener HC, Almonte M, Gilham C et al, on behalf of the ARTISTIC Trial Study Group. ARTISTIC: a randomised trial of human papillomavirus (HPV) testing in primary cervical screening. Health Technol Assess, 2009, 13(51):1–150.
58. Rijkaart DC, Berkhof J, Rozendaal L, van Kemenade FJ, Bulkmans NW, Heideman DA, Kenter GG, Cuzick J, Snijders PJ, Meijer CJ. Human papillomavirus testing for the detection of high-grade cervical intraepithelial neoplasia and cancer: final results of the POBASCAM randomised controlled trial. Lancet Oncol. 2012 Jan;13(1):78-88.

59. Castle PE, Stoler MH, Wright TC, et al Performance of carcinogenic human papillomavirus (HPV) testing and HPV16 or HPV18 genotyping for cervical cancer screening of women aged 25 years and older: a sub analysis of the ATHENA study. Lancet Oncol 2011 Sep; 12(9) :880-90.
60. Rijkaart DC, Berkhof J, Rozendaal L, et al, on behalf of the POBASCAM Study Group. High-risk HPV type-specific clearance rates in cervical screening. Br J Cancer, 2007, 96(9): 1419–1424.
61. www.gov.uk/government/publications/the-national-cancer-strategy.
62. Anderson DJ, Flannelly GM, Kitchener H et al. Mild and moderate dyskaryosis: can women be selected for colposcopy on the basis of social criteria? *Br Med J,* 1992, 305:84-87.
63. Soutter WP, Wisdom S, Brough AK et al. Should patients with mild atypia in a cervical smear be referred for colposcopy? *British Journal of Obstetrics and Gynaecology,* 1986, 93:70-74.
64. Bigrigg MA, Codling BW, Pearson P et al. Colposcopic diagnosis and treatment of cervical dysplasia at a single clinic visit: Experience of low-voltage diathermy loop in 1000 patients. *Lancet,* 1990, 336:229-231.
65. Tables 18, 18a. *National statistics: cervical screening programme, England 2011-12.* NHS Health and Social Care Information Centre, 2012.
66. Soutter WP, Fletcher A. Invasive cancer of the cervix in women with mild dyskaryosis followed up cytologically. *Br Med J,* 1994, 308: 1421-1403.
67. Johnson SJ, Wadehra V. How predictive is a cervical smear suggesting invasive squamous cell carcinoma? *Cytopathology,* 2001, 12: 144-150 .
68. Cullimore J and Scurr J. The abnormal glandular smear: cytological prediction, colposcopic correlation and clinical management. *Journal of Obstetrics and Gynaecology*, 2000, 403-407.
69. Leeson SC, Inglis TCM, Salman WD. A study to determine the underlying reason for abnormal glandular cytology and the formulation of a management protocol. *Cytopathology,* 1997, 8:20-26.
70. Fadare O, Ghofrani M, Chacho MS, et al. The significance of benign endometrial cells in cervicovaginal smears. *Advances in Anatomic Pathology,* 2005, 12(5):274-87.
71. Canfell K, Kany YJ, Clements M et al. Normal endometrial cells in cervical cytology: systematic review of prevalence and relation to significant endometrial pathology. *Journal of Medical Screening,* 2008, 15(4):188-198.
72. Rosenthal AN, Panoskaltsis T, Smith T et al. The frequency of significant pathology in women attending a general gynaecological service for postcoital bleeding. *BJOG,* 2001, 108: 103-106.
73. Soutter WP, de Barros Lopes A, Fletcher A et al. Invasive cervical cancer after conservative therapy for cervical intraepithelial neoplasia. *The Lancet,* 1997, 348:978-980.
74. Department of Health. The Operating Framework for the NHS in England 2012/13. Published 24/11/11

www.gov.uk/government/uploads/system/uploads/attachment_data/file/216590/dh_131428.pdf.
75. NHS England. Everyone Counts: Planning for Patients 2014/5 to 2018/19. Published 20/12/13 www.england.nhs.uk/wp-content/uploads/2013/12/5yr-strat-plann-guid-wa.pdf.
76. Audit of Invasive Cervical Cancers. NHSCSP No 28. Sheffield: NHS Cancer Screening Programmes, 2006.
77. Posner T, Vessey M. *Prevention of Cervical Cancer: The Patient's View.* King Edward's Hospital Fund for London, 1988.
78. Smith T. Colposcopy*. Nurs Stand*. 1997, 11(45): 49–54.
79. Wilson JD, Hines B. Nurse counselling for women with abnormal cervical cytology improves colposcopy and cytology follow up attendance rates. *Sex Transm Infect*, 2000, 76(4): 322.
80. Swancutt DR, Greenfield SM, Luesley DM, et al. Women's experience of colposcopy: a qualitative investigation. *BMC Womens Health*. 2011 13(11):11.
81. Austoker J, Davey C, Jansen C. *Improving the quality of the written information sent to women about cervical screening* (NHSCSP Publication No 5). Sheffield: NHS Cancer Screening Programmes, 1997.
82. Marteau TM.. Reducing anxiety in women referred for colposcopy using an information booklet. Br J Health Psych, 1996, 1: 181–189.
83. Marteau TM, Bekker H. The development of a six-item short-form of the State scale of the Spielberger State-Trait Anxiety Inventory. *Br J Clin Psychol*, 1992, 31: 301–306.
84. Marteau T, Walker P, Giles J, Smail M. Anxieties in women undergoing colposcopy. *Br J Obstet Gynaecol*, 1990, 97: 859–861.
85. Lerman C, Miller S, Scarborough R, et al. Adverse psychologic consequences of positive cytologic cervical screening. *American Journal of Obstetrics & Gynecology*, 1991, 163(3): 658–662.
86. Gath D, Hallam N, Mynors-Wallis L et al. Emotional reactions in women attending a UK colposcopy clinic. *Journal of Epidemiology and Community Health*, 1995, 49: 79–83.
87. Chiu, LF. *Promoting Informed Choices on Cancer Screening in a Diverse Community: Guidance for Service Providers and Health Promoters* (NHS Cancer Screening Series No 6). Sheffield: NHS Cancer Screening Programmes, 2009.
88. Bigrigg A, Haffenden DK*,* Sheehan ***AL*** et al. Efficacy and safety of large-loop excision of the transformation zone. *Lancet,* 1994, 343: 32–34.
89. Sharp L, Cotton S, Cochran C et al. After-effects reported by women following colposcopy, cervical biopsies and LLETZ: results from the TOMBOLA trial. TOMBOLA (Trial Of Management of Borderline and Other Low-grade Abnormal smears) Group. *BJOG*, 2009, 116(11): 1506–1514.
90. Jo's Trust. *CIN (Pre-cancer)Treatment*. Available at www.jotrust.co.uk/about_cervical_cancer/cervical_screening_and_cin/cin__pre_cancer__treatment.cfm. Accessed 29.01.10.

