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The research reported in this issue of the journal was commissioned by the HTA programme as project number 98/04/64. The contractual start date was in June 2001. The draft report began editorial review in February 2008 and was accepted for publication in March 2009. As the funder, by devising a commissioning brief, the HTA programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

ARTISTIC: a randomised trial of human papillomavirus (HPV) testing in primary cervical screening

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Objectives: Primary cervical screening uses cytology to detect cancer precursor lesions [cervical intraepithelial neoplasia stage 3 or beyond (CIN3+)]. Human papillomavirus (HPV) testing could add sensitivity as an adjunct to cytology or as a first test, reserving cytology for HPV-positive women. This study addresses the questions: Does the combination of cytology and HPV testing achieve a reduction in incident CIN3+?; Is HPV testing cost-effective in primary cervical screening?; Is its use associated with adverse psychosocial or psychosexual effects?; and How would it perform as an initial screening test followed by cytology for HPV positivity?
Design: ARTISTIC was a randomised trial of cervical cytology versus cervical cytology plus HPV testing, evaluated over two screening rounds, 3 years apart. Round 1 would detect prevalent disease and round 2 a combination of incident and undetected disease from round 1.
Setting: Women undergoing routine cervical screening in the NHS programme in Greater Manchester.
Participants: In total 24,510 women aged 20–64 years were enrolled between July 2001 and September 2003.
Interventions: HPV testing was performed on the liquid-based cytology (LBC) sample obtained at screening. Women were randomised in a ratio of 3:1 to have the HPV test result revealed and acted upon if persistently positive in cytology-negative cases or concealed. A detailed health economic evaluation and a psychosocial and psychosexual assessment were also performed.
Main outcome measures: The primary outcome was CIN3+ in round 2. Secondary outcomes included an economic assessment and psychosocial effects. A large HPV genotyping study was also conducted.
Results: In round 1 there were 313 CIN3+ lesions, representing a prevalence in the revealed and concealed arms of 1.27% and 1.31% respectively ($p = 0.81$). Round 2 (30–48 months) involved 14,230 (58.1%) of the women screened in round 1 and only 31 CIN3+ were detected; the CIN3 rate was not significantly different between the revealed and concealed arms. A less restrictive definition of round 2 (26–54 months) increased CIN3+ to 45 and CIN3+ incidence in the arms was significantly different ($p = 0.05$). There was no difference in CIN3+ between the arms when rounds 1 and 2 were combined. Prevalence of high-risk HPV types was age-dependent. Overall prevalence of HPV16/18 increased with severity of dyskaryosis. Mean costs per woman in round 1 were £72 and £56 for the revealed and concealed arms ($p < 0.001$); an age-adjustment reduced these mean costs to £65 and £52. Incremental cost-effectiveness ratio for detecting additional CIN3+ by adding HPV testing to LBC screening in round 1 was £38,771. Age-adjusted mean cost for LBC primary screening with HPV triage was

£39 compared with £48 for HPV primary screening with LBC triage. HPV testing did not appear to cause significant psychosocial distress.
Conclusions: Routine HPV testing did not add significantly to the effectiveness of LBC in this study. No significant adverse psychosocial effects were detected. It would not be cost-effective to screen with cytology and HPV combined but HPV testing, as either triage or initial test triaged by cytology, would be cheaper than cytology without HPV testing. LBC would not benefit from combination with HPV; it is highly effective as primary screening but HPV testing has twin advantages of high negative predictive value and automated platforms enabling high throughput. HPV primary screening would require major contraction and reconfiguration of laboratory services. Follow-up continues in ARTISTIC while maintaining concealment for a further 3-year round of screening, which will help in screening protocol development for the post-vaccination era.