91. Sellars JW and Sankaranarayanan R (eds). *Colposcopy and Treatment of Cervical Intraepithelial Neoplasia*. Lyon, IARC, 2003/4.
92. Royal Australasian College of Surgeons. *Fitness to Drive after Anaesthesia*. Available at www.surgeons.org/Content/NavigationMenu/WhoWeAre/Affiliatedorganisations/AustraliaDaySurgeryCouncil/Appendix_C_Anaesthet.htm#Fitness_to_drive. Accessed 31.08.2008.
93. Ind T. *Treatment for CIN* (2004). Available at ww.colposcopy.co.uk/treatment.htm. Accessed Aug 2008.
94. Apgar BS, Brotzman GL, Spitzer M. *Colposcopy. Principles and Practice*, (Chapter 5). Philadelphia, WB Saunders, 2002.
95. Castanon A, Landy R, Brocklehurst P, Evans H, Peebles D, Singh N, Walker P, Patnick J, Sasieni P; PaCT Study Group. Risk of preterm delivery with increasing depth of excision for cervical intraepithelial neoplasia in England: nested case-control study. *BMJ*, 2014, 349:g6223. doi: 10.1136/bmj.g6223.
96. Le Riche, HR, Botha MH. Cervical conisation and reproductive outcome. *S African J Obstet Gynaecol,* 2006, 12: 150–154.
97. Kyrgiou M, Mitra A, Arbyn M, Stasinou SM, Martin-Hirsch P, Bennett P, Paraskevaidis E. Fertility and early pregnancy outcomes after treatment for cervical intra-epithelial neoplasia: systematic review and meta-analysis. *BMJ*, 2014; 349:g6192. doi: 10.1136/bmj.g.6192.
98. Freeman-Wang T, Walker P, Linehan J et al. Anxiety levels in women attending colposcopy clinics for treatment for cervical intraepithelial neoplasia: a randomised trial of written and video information. *Brit J Obstet Gynaecol*, 2001, 108(5): 482–484.
99. Howells REJ, Lockett J, Dunn PDJ et al. Do women referred for colposcopy receive adequate information from the primary care team? *J Obstet Gynaecol*, 1999, 19(1): 59–60.
100. Meerabeau J. The management of embarrassment and sexuality in health care. *J Ad Nurs*, 1999, 29: 1507–1513.
101. Guidance Notes on Electrical Safety in Rooms used for Colposcopy and the Safe Use of Electrosurgery for LLETZ Procedures. Sheffield: NHS Cancer Screening Programmes, 2004. (NHSCSP Equipment Report 0401).
102. Implementation of the Dynamic Spectral Imaging System (DySIS) as an adjunctive colposcopic technique for examination of the uterine cervix. NHSCSP Equipment Report 1201. Sheffield: NHS Cancer Screening Programmes, 2012.
103. Adjunctive colposcopy technologies for examination of the uterine cervix - DySIS and Niris Imaging System. London: NICE, 2012.
104. www.nice.org.uk/advice/mib20.
105. Lester H, Wilson S. Is default from colposcopy a problem, and if so what can we do? A systematic review of the literature. *BJGP*, 1999, 49: 223–229.
106. Sanders G, Craddock C Waggstaff I. Factors influencing default at a colposcopy clinic. *Quality Health Care*, 1992, 1: 236–240.

107. Patterson T, Roworth M, Hill M. An investigation into the default rate at the Fife colposcopy clinic. *Journal of Reproductive Medicine*, 1995, 17(1): 65–69.
108. Freeman-Wang T, Coffey C, Walker PG. Non attendance for colposcopy: is it really a problem? *Poster Presentation BSCCP Annual General Meeting, Harrogate*, 2001.
109. Miller S, Seijak KK, Schroeder CM et al. Enhancing adherence following abnormal pap smears among low income women: a preventive telephone counselling strategy. *JNCI,* 1997, 89(10): 703–708.
110. Lerman C, Hanjani P, Caputo C et al. Telephone counselling improves adherence to colposcopy in lower income minority women. *J Clinical Oncology*, 1992, 10(2): 330–333.
111. Charman CR, English JS. Impact of partial booking on Dermatology outpatient activity. *British Association of Dermatologists*, 2003, 148(3): 169.
112. Mehmet S, Rampton DS. Partial booking for outpatient gastroscopy: are some patients disadvantaged? *Gut*, 2006, 55 (Supplement 2): A91.
113. Lloyd J, Dillon D, Hariharan K. Down the line. *Health Service Journal*, 2003, 113 (5837): 22–23.
114. Shen RN, Hicks DA, Cruickshank ME. Colposcopy services provided by genito-urinary medicine clinics in the United Kingdom. BSCCP/ National Co-ordinating Network Survey 1993. *Int J STD AIDS*, 1996, 7: 98–101.
115. Shehmar M, Leeson S. Delivering the BSCCP/RCOG advanced training skills module in colposcopy: a practical guide for trainers. The Obstetrician & Gynaecologist 2011; 13.2; 112-9.
116. Shehmar M, Cruikshank M, Finn C, Redman C, Fraser I, Peile E. A validity study of the national UK colposcopy objective structured clinical examination – is it a test fit for purpose? BJOG 2009; 116; 1796-9.
117. Etherington IJ, Luesley DM, Shafi MI et al. Observer variability among colposcopists from the West Midlands region. *BJOG*, 1997, 104: 1380–1384.
118. Kierkegaard O, Byrjalsen C, Frandsen KH et al. Diagnostic accuracy of cytology and colposcopy in cervical squamous intraepithelial lesions*. Acta Obstet Gynecol Scand*, 1994, 738: 648–651.
119. Pretorius RG, Belinson JL, Zhang WH et al. The colposcopic impression. Is it influenced by the colposcopist's knowledge of the findings on the referral Papanicolaou smear? *J Reprod Med*, 2001, 46(8): 724–728.
120. Kourounis GS, Michail GD, Ravazoula P. A second Pap smear during colposcopy: is it really worth it? *European Journal of Gynaecological Oncology*, 2004, 25(4): 475–477.
121. Mao C, Balasubramanian A, Koutsky LA. Should liquid-based cytology be repeated at the time of colposcopy? *J Low Genit Tract Dis,* 2005, 9(2): 82–88.
122. Panos JC, Jones BA, Mazzara PF. Usefulness of concurrent Papanicolaou smear at time of cervical biopsy. *Diagn Cytopathol*, 2001, 25(4): 270–273.
123. Rubin A. Clinical value of repeat Pap smear at the time of colposcopy. *Acta Cytol*, 2003, 47(4): 698.

124. Simsir A, Ioffe OB, Bourquin P et al. Repeat cervical cytology at the time of colposcopy. Is there an added benefit? *Acta Cytol*, 2001, 45(1): 23–27.
125. Spitzer M, Ryskin M, Chernys AE et al. The value of repeat Pap smear at the time of initial colposcopy. *Gynecol Oncol,* 1997, 67(1): 3–7.
126. Young NA, Naryshkin S, Bowman RL. Value of repeat cervical smears at the time of colpsocopic biopsy. *Diagn Cytopathol,* 1993, 9: 646–649.
127. Zardawi IM, Rode JW. Clinical value of repeat Pap smear at the time of colposcopy. *Acta Cytol,* 2002, 46(3): 495–498.
128. Dolman G, Tan J, Quinn M. Should the Pap smear be repeated at the first colposcopy visit? *Aust NZ J Obstet Gynaecol*, 2005, 45: 514–517.
129. Koss LG. Pap prior to Colposcopy. *Diagn Cytopathol,* 2002, 26(6): 405
130. Rieck GC, Bhaumik J, Beer HR et al. Repeating cytology at initial colposcopy does not improve detection of high-grade abnormalities: A retrospective cohort study of 6595 women. *Gynecol Oncol,* 2006, 101: 228–233.
131. Bishop JW, Hartinger JS, Pawlick GF. Time interval effect on repeat cervical smear results. *Acta Cytol,* 1997, 41: 269–276.
132. Jordan J, Arbyn M, Martin-Hirsch P et al. European guidelines for the quality assurance in cervical cancer screening: recommendations for clinical management of abnormal cervical cytology, part 1. Cytopathology 2008, 19: 342-354.
133. Bornstein J,Bentley J, Bösze P, " Girardi F, Haefner H, Menton M, Perrotta M, Prendiville W, Russell P, Sideri M, Strander B, Tatti S, Torne A, Walker P. 2011 colposcopic terminology of the International Federation for Cervical Pathology and Colposcopy. Obstet Gynecol. 2012; 120 :166-72.
134. Hopman EH, Kenemans P, Helmerhorst TJ. Positive predictive rate of colposcopic examination of the cervix uteri: an overview of the literature. Obstet Gynecol Surv, 1998, 53(2): 97-106.
135. Benedet JL, Anderson GH, Boyes DA. Colposcopic accuracy in the diagnosis of microinvasive and occult invasive carcinoma of the cervix. *Obstet Gynecol*, 1985, 65(4): 557–662.
136. Liu WM, Chao KC, Wang KI, Ng HT. Colposcopic assessment in microinvasive carcinoma of the cervix. *Chung Hua I Hsueh Tsa Chih* (Taipei), 1989, 43(3): 171–176.
137. Tidbury P, Singer A, Jenkins D. CIN 3: the role of lesion size in invasion. *Br J Obstet Gynaecol*, 1992, 99: 583–586.
138. Skehan M, Soutter WP, Lim K et al. Reliability of colposcopy and directed punch biopsy. *Br J Obstet Gynaecol*, 1990, 97(9): 811–816.
139. Buxton EJ, Luesley DM, Shafi MI, Rollason M. Colposcopically directed punch biopsy: a potentially misleading investigation. *Br J Obstet Gynaecol*, 1991, 98(12): 1273–1276.
140. Ang MS, Kaufman RH, Adam E, Riddle G, Irwin JF, Reeves KO et al. Colposcopically directed biopsy and loop excision of the transformation zone. Comparison of histologic findings. *J Reprod Med*, 1995, 40(3): 167–170.

141. Sillman F, Boyce J, Fruchter R. The significance of atypical vessels and neovascularization in cervical neoplasia. *Am J Obstet Gynecol*, 1981, 139(2): 154–159.
142. Olaniyan OB. Validity of colposcopy in the diagnosis of early cervical neoplasia – a review. Afr J Reprod Health, 2002, 6(3); 59-69.
143. Cantor SB, Cardenas-Turanzas M, Cox DD, Atkinson EN, Nogueras-Gonzalez GM, Beck JR, Follen M, Benedet JL. Accuracy of colposcopy in the diagnostic setting compared with the screening setting; Obstet Gynecol; 2008; 111; 7-14.
144. Nazeer S, Shafi MI. Objective perspective in colposcopy. Best Practice and Research Clinical Obstetrics and Gynaecology 25 (2011); 631-640.
145. Parham DM, Wiredu EK, Hussein KA. The cytological prediction of cervical intraepithelial neoplasia in colposcopically directed biopsies. *Cytopathology*, 1991, 2(6): 285–290.
146. Howells RE, O'Mahoney F, Tucker H et al. How can the incidence of negative specimens resulting from large loop excision of the cervical transformation zone (LLETZ) be reduced? An analysis of negative LLETZ specimens and development of a predictive model. *BJOG*, 2000, 107(9): 1075–1082.
147. Jones MH, Jenkins D, Singer A. Regular audit of colposcopic biopsies from women with a mildly dyskaryotic or borderline cervical smear results in fewer cases of CINIII. *Cytopathology*, 1996, 7(1): 17–24.
148. Cinel A, Oselladore M, Insacco E, Minucci D. The accuracy of colposcopically directed biopsy in the diagnosis of cervical intraepithelial neoplasia. *Eur J Gynaecol Oncol*, 1990, 11(6): 433–437.
149. Baldauf JJ, Dreyfus M, Ritter J, Philippe E. An analysis of the factors involved in the diagnostic accuracy of colposcopically directed biopsy. *Acta Obstet Gynecol Scand*, 1997, 76(5): 468–473.
150. Heatley MK, Bury J. The correlation between the grade of dyskaryosis on cervical smear, grade of cervical intraepithelial neoplasia (CIN) on punch biopsy and the final histological diagnosis on cone biopsies of the cervix. *Cytopathology*, 1998, 9(2): 93–99.
151. Hopman EH, Voorhoorst FJ, Kenemans P et al. Observer agreement on interpreting colposcopic images of CIN. *Gynecol Oncol*, 1995, 58(2): 206–209.
152. Underwood M, Arbyn M, Parry-Smith W, De Bellis-Ayers S, Todd R Redman CW, Moss EL. Accuracy of colposcopic-directed punch biopsies: a systematic review and meta-analysis. *BJOG*, 2012, 119: 1293-301.
153. Labeja Acellam ET, Harris VG. A study to evaluate Chlamydia screening in colposcopy clinics. *J Obstet Gynaecol.,* 1997, 17(5): 472-5
154. Matiluko A, Crystal A. Chlamydia in colposcopy clinics: to screen or not to screen? *J Obstet Gynaecol*, 2006, 26(5): 453-6.
155. Hopwood J, Mallinson H, Hodgson E et al Liquid based cytology: an examination of its potential in a chlamydia screening programme. *Sex transm Infect,* 2004, 80: 371-373.