Contents

List of abbreviations

ARTISTIC	A Randomised Trial In Screening To Improve Cytology
BMS	biomedical scientist
CGIN	cervical glandular intraepithelial neoplasia
CI	confidence interval
CIN	cervical intraepithelial neoplasia
CIN2+	any lesion of CIN2 or worse
CIN3+	any lesion of CIN3 or worse
CM&MC	Central Manchester and Manchester Children's Hospital
CSP	cervical screening programme
DNA	deoxyribonucleic acid
FPC	family planning clinic
GHQ	General Health Questionnaire
GP	general practitioner
HC2	Hybrid Capture 2
HPV	human papillomavirus
HPV 5 HR types	HPV16+ and/or HPV18+ and/or HPV31+ and/or HPV33+ and/or HPV45+
HPV +ve	positive result using HC2 at a cut-off of ≥1 RLU/Co
HPV –ve	negative HC2 result
HR-HPV	high-risk human papillomavirus
HSIL	high-grade squamous intraepithelial lesion
ICER	incremental cost-effectiveness ratio
IQR	interquartile range
LA	Linear Array
LBA	line blot assay
LBC	liquid-based cytology
LLETZ	large loop excision of the transformation zone
LSHTM	London School of Hygiene and Tropical Medicine
LSIL	low-grade squamous intraepithelial lesion
MCC	Manchester Cytology Centre
MRI	Manchester Royal Infirmary
NHSCSP	National Health Service Cervical Screening Programme
NICE	National Institute for Health and Clinical Excellence
OD	optical density
PCR	polymerase chain reaction
QALY	quality adjusted life-year
QARC	Quality Assurance Reference Centre
RLU	relative light unit
RLU/Co	relative light unit/mean control
RNA	ribonucleic acid
SA-HRP	streptavidin–horseradish peroxidase
SD	standard deviation
SRS	Sexual Rating Scale
STAI	Spielberger State–Trait Anxiety Inventory
TMB	tetramethylbenzidene
TTO	time trade-off
VAT	value added tax
WNL	within normal limits

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Objectives

Primary cervical screening is currently based on using cervical cytology to detect cancer precursor lesions. Human papillomavirus (HPV) testing could add sensitivity to the detection of these lesions [cervical intraepithelial neoplasia stage 3 or beyond (CIN3+)] either as an adjunct to cytology, or as a first test with cytology reserved for women who are HPV positive. We aimed to answer the following principal questions:

- Do cytology and HPV testing combined achieve a reduction in incident CIN3+ by detecting significantly more prevalent disease?
- Is the use of HPV testing cost-effective in primary cervical screening?
- Is HPV testing in primary cervical screening associated with adverse psychosocial or psychosexual effects?
- How would HPV perform as an initial screening test followed by cytology for HPV positivity?

Design

ARTISTIC was a randomised trial of cervical cytology versus cervical cytology plus HPV testing, evaluated over two screening rounds, 3 years apart. Round 1 would detect prevalent disease and round 2 a combination of incident and undetected disease from round 1.

Setting

Women undergoing routine cervical screening in the NHS programme were recruited in general practices and family planning clinics in Greater Manchester.

Participants

In total 24,510 women aged 20–64 years were enrolled between July 2001 and September 2003.

Interventions

HPV testing was performed on the liquid-based cytology (LBC) sample obtained at screening. Women were randomised in a ratio of 3 : 1 either to have the HPV test result revealed and acted upon if persistently positive in cytology-negative cases, or concealed from the woman, her doctor and the investigators. In addition, a detailed health economic evaluation and a psychosocial and psychosexual assessment were performed.

Main outcome measures

The primary outcome was CIN3+ in round 2. Secondary outcomes included an economic assessment and psychosocial effects. We have also conducted a large HPV genotyping study.

Results

In round 1 there were a total of 313 CIN3+ lesions representing a prevalence in the revealed and concealed arms of 1.27% and 1.31% respectively ($p = 0.81$). Round 2 involved 14,230 women (58.1%) of those screened in round 1. In round 2, (30–48 months) only 31 CIN3+ were detected and although the CIN3 rate was lower in the revealed arm (0.18% revealed versus 0.34% concealed; $p = 0.09$), this was not statistically significant. A less restrictive definition of round 2, (26–54 months) increased the CIN3+ numbers in round 2 from 31 to 45, with a statistically significant reduction in CIN3+ incidence in the revealed arm (0.24% revealed versus 0.41% concealed; $p = 0.05$). There was no difference in CIN3+ between the arms when round 1 and 2 were combined (1.45% revealed versus 1.65% concealed; $p > 0.1$). Among 2226 women who screened as cytology negative and HPV positive in round 1, 32 CIN2+ lesions were detected among the 1657 women in the revealed arm as a consequence of adjunctive HPV testing. This resulted in a lower CIN2+ rate in the revealed arm in round 2 (30–48 months; 1.92% versus 3.99%; $p = 0.06$), which just failed to reach significance.

The prevalence of high-risk types was highly age-dependent: 27.9% in women aged 25–29 years compared with 6.5% at age 50–64 years. The overall prevalence of HPV type 16 and/or type 18 in borderline, mild, moderate and severe dyskaryosis was 10.0%, 22.0%, 46.8% and 62.4% respectively. Type-specific viral persistence rates declined from over 80% after 6 months to 20–25% after 48 months.

Mean (SD) costs per woman (covering screening and colposcopy-related events) in round 1 were £72 (£175), [95% confidence interval (95% CI), £70 to £75] for the revealed arm and £56 (£178), (95% CI, £52 to £60) for the concealed arm ($p < 0.001$). Costs were age-dependent, so an age-adjustment based on the age profile for the national screening programme reduced the mean costs to £65 and £52 respectively. The incremental cost-effectiveness ratio for detecting an additional CIN3+ by the addition of HPV testing to LBC screening in round 1 was £38,771. The experiences of revealed women in round 1 informed the development of alternative screening policies with simplified management protocols. An age-adjusted mean cost for LBC primary screening with HPV triage was £39 compared with £48 for HPV primary screening with LBC triage, the main influence on the costs being the rates of referral for colposcopy.

HPV testing did not appear to cause significant psychosocial distress.

Conclusions

Routine HPV testing did not add significantly to the effectiveness of LBC in this study. The use of LBC was associated with an unexpectedly low number of CIN3+ lesions in round 2, suggesting an increase in sensitivity compared to conventional cytology. No significant adverse psychosocial effects were detected, which is reassuring for the wider use of HPV testing. It is clear that it would not be cost-effective to screen with cytology and HPV combined but there was evidence that HPV testing, either as a triage or as an initial test triaged by cytology, would be cheaper than the current use of cytology without HPV testing.

The introduction of HPV vaccination against types 16/18 for 12- to 13-year-old girls in 2008 will reduce the risk of the most severe abnormalities in vaccinees by 65% but only 10–20% of low-grade cytological abnormalities will be prevented.

The ARTISTIC findings suggest that LBC, which has been implemented countrywide, would not benefit from combined testing with HPV. While LBC is highly effective as primary screening, HPV testing has the twin advantages of a high negative predictive value, which should allow longer screening intervals, and automated platforms enabling high throughput. HPV primary screening would have a major impact on the volume of cytology, which would require major contraction and reconfiguration of laboratory services.

Further research

There is a need to confirm from other UK laboratories, the finding in the ARTISTIC cohort of a very low incidence of CIN3+ in subsequent screening rounds of women previously screened with LBC. This would suggest that LBC in the quality-assured setting of the NHS can indeed achieve a greater degree of sensitivity than hitherto recognised.

The ARTISTIC trial is continuing to follow up women while maintaining the randomised concealment of HPV testing results for a further 3-year round of screening. This will allow evaluation of the risk of developing cytological abnormalities in type-specific HPV-positive and HPV-negative women over a 6-year interval, which will be important in developing screening protocols for the post-vaccination era, when the case for initial HPV testing with cytology triage will become stronger. The 6-year follow-up will also provide data on the relative protection of a negative cytology and negative hybrid capture 2 over 6 years in different age ranges.

Chapter 1
Introduction

Cervical screening in the English NHS Programme

Current design

The purpose of the National Health Service Cervical Screening Programme (NHSCSP) is to reduce cervical cancer incidence and mortality. Currently all women in England aged between 25 and 64 years are invited to attend for a cytology sample – a sampling of exfoliated cervical cells, formerly known as a 'smear test' – every 3 years between the ages of 25 and 49, and every 5 years between the ages of 50 and 64. The rationale of cervical screening is based on the detection of preinvasive lesions known as cervical intraepithelial neoplasia (CIN). These lesions precede the development of invasive disease, usually by many years, and offer the opportunity of detection and treatment before the development of cancer. Treatment of CIN involves excision or ablation of disease. Treatment is highly effective in preventing cancer[1] and generally preserves reproductive potential. The National Screening Committee's criteria for appraising the viability, effectiveness and appropriateness of a screening programme are included for reference (Appendix 1).