156. Eltabbakh GH, Eltabbakh GD, Broekhuisen FF et al Value of wet mount and cervical cultures at the time of cervical cytology in asymptomatic women. *J Obstet Gynaecol*, 1995, 85: 499-503.
157. Wilbur DC, Prey Mu, Millar WM et al AutoPap system detection of infections and benign cellular changes: results from primary screener clinical trials. *Diag Cytopathol.*, 1999, 21: 355-8.
158. Westhoff C. IUD's and colonisation or infection with Actinomyces. *Contraception,* 2007; 75(6 supp): 548-50.
159. Audisio T, Pigini T, De Riutort et al Validity of the Papanicolaou Smear in the Diagnosis of Candida spp., Trichomonas vaginalis, and Bacterial Vaginosis. *J Low Genit Tract Dis*, 2001, 5: 223-5.
160. Occhino J, Smith K, Dryfhout V et al Incidental finding of Vaginitis on Liquid-Based Papanicolaou Test Compared to Wet Mount and DNA Probe. *J Gynaecol Surg,* Sept 2008, 24(3): 93-100.
161. Fitzhugh VA, Heller DS. Significance of a diagnosis of microorganisms on Pap Smear. *J Low Genit Tract Dis*, 2008, 12(1): 40-51.
162. Aslan DL, Pambuccian SE, Prekker FL et al Accuracy of Herpes Simplex virus detection in Liquid-based (Sure Path) Papanicolaou tests: a comparison with polymerase chain reaction. *Diagn. Cytopathol.*, 2008, 36 (2): 94-103.
163. Martin-Hirsch PL, Paraskevaidis E, Kitchener H. *Cochrane Database of Systematic Reviews [Computer File]*, 2000(2): CD001318.
164. Dey P, Gibbs A, Arnold DF et al. Loop diathermy excision compared with cervical laser vaporisation for the treatment of intraepithelial neoplasia: a randomised controlled trial. *Brit J Obstet Gynaecol*, 2002, 109 (4): 381–385.
165. Ostor AG. Natural history of cervical intraepithelial neoplasia: a critical review. *Int J Gynecol Pathol.* 1993, 12(2):186-92.
166. Legood R, Smith M, Lew JB et al. Cost effectiveness of human papillomavirus test of cure after treatment for cervical intraepithelial neoplasia in England: economic analysis from NHS Sentinel Sites Study. *BMJ,* 2012, 345.
167. Anderson MC. Invasive carcinoma of the cervix following local destructive treatment for cervical intraepithelial neoplasia. *Br J Obstet Gynaecol*, 1993, 100(7): 657–663.
168. Shumsky AG, Stuart GC, Nation J. Carcinoma of the cervix following conservative management of cervical intraepithelial neoplasia. *Gynecol Oncol*, 1994, 53(1): 50–54.
169. Duncan ID. Cold coagulation. Baillière's Clinical Obstetrics and Gynaecology, 1995, 9: 145–155.
170. Loobuyck HA, Duncan ID. Destruction of CIN 1 and 2 with the Semm cold coagulator: 13 years' experience with a see-and-treat policy. Br J Obstet Gynaecol, 1993, 100: 465–468.
171. Gordon HK, Duncan ID. Effective destruction of cervical intraepithelial neoplasia (CIN) 3 at 100°C using the Semm cold coagulator: 14 years' experience. Br J Obstet Gynaecol, 1991, 98: 14–20.

172. Zawislak A, Price JH, McClelland HR, Storey RGN, Caughley L. Efficacy of cervical intraepithelial neoplasia (CIN) treatment by cold coagulation. Ulster Medical Journal, 2003, 72; 10-15.
173. Ostergard DR. Cryosurgical treatment of cervical intraepithelial neoplasia. *Obstetrics & Gynecology,* 1980, 56(2): 231–233.
174. Walton LA, Edelman DA, Fowler WC Jr, Photopulos GJ. Cryosurgery for the treatment of cervical intraepithelial neoplasia during the reproductive years. *Obstetrics & Gynaecology,* 1980, 55(3): 353–357.
175. Creasman WT, Hinshaw WM, Clarke-Pearson DL. Cryosurgery in the management of cervical intraepithelial neoplasia. *Obstetrics & Gynecology*, 1984, 63(2): 145–149.
176. Schantz, A, Thormann L. Cryosurgery for dysplasia of the uterine ectocervix. A randomized study of the efficacy of the single- and double-freeze techniques. *Acta Obstetricia et Gynecologica Scandinavica*, 1984, 63(5): 417–420.
177. Anderson MC, Hartley RB. Cervical crypt involvement by intraepithelial neoplasia. *Obstet Gynecol*, 1980, 55(5): 546–550.
178. Boonstra H, Aalders JG, Koudstaal J et al. Minimum extension and appropriate topographic position of tissue destruction for treatment of cervical intraepithelial neoplasia. *Obstet Gynecol*, 1990, 75(2): 227–231.
179. Ghaem-Maghami S, Sagi S, Majeed G et al. Incomplete excision of cervical intraepithelial neoplasia and risk of treatment failure: a meta-analysis. *Lancet Oncol*, 2007; 8: 985-93.
180. Ghaem-Maghami S, De-Silva D, Tipples M et al. Determinants of success in treating cervical intraepithelial neoplasia. *Br J Obstet Gynaecol,* 2011, 118: 679-684.
181. Khalid S, Dimitriou E, Conroy R et al. The thickness and volume of LLETZ specimens can predict the relative risk of pregnancy-related morbidity. *Br J Obstet Gynaecol,* 2012,119: 685-691.
182. TOMBOLA group. Cytological surveillance compared with immediate referral for colposcopy in management of women with low grade cervical abnormalities: multicentre randomised controlled trial*. BMJ*, 2009, 339: b2546.
183. Murdoch JB, Morgan PR, Lopes A, Monaghan JM. Histological incomplete excision of CIN after large loop excision of the transformation zone (LLETZ) merits careful follow up, not retreatment. *British Journal of Obstetrics & Gynaecology*, 1992, 99(12): 990–993.
184. Dobbs SP. Asmussen T, Nunns D et al. Does histological incomplete excision of cervical intraepithelial neoplasia following large loop excision of transformation zone increase recurrence rates? A six year cytological follow up. *British Journal of Obstetrics & Gynaecology*, 2000, 107(10): 1298–1301.
185. Zaitoun AM, McKee G, Coppen MJ et al. Completeness of excision and follow up cytology in patients treated with loop excision biopsy. *Journal of Clinical Pathology*, 2000, 53(3): 191–196.
186. Flannelly G, Bolger B, Fawzi H et al. Follow up after LLETZ: could schedules be modified according to risk of recurrence? *British Journal of Obstetrics & Gynaecology*, 2001, 108(10): 1025–1030.