Two important developments in the screening programme have occurred in the last 3 years. The first was the introduction of liquid-based cytology (LBC), and the second was that the age at which women were initially invited for screening was increased from 20 to 25 and the screening interval was reduced from 5-yearly to 3-yearly for women aged 25 to 49. The reasons for these changes were:

- to avoid ineffective screening among 20- to 24-year-olds in whom over 400,000 samples per year were being read in an age range in which there were fewer than 50 cancers/year (this screening resulted in large numbers of low-grade abnormalities with the potential that overtreatment would do more harm than good)
- epidemiological data from the NHSCSP had demonstrated that in younger women, 3-yearly cytology was required to maintain the necessary level of protection.[2]

Effectiveness

Although no randomised trials of cervical cytology as a means of secondary prevention have been performed, there is convincing evidence from disease-incidence rates in countries that have achieved systematic screening to demonstrate that cytology screening is effective. Wide population coverage is essential for a successful programme. In the UK, cervical screening was essentially opportunistic until 1988 with little impact on disease rates. Following the introduction of a systematic computerised call/recall system that issued invitations to every eligible woman at regular intervals, there has been an increase in coverage from 40% to over 80%,[3] and a 50% reduction in disease incidence between 1988 and 2004. This has been accompanied by a fall in deaths UK-wide from 2000 per year to around 1000 per year when a continuing increase would have been expected from the increasing trend in mortality in younger women since the 1960s.[4] Furthermore, screening has led to a higher proportion of cancer being discovered sufficiently early that fertility can be preserved.

This success disguises the fact that a proportion of women who undergo screening develop interval cancers even if they comply with regular tests. The most common reason for such screening failure is inadequate sampling, but reading errors account for a proportion of cases. Internationally the sensitivity of cervical screening to detect CIN2 or greater has been estimated to be between 30% and 80%,[5] but this is dependent on the quality assurance systems in place. The UK has one of the best programmes in the world with strict national quality assurance and accreditation processes in place for every step of the pathway from sample taking to colposcopic management.

Human papillomavirus

Epidemiology

For 50 years cervical cancer has been considered to have an infectious aetiology, and it is now universally accepted that the necessary initial event is infection of the cervix by human papillomavirus (HPV).[6] There are over 100 types of HPV, of which a subset of around 20 have been associated with cervical cancer by virtue of the presence of HPV DNA being detectable in the cancer cells. Indeed, around 80% of cervical tumours worldwide are associated with types 16, 18, 31, 33 and 45, with type 16 being by far the most important, accounting for at least 50% of cases.[7]

The accepted model of tumour development involves infection by HPV as a result of sexual exposure, following which most women clear the infection. In a proportion of cases, however, integration of the HPV genome into the cervical cells and expression of the oncogenes E6 and E7 result in dysregulation of the cell cycle and malignant transformation. HPV infection is a necessary event for cervical carcinogenesis, but other promoters such as cigarette smoking increase the risk. The majority of women will acquire an HPV infection at some time, but only a minority will develop cervical cancer, which can therefore be regarded as an uncommon complication of HPV infection. This necessity for HPV in cervical carcinogenesis is demonstrated by the fact that viral DNA can be identified in almost 100% of cervical cancers.[6] Type-specific HPV DNA detection which persists over 1 or 2 years or more confers a very high relative risk (> 400 in one study),[8] when compared with women who were cytology negative (–ve) and HPV –ve. This is compelling evidence of an aetiological role requiring the persistent presence of HPV DNA before development of CIN3.

Potential uses of HPV testing

This scientific background suggests two important clinical applications. The first is a strategy of primary prevention through prophylactic HPV vaccination. This has become a reality with two recently published phase III trials[9,10] demonstrating that vaccines against HPV16 and HPV18 can prevent the development of type-16-associated and type-18-associated high-grade CIN. A UK-wide vaccination programme was introduced for 12- to 13-year-old girls in 2008 with a catch-up to age 18 over a 3-year period. The bivalent vaccine directed against HPV types 16 and 18 (Cervarix®, GlaxoSmithKline) was selected for the UK vaccine programme.

The second important role for HPV is as a biomarker of cervical neoplasia, so that HPV testing can be implemented as a test for screening or to aid clinical management. There are three obvious settings for HPV testing: (1) triage of mild cytological abnormalities to select for colposcopy, (2) as a 'test of cure' following treatment of CIN and (3), potentially most importantly, as a primary screening test. HPV testing for triage and test of cure are currently being evaluated in a Sentinel Site project being conducted by the NHSCSP. The effectiveness and cost-effectiveness of HPV testing in primary screening required rigorous testing in a controlled trial within the NHSCSP.

Screening technologies

Liquid-based cytology

Nationwide conversion from so-called conventional cytology, which relied on 'smearing' exfoliated cells onto a glass slide before fixation, to LBC was completed in 2008. The LBC process involves the exfoliated cells being put into a liquid preservative suspension and either mechanically filtered onto a glass slide or collected by a cell-enrichment process. The principal advantages of LBC are a major reduction in inadequate samples for reading and more rapid throughput of samples in laboratories.[11]

Rationale for study design

Clinical issues

The rationale for HPV testing in primary cervical screening is to increase the sensitivity to detect CIN3, which is generally accepted as the true cancer precursor lesion. By doing so, a drop in deaths could be expected among screened women who develop cancer despite being screened. The evidence for increased sensitivity comes from a number of studies which compare estimates of sensitivity for cytology and HPV testing in primary screening. In a meta-analysis of European studies[12] the median sensitivity of cytology was about 50% although sensitivity in the only UK study in the analysis was almost 80%. By contrast, HPV sensitivity for detecting CIN2 or worse was estimated at over 95%. Furthermore, because HPV testing is an objective procedure there was far less variation in results than was the case for cytology. Other evidence for increased sensitivity comes from studies of HPV 'triage' to manage women with low-grade cytological changes. In the ALTS trial in the USA,[13] HPV testing identified more disease than repeated cytology. Furthermore, this added sensitivity comes with a very high negative predictive value suggesting a role for HPV as an initial 'stand-alone' test without cytology. The problem with HPV testing is a lack of specificity, particularly in young women (< 30 years) in whom the high-risk HPV positive (+ve) rates are around 20%. Typing the HPV infection is needed not only to estimate true viral persistence, but also to determine which specific types are responsible for high-grade disease and which are less relevant in that respect. The Hybrid Capture (HC2, QIAGEN) test used in ARTISTIC (A Randomised Trial In Screening To Improve Cytology) uses a cocktail of probes to detect 13 high-risk (HR-) HPV types.

The purpose of the present study was to evaluate HPV testing in primary screening both as an adjunctive test with cytology and as a stand-alone test which would be backed up by cytology for HPV +ve women. At the time of planning the study it was not possible to undertake a trial that would involve HPV testing alone because cytology was, and remains, the international standard of screening and there was insufficient evidence regarding the role of HPV as a stand-alone test. The most rigorous acceptable design was considered to be a randomised trial that compared the current standard, i.e. cytology versus cytology plus HPV testing. To maximise the opportunity to evaluate HPV as a stand-alone test, it was decided to undertake HPV testing with cytology in all women but to conceal the HPV result in the standard arm. This would also permit controlled observation of the psychological impact of HPV testing.

Not only would a randomised trial be capable of robust comparisons of cytology versus cytology plus HPV testing as a primary screen, but the entire cohort data would provide valuable data on which could be modelled the outcomes of different screening strategies. This could include: (1) the current standard, (2) cytology with HPV triage and (3) HPV screening (including varying cut-offs) with cytology triage.