187. Chang DY, Cheng WF, Torng PL et al. Prediction of residual neoplasia based on histopathology and margin status of conization specimens. *Gynecol Oncol*, 1996, 63: 53–6.
188. Winter R. Conservative surgery for microinvasive carcinoma of the cervix. *Journal of Obstetrics & Gynaecology Research*, 1998, 24(6): 433–436.
189. Jackson SR, Hollingworth TA, Anderson MC et al. Glandular lesions of the cervix-cytological and histological correlation. *Cytopathology*, 1996, 7(1):10–16.
190. Laverty CR, Farnsworth A, Thurloe J, Bowditch R. The reliability of a cytological prediction of cervical adenocarcinoma in situ. Aust N Z J Obstet Gynaecol, 1988, 28(4): 307–312.
191. Williams AR.Liquid-based cytology and conventional smears compared over two 12-month periods. *Cytopathology*. 2006, 17(2): 82-5.
192. Marise AR, Moreira R, Longatto Filho A, et al How accurate is cytological diagnosis of cervical glandular lesions? *Diagnostic Cytopathology.* 200836(4): 270-274.
193. Mohammed DK, Lavie O, de B Lopes A, et al. A clinical review of borderline glandular cells on cervical cytology. *BJOG*, 2000 107(5): 605-9.
194. Lickrish GM, Colgan TJ, Wright VC. Colposcopy of adenocarcinoma in situ and invasive adenocarcinoma of the cervix. *Obstet Gynecol Clin North Am*, 1993, 20(1):111–122.
195. Ostor AG, Duncan A, Quinn M, et al. Adenocarcinoma in situ of the uterine cervix: an experience with 100 cases. *Gynecol Oncol*, 2000, 79(2): 207–210.
196. Ullal, A. Roberts M, Bulmer JN et al. The role of cervical cytology and colposcopy in detecting cervical glandular neoplasia. *Cytopathology,* 20(6): 359-366.
197. Waddell CA. Glandular abnormalities: dilemmas in cytological prediction and clinical management. *Cytopathology*, 1997, 8(1): 27–30.
198. Talaat A, Brinkmann D, Dhundee J, et al. Risk of significant gynaecological pathology in women with ?glandular neoplasia on cervical cytology. *Cytopathology*. 2011, doi: 10.1111/j.1365-2303.2011.00891.x.
199. Valente PT, Schantz HD, Schultz M. Cytologic atypia associated with microglandular hyperplasia. *Diagn Cytopathol,* 1994, 10(4): 326–331.
200. Lee KR, Manna EA, St John T. Atypical endocervical glandular cells: accuracy of cytologic diagnosis. *Diagn Cytopathol*, 1995, 13(3): 202–208.
201. Shafi MI, Luesley DM, Jordan JA et al. Randomised trial of immediate versus deferred treatment strategies for the management of minor cervical cytological abnormalities. *Br J Obstet Gynaecol*, 1997, 104: 590–594.
202. The Bethesda System for reporting cervical/ vaginal cytologic diagnoses: revised after the second National Cancer Institute Workshop, April 29–30, 1991. *Acta Cytol*, 1993, 37(2): 115–124.
203. Korn AP, Judson PL, Zaloudek CJ. Importance of atypical glandular cells of uncertain significance in cervical cytologic smears. *J Reprod Med*, 1998, 43(9): 774–778.

204. Zweizig S, Nollar K, Reale F et al. Neoplasia associated with atypical glandular cells of undetermined significance on cervical cytology. *Gynecol Oncol*, 1997, 65(2): 314–318.
205. Jadoon BA, Kehoe S, Romain K, et al. Analysis of outcome in women with borderline glandular change on cervical cytology. *Eur J Obstet Gynecol Reprod Biol.,* 2009, 147(1): 83-5.
206. Patel A, Thampy N, Hemming D, et al. A clinical review of borderline glandular cells reported on liquid-based cervical cytology. *BJOG,* 2010, 117(9): 1051-59.
207. National Coordinating Network (National Cervical Screening Programme), British Society for Clinical Cytology, and Royal College of Pathologists' Working Party. Borderline nuclear changes in cervical smears: guidelines on their recognition and management.. *J Clin Pathol*, 1994, 47(6): 481–492.
208. Siebers AG, Verbeek ALM, Massuger LF et al. Normal appearing endometrial cells in cervical smears of asymptomatic postmenopausal women have predictive value for significant endometrial pathology. *International Journal of Gynecological Cancer*, 2006, 16: 1069–1074.
209. Saad RS, Takei H, Liu YL et al. Clinical significance of a cytologic diagnosis of atypical glandular cells, favor endometrial origin, in Pap. smears. *Acta Cytologica,* 2006, 50(1): 48–54.
210. Chhieng DC, Elgert P, Cohen JM et al. Clinical implications of atypical glandular cells of undetermined significance, favour endometrial origin. *Cancer*, 2001, 93: 351–356.
211. Luesley DM, Jordan JA, Woodman CB et al. A retrospective review of adenocarcinoma in situ and glandular atypia of the uterine cervix. *Br J Obstet Gynaecol*, 1987, 94(7): 699–703.
212. Cullimore JE, Luesley DM, Rollason TP et al. A prospective study of conization of the cervix in the management of cervical intraepithelial glandular neoplasia (CIGN): preliminary report. Br J Obstet Gynaecol, 1992, 99(4): 314–318.
213. DeSimone CP, Day ME, Dietrich CS et al. Risk for residual adenocarcinoma in situ or cervical adenocarcinoma in women undergoing loop electrosurgical excision procedure/conization for adenocarcinoma in situ. *J Reprod Med*, 2011, 56(9-10): 376-80.
214. Kim JH, Park JY, Kim DY, et al. The safety of conization in the management of adenocarcinoma in situ of the uterine cervix. *Eur J Obstet Gynecol Reprod Biol*, 2009, 145(1): 100-3.
215. Azodi M, Chambers SK, Rutherford TJ et al. Adenocarcinoma in situ of the cervix: management and outcome. *Gynecol Oncol*, 1999, 73(3): 348-53.
216. Denehy TR, Gregori CA, Breen JL. Endocervical curettage, cone margins, and residual adenocarcinoma in situ of the cervix. *Obstet Gynecol*, 1997, 90(1): 1-6.
217. Lea JS, Shin CH, Sheets EE, et al. Endocervical curettage at conization to predict residual cervical adenocarcinoma in situ. *Gynecol Oncol*,. 2002, 87(1):129-32.
218. *Histopathology Reporting in Cervical Screening* (NHSCSP Publication No 10). Second edition. Sheffield: NHS Cancer Screening Programmes, 2012.