Other current randomised studies of HPV testing in primary cervical screening

Four other European randomised trials are evaluating HPV in primary screening in addition to ARTISTIC. These are being conducted in Sweden (*Swedescreen*), the Netherlands (*POBASCAM*), Finland (*Finnish Public Health Trial*), and Italy (*NTCC*). They began in 1997, 1999, 2002 and 2003 respectively. The characteristics of the trials are shown in *Table 1*. Results from Swedescreen[14] and POBASCAM[15] have been published – reporting data over two rounds of screening. The NTCC study[16] has reported data from a prevalence round. All employed conventional cytology.

Implications of vaccination

Since the initiation of this study, prophylactic HPV vaccines have become licensed for the prevention of CIN2/3 for females aged 9–26 years. Currently available vaccines against types 16 and 18 will be capable of reducing the incidence of high-grade CIN (CIN2/3) by over 50% but low-grade cytological abnormality, most of which is either HPV –ve or associated with other HPV types, by perhaps only 20%. It will be important to determine how best to screen vaccinated females aged 25 years and over. If HPV testing were

TABLE 1 *Characteristics of five European randomised trials of HPV testing in primary cervical screening*

Country	Study	Recruitment	Age range	Cytology HPV test	Comparison	Outcomes
Sweden	Swedescreen	12,517	32–38	Conventional/ PCR/GP5+/6+[a]	Cytology vs Cytology + HPV	CIN2+ at round 2 3 years later
the Netherlands	POBASCAM	44,102	30–60	Conventional/ HC2	Cytology vs Cytology + HPV	CIN3+ at round 2 5 years later
UK	ARTISTIC	24,510	20–64	Liquid based/ HC2	Cytology vs Cytology + HPV	CIN3+ at round 2 3 years later
Italy	NTCC	50,000 (Phase 1)	25–60	Conventional/ HC2	HPV/LBC vs Conventional	CIN2+
		50,000 (Phase 2)		Conventional vs HPV as a stand-alone		CIN2+

a General Primer 5+/6+.

proposed as a primary determinant of risk followed by cytology if HPV +ve, then understanding the risk over time for cytology –ve/HPV +ve women, will be important. The data from the ARTISTIC trial will allow useful estimates of the impact of these vaccines on the prevention of abnormal cytology as well as CIN2/3, and will also provide a valuable contribution to the development of models of the cost-effectiveness of vaccination.

Economic issues

Cervical screening is generally accepted as a cost-effective intervention costing the NHS around £150–180 million[17] with an estimated 800–1000 lives saved per year,[18] although in the long term up to 5000 future deaths per year may be prevented by current screening.[4] Given that the average age at which cervical cancer deaths occur lies between 60 and 65 years,[19] the number of life-years saved is well within the accepted range for a cost per quality-adjusted life-year (QALY) gained.

Any major change to the screening programme would need to be more effective and cost-effective, either in terms of saving more lives or in achieving greater programme efficiency. It could be expected that the use of HPV testing will save lives by more sensitive disease detection.

The systematic review by Cuzick *et al.*,[20] which informed the design of the ARTISTIC economic evaluation, undertook a modelling exercise to assess whether HPV testing could be cost-effective in primary screening. Three test combinations (cytology, cytology plus HPV testing, and HPV testing alone) were examined in two models in which the screening outcomes were adjusted favourably or less favourably towards the use of the HPV test. NHS-derived costs for cervical screening and the management or treatment of cervical dysplasia were applied, and the effective measures of screening were life-years gained and deaths prevented. Effects and costs were calculated for both 3-yearly and 5-yearly screening between 20 and 64 years of age. The authors concluded that additional HPV testing in primary screening would not be cost-effective unless the cost of HPV testing could be substantially reduced, or, alternatively, fewer tests were performed by lengthening the screening interval from 3 years or by lowering the age at which women are no longer invited for screening following a series of –ve HPV tests. As it was, the costs for HPV screening entered in the models omitted laboratory costs for analysing cervical samples. The authors acknowledged that the issues of cost were not clearly resolved; would the cost of the HPV test be substantially reduced if tests were used at a very high volume? Further modelling was needed to quantify uncertainties of the key parameters, preferably in a large-scale study with at least a 5-year follow-up.