219. Bertrand M, Lickrish GM, Colgan TJ. The anatomic distribution of cervical adenocarcinoma in situ: implications for treatment. *Am J Obstet Gynecol*, 1987, 157(1): 21–25.
220. Poyner EA, Barakat RR, Hoskins WJ. Management and follow up of patients with adenocarcinoma in situ of the uterine cervix. *Gynecol Oncol*, 1995, 57(2): 158–164.
221. Widrich T, Kennedy AW, Myers TM, Hart WR, Wirth S. Adenocarcinoma in situ of the uterine cervix: management and outcome. *Gynecol Oncol,* 1996, 61(3):304–308.
222. Colgan TJ, Lickrish GM. The topography and invasive potential of cervical adenocarcinoma in situ, with and without associated squamous dysplasia. *Gynecol Oncol*, 1990, 36(2): 246–249.
223. Teshima S, Shimosato Y, Kishi K, et al. Early stage adenocarcinoma of the uterine cervix. Histopathalogic analysis with consideration of histogenesis. *Cancer,* 1985, 56(1): 167–172.
224. Salani R, Puri I, Bristow RE.Adenocarcinoma in situ of the uterine cervix: a metaanalysis of 1,278 patients evaluating the predictive value of conization margin status. *Am J Obstet Gynecol*, 2009, 200(2):18.e1-5.
225. Nicklin JL, Wright RG, Bell JR, et al. A clinicopathological study of adenocarcinoma in situ of the cervix. The influence of cervical HPV infection and other factors, and the role of conservative surgery. *Aust N Z J Obstet Gynaecol,* 1991, 31(2): 179–183.
226. Roberts JM, Thurlow JK, Bowditch RC, et al. Subdividing atypical glandular cells of undetermined significance according to the Australian modified Bethesda system: analysis of outcomes. *Cancer*, 2000, 90(2): 87–95.
227. Hatch EE, Herbst AL, Hoover RN et al. Incidence of squamous neoplasia of the cervix and vagina in women exposed prenatally to diethylstilbestrol (United States). *Cancer Causes and Control,* 2001, 12: 837–45.
228. Strander B, Andersson-Ellström A, Milsom I et al. Long term risk of invasive cancer after treatment for cervical intraepithelial neoplasia grade 3: population based cohort study cervical intraepithelial neoplasia grade 3. *BMJ*, 2007, 335(7629): 1077.
229. Andersen ES, Nielsen K, Larsen G. Laser conization: follow up in patients with cervical intraepithelial neoplasia in the cone margin. *Gynecol Oncol*, 1990, 39: 328–31.
230. Andersen ES, Pedersen B, Nielsen K. Laser conization: the results of treatment of cervical intraepithelial neoplasia. *Gynecol Oncol*, 1994, 54: 201–204.
231. Gardeil F, Barry-Walsh C, Prendiville W et al. Persistent intraepithelial neoplasia after excision for cervical intraepithelial neoplasia grade III. *Obstet Gynecol*, 1997, 89: 419–422.
232. Gold M, Dunton CJ, Murray J et al. Loop electrocautery excisional procedure: therapeutic effectiveness as an ablation and a conization equivalent. *Gynecol Oncol*, 1996, 61: 241–244.
233. Lopes A, Morgan P, Murdoch J et al. The case for conservative management of 'incomplete excision' of CIN after laser conization. *Gynecol Oncol*, 1993 49: 247–249.

234. Moore BC, Higgins RV, Laurent SL et al. Predictive factors from cold knife conization for residual cervical intraepithelial neoplasia in subsequent hysterectomy. *Am J Obstet Gynecol*, 1995, 173: 361–6 (discussion 366–8).
235. Lapaquette TK, Dinh TV, Hannigan EV et al. Management of patients with positive margins after cervical conization. *Obstet Gynecol*, 1993, 82: 440–443.
236. Paterson-Brown S, Chappatte OA, Clark SK et al. The significance of cone biopsy resection margins. *Gynecol Oncol*, 1992, 46: 182–185.
237. Paraskevaidis E, Lolis ED, Koliopoulos G et al. Cervical intraepithelial neoplasia outcomes after large loop excision with clear margins. *Obstet Gynecol*, 2000, 95: 828–831.
238. Nobbenhuis MA, Meijer CJ, van den Brule AJ et al. Addition of high-risk HPV testing improves the current guidelines on follow up after treatment for cervical intraepithelial neoplasia. Br J Cancer, 2001; 84: 796–801.
239. Soutter WP, Sasieni P, Panoskaltsis T. Long-term risk of invasive cervical cancer after treatment of squamous cervical intraepithelial neoplasia. Int J Cancer, 2006; 118: 2048–2055.
240. Kitchener H, Walker P, Nelson L et al. HPV testing as an adjunct to cytology in the follow up of women treated for cervical intraepithelial neoplasia. BJOG, 2008; 15(8): 1001–1007.
241. Results from the Test of Cure Study, personal communication Professor Kitchener 2011.
242. Zielinski GD, Bais AG, Helmerhorst ThJ, Verheijen RHM, de Schipper FA, Snijders PJF, Voorhorst FJ, van Kemenade FJ, Rozendaal L, Meijer CJLM. HPV testing and monitoring of women after treatment of CIN3: review of the literature and meta-analysis. Obstet and Gynecol Surv. 2004, 59: 543-533.
243. Kocken M, Helmerhorst TJM, Berkhof J, et al. Risk of recurrent high-grade cervical intraepithelial neoplasia after successful treatment: a long-term multi-cohort study. *The Lancet Oncology,* 2011; 12(5):441-450.
244. Gemmell J, Holmes DM, Duncan ID. How frequently need vaginal smears be taken after hysterectomy for cervical intraepithelial neoplasia? Br J Obstet Gynaecol, 1990, 97: 58–61.
245. Burghardt E, Holzer E. Treatment of carcinoma in situ: evaluation of 1609 cases. Obstet Gynecol, 1980, 55: 539–545.
246. Mitchel MF, Schottenfeld D, Tortolero-Luna G et al. Colposcopy for the diagnosis of squamous intraepithelial lesions: a meta-analysis. Obstet Gynecol, 1998, 91(4): 626–631.
247. DiBonito L, Falconieri G, Bonifacio-Gori D. Multicentric papillomavirus infection of the female genital tract. A study of morphologic pattern, possible risk factors and viral prevalence. Pathol Res Pract, 1993, 189(9): 1023–1029.
248. Soost HJ, Lange H, Lehmacher W, Ruffing-Kullman B. The validation of cervical cytology. Sensitivity, specificity and predictive values. Acta Cytol, 1991, 35(1): 8–14.

249. Hellberg D, Nilsson S, Valentin J. Positive cervical smear with subsequent normal colposcopy and histology –frequency of CIN in a long-term follow up. Gynecol Oncol, 1994, 53(2): 148–151.
250. Milne DS, Wadehra V, Mennim D, Wagstaff TI. A prospective follow up study of women with colposcopically unconfirmed positive cervical smears. Br J Obstet Gynaecol, 1999, 106: 38–41.
251. DiBonito L, Falconieri G, Tomasic G et al. Cervical cytopathology. An evaluation of its accuracy based on cytohistologic comparison. Cancer, 1993, 72(10): 3002–3006.
252. Teale GR, Moffitt DD, Mann CH, Luesley DM. Management guidelines for women with normal colposcopy after low grade cervical abnormalities: population study. BMJ, 2000, 320: 1693–1696.
253. Coppola A, Sorossky J, Casper R et al. The clinical course of cervical carcinoma in situ diagnosed during pregnancy. *Gynecol Onco*, 1997, 67: 162–165.
254. Palle C, Bangsboll S and Andreasson B. Cervical intraepithelial neoplasia in pregnancy. *Acta Obstet et Gynecol*, 2000, 79: 306–310.
255. Woodrow N, Permezel M, Butterfield L et al. Abnormal cytology in pregnancy. *Austral & NZ J of Obstet Gynaecol*, 1998, 38: 161–165.
256. Nevin J, Soeters, Dehaeck et al. Cervical carcinoma associated with pregnancy. *Obstet & Gynecol Survey*, 1995, 50: 228–239.
257. Pettersson BF, Hellman K, Vaziri R, et al. Cervical cancer in the screening era: who fell victim in spite of successful screening programs?. *Journal of Gynecologic Oncology*, 2011; 22(2): 76-82.
258. Wetta LA, Matthews KS, Kemper ML, et al. The management of cervical intraepithelial neoplasia during pregnancy: is colposcopy necessary?.*JLGTD,* 2009*,* 13(3): 182-5.
259. Dunn TS, Bajaj JE, Stamm CA et al. Management of the minimally abnormal papanicolaou smear in pregnancy. *Journal of Lower Genital Tract Disease,* 2001, 5(3): 133-7.
260. Ackermann S, Gehrsitz C, Mehlhorn G and Beckmann MW. Management and course of histologically verified cervical carcinoma in situ during pregnancy. *Acta Obstetrica et Gynecologica,* 2006, 85(9): 1134-7.
261. Everson JA, Stika CS and Lurain JR. Postpartum evolution of cervical squamous intraepithelial lesions with respect to the route of delivery. *JLGTD*, 2002, 6(4): 212-7.
262. Lapolla IP, O'Neill C, Wetrich DJ. Colposcopic management of abnormal cervical cytology in pregnancy. *Reprod Med*, 1988, 33: 301–306.
263. Robinson WR, Webb S, Tirpack J et al. Management of cervical intraepithelial neoplasia during pregnancy with loop excision. *Gynecol Oncol*, 1997, 64(1): 153–155.
264. Dunn, T S. Bajaj, J E. Stamm, C A. et al. Management of the minimally abnormal papanicolaou smear in pregnancy. *Journal of Lower Genital Tract Disease,* 2001, 5(3): 133-7.
265. International Collaboration of Epidemiological Studies of Cervical Cancer. Cervical cancer and hormonal contraceptives: collaborative reanalysis of individual data for

16,573 women with cervical cancer and 35,509 women without cervical cancer from 24 epidemiological studies. *Lancet,* 2007,370: 1609-1621.
266. Clarke EA, Hatcher J, McKeown-Eyssen GE, Lickrish GM. Cervical dysplasia: association with sexual behaviour, smoking and oral contraceptive use? *Am J Obstet Gynecol*, 1985, 151(5): 612–616.
267. Ylitalo N, Sorensen P, Josefsson A et al. Smoking and oral contraceptives as risk factors for cervical carcinoma in situ. *Int J Cancer*, 1999, 81(3): 357–365.
268. Cibula D, Gompel A, Mueck AO, La Vecchia C, Hannaford PC, Skouby SO, Zikan M and Dusek L. Hormonal contraception and risk of cancer. *Human Reproduction Update,* 2010, 16(6): 631-50.
269. Gorenoi V. Schonermark MP. Hagen A. Benefits and risks of hormonal contraception for women. *GMS Health Technology Assessment,* 2007, 3.
270. Vessey M, Yeates D and Flynn S. Factors affecting mortality in a large cohort study with special reference to oral contraceptive use. *Contraception*, 2010, 82(3): 221-9.
271. Smith JS, Green J, Berrington de Gonzalez A et al. Cervical cancer and use of hormonal contraceptives: a systematic review. *Lancet*, 2003, 361: 1159-1167.
272. Hogewoning CJ, Bleeker MC, van den Brule AJ, et al. Condom use promotes regression of cervical intraepithelial neoplasia and clearance of human papillomavirus: a randomized clinical trial. *International Journal of Cancer,* 2003, 107(5): 811-6.
273. Manhart LE. Koutsky LA. Do condoms prevent genital HPV infection, external genital warts, or cervical neoplasia? A meta-analysis. *Sexually Transmitted Diseases,* 2002, 29(11): 725-35.
274. Sawaya GF, Grady D, Kerlikowske K et al. The positive predicative value of cervical smears in previously screened postmenopausal women: the Heart and Estrogen/progestin Replacement Study (HERS). *Am Intern Med*, 2000, 133(12): 942–950.
275. Parazzini F, La Vecchia C, Negri E et al. Case-control study of oestrogen replacement therapy and risk of cervical cancer. *BMJ,* 1997, 315(7100): 85–88.
276. Cruickshank ME, Chambers G, Murray GI et al. *HPV Testing: Age Restricted Cervical Screening*. Sunderland: British Society for Colposcopy and Cervical Pathology, 1999.
277. Roman LD, Morris M, Eifel PJ et al. Reasons for inappropriate simple hysterectomy in the presence of invasive cancer of the cervix. *Obstet Gynecol*, 1992, 79(4): 485–489.
278. Chen RJ, Chang DY, Yen M et al. Independent clinical factors which correlate with failures in diagnosing early cervical cancer. *Gynecol Oncol*, 1995, 58(3): 356–361.
279. Mohamed-Noor K, Quinn MA, Tan J. Outcomes after cervical knife conisation with complete and incomplete excision of abnormal epithelium. *Gynecol Oncol*, 1997, 67(1): 34–38.
280. Schiffman M, Castle PE, Jeronimo J et al. Human papaillomavirus and cervical cancer. *Lancet,* 2007, 370: 890.

281. Ghazizadeh S, Lessan-Pezeshki M., Einollahi B et al. Uterine cervical intraepithelial neoplpasia in renal transplantation. *Transplant Proc*, 2001, 33: 2871.
282. Veroux M., Corona D., Scalia G., et al. Surveillance of Human Papilloma Virus infection and cervical cancer in kidney transplant recipients: preliminary data, *Transplant Proc,* 2009: 41: 1191-94.
283. Brown MR., Noffsinger A., First MR et al. HPV subtype analysis in lower genital tract neoplasms of the female renal transplant recipients*. Gynaecol Oncol,* 2000, 79: 22
284. Sheil PW, Daunter B, Wright RG. The pap smear revisited. *Aust NZJ Obstet Gynecol,* 1987, 27: 269-82.
285. Cochrane R., Regan L. Undetected gynaecological disorders in women with renal disease. *Hum Reprod,* 1997, 12(4): 667-670.
286. Ter Haar-Van Eck SA., Rischen-Vos J., et al. The incidence of cervical intraepithelial neoplasia among women with renal transplant in relation to cyclosporine. *Br J Obstet Gynaecol*, 1995, 102: 58-61.
287. Savani BN., Stratton P., Shenoy A et al. Increased incidence of cervical dysplasia in long term survivors of allogenic stem cell transplantation – implications for screening and HPV vaccination. *Biol Blood Marrow Transplant,* 2008, 14: 1072-75.
288. Curtis RE., Rowlings PA., Deeg HJ et al.Solid cancers after bone marrow transplantation. *N Engl J Med,* 1997, 336(13): 897-904.
289. Courtney AE., Leonard N., O'Neill CJ et al. The uptake of cervical cancer screening by renal transplant recipients. *Nephrol Dial Transp,* 2009, 24(2): 647-52.
290. Downey GP., Emery VC., Walker PG. A longitudinal study of human papillomavirus positivity in the development of lower genital intraepithelial neoplasia in immunosuppressed women. *Journal Of Lower Genital Tract Disease*, 1999; 3: 163-170.
291. Rizzo JD., Curtis RE., Socie G et al. Solid cancers after allogenic hematopoietic cell transplant. *Blood,* 2009, 113(5): 1175-83.
292. Bhatti S, Louie AD., Bhatia R et al. Solid cancers after bone marrow transplant. *J Clinical Oncol*, 2001, 19(2): 464-71.
293. Dhar JP, Kmak D, Bhan ., et al. Abnormal cervical cytology in women with lupus: a retrospective cohort study. *Gynecol Oncol,* 2001, 82(1): 4-6.
294. Nath R., Mant C., Luxton J et al. High risk of human papaillomavirus type 16 infections and the development of squamous epithelial lesions in systemic lupus erythematous patients. *Arthritis Rheum*, 2007, 57(4): 619-25.
295. Liu K., Marshall J., Shaw HS., et al. Effects of chemotherapy and tamoxifen on cervical and vaginal smears in bone marrow transplant recipients .*Acta Cytol,* 1999, 43(6): 1027-33.
296. Abadi MA, Barakat RR, Saigo PE. Effects of tamoxifen on cervico-vaginal smears from patients with breast cancer. *Acta Cytol,* 2000, 44(2): 141-146.
297. Schachter A, Kopmar Avram E, Gorodiski IG, et al. Hormonal and cytopathological changes in vaginal and cervical smears from women undergoing chemotherapy for extragenital malignant diseases. *Acta Obstet Gynecol Scand,* 1983, 62(6): 621-24.

298. Maiman M, Fruchter RG, Sedlis A et al. Prevalence, risk factors, and accuracy of cytologic screening for cervical intraepithelial neoplasia in women with the human immunodeficieny virus. *Gynecol Oncol*, 1998, 68: 233–239.
299. Schiffman M, Brinton LA. The epidemiology of cervical carcinogenosis. *Cancer*, 1995, 76: 1888–1901.
300. Wright TC Jr, Koulas J, Schnoll F et al. Cervical intraepithelial neoplasia in women infected with human immunodeficiency virus: prevalence, risk factors and validity of papanicolaou smears. *Obstet Gynecol*, 1994, 84: 591–597.
301. Smith JR, Kitchen VS, Botcherby M et al. Is HIV infection associated with an increase in the prevalence of cervical neoplasia? *BJOG*, 1993, 100(2): 149–!53.
302. Schaffer A et al. The increased frequency of cervical dysplasia-neoplasia in women infected with human immunodeficiency virus is related to the degree of immunosuppression. *Am J Obstet Gynecol*, 1994, 164: 593–599.
303. Mandelblatt JS, Fahs M, Garibaldi K et al. Association between HIV infection and cervical neoplasia: implication for clinical care of women at risk of both conditions. *AIDS*, 1992, 6: 173–178.
304. Ellerbrock TV, Chiasson MA, Bush TJ et al. Incidence of cervical squamous intraepithelial lesions in HIV infected women. *JAMA*, 2000, 283: 1031–1037.
305. Heard I, Bergeron C, Jeannel D et al. Papanicolaou smears in human immunodeficiency virus-seropositive women during follow up. *Obstet Gynecol*, 1995, 85: 749–753.
306. Fruchter RG et al. Multiple recurrences of cervical intraepithelial neoplasia in women with the human immunodeficiency virus. *Obstet Gynecol*, 1996, 87: 338–344.
307. Heard I, Schmitz V, Costagliola D et al. Early regression of cervical lesions in HIV seropositive women receiving highly active with retroviral therapy. *AIDS*, 1998, 12:1459–1464.
308. Kitchener H, Nelson L, Adams J, Mesher D et al on behalf of the MACH-1 Group. Colposcopy is not necessary to assess the risk to the cervix in HIV-positive women: an international cohort study of cervical pathology in HIV-1 positive women. *International Journal of Cancer*, 2007, 121(11): 2484–2491.