The data capturing methods for ARTISTIC were designed to record cost-generating events (cervical screening, cytology, HPV testing, colposcopy, biopsy and treatment) for all women from the point of recruitment until their end point in the trial. Associated unit costs for these events would be estimated and attached to the individuals' events. By performing HPV tests on cervical samples in both the control and intervention arms, the three test combinations of cytology, cytology plus HPV testing, and HPV testing alone could be evaluated through modelling. Economic evaluations of screening programmes often included travel and time costs incurred by those being screened on the basis that these may affect uptake and, ultimately, cost-effectiveness of a programme. Although women undergoing cervical screening incur personal expenses, mostly when attending a general practitioner (GP) surgery, women's costs were not measured.

The systematic review[20] was limited to modelling a cost per life-year gained because information on the value of health states associated with cervical cancer was not available. However, such information is required if a cost per QALY is to be estimated. As cervical screening impacts intermittently and temporarily on the lives of most women, the time trade-off (TTO) technique for valuing descriptions of cervical screening outcomes was selected for administration with women drawn from the general population. Previous research had shown that respondents more easily follow the TTO technique for eliciting valuations than an alternative method, the standard gamble technique.[21]

In the protocol for the ARTISTIC trial, follow-up of women was limited to 3 years, hence modelling beyond the end point of the trial would be needed to determine whether the HPV test would have an impact on life-years gained. The model used in the systematic review[20] was based on the natural history of the disease. Modelling had been applied previously to determine the effectiveness of cervical screening intervals[22] and the cost-effectiveness of alternative technologies for Papanicolaou testing of the cervix.[23] For our purposes, a time-varying Markov model would be appropriate to estimate the lifetime costs and effects associated with different screening strategies. This assumed, however, that the trial results would show that the cytology and virology screening techniques performed differently in identifying women with precursor lesions of carcinoma.

Psychological/psychosocial issues

Cervical screening creates anxiety among a proportion of women who receive an abnormal result,[24–26] although this tends to resolve following diagnosis and treatment.[27] Studies have indicated that testing +ve for HPV may be responsible for an adverse psychosocial impact, which is related to the sexually transmitted nature of HPV infection.

This effect has been shown in a quantitative study using psychometric measures, which compared women with negative or abnormal cytology who were identified as HPV +ve, with corresponding women who were identified as HPV –ve.[28] Qualitative research[29] has identified a number of key concerns that women may have when told that they have tested HPV +ve. These include the stigma of a sexually transmitted infection, the link with cervical cancer and the fact that it may persist. The primary outcome measure of ARTISTIC is detection of CIN3 or worse (CIN3+) at 3-year follow-up, but these concerns reinforce the importance of measuring the psychosocial and psychosexual impact of HPV testing in the ARTISTIC trial.

The objective of the psychological study in ARTISTIC was to determine whether receiving an HPV +ve test result could be associated with increased psychological distress when compared with cytology alone and whether it could also exert a negative effect on psychosexual functioning. The randomised structure of the ARTISTIC trial offered an opportunity to compare the impact of HPV testing when combined with cytology in the revealed arm with a control group of women defined by randomisation in the concealed arm whose HPV status could be matched, but who were unaware of the HPV result.

It was also hypothesised that among women with –ve cytology, receiving an HPV +ve result could be associated with increased distress compared with women receiving an HPV –ve report. If we are to evaluate HPV testing in primary cervical screening we need to understand its psychological effects.

Chapter 2
Methods

Aim

The aim of the trial was to determine whether HPV testing added to cytology increases detection of CIN3+. If this were the case it would be expected that more CIN3+ would be detected in the HPV revealed arm in the first (prevalence) round and that there would therefore be less CIN3+ in the second (incidence) round. Because cervical screening is a process of repeated rounds of screening it is important to determine whether HPV testing in addition to cytology impacted significantly over the two rounds. Such an effect would be the result of added detection in women with –ve cytology and HPV +ve tests prompting further investigations.

Other research questions were:

- Is cytology plus HPV testing cost-effective when compared with cytology alone?
- What were the psychological and psychosexual effects of HPV testing?
- What is the true sensitivity of cytology combined with HPV testing when backed up by routine use of colposcopy as a form of verification?
- Does the optimal 'cut-off' for a +ve Hybrid Capture (HC2) test in this screening setting differ from the manufacturer's recommended threshold?
- Is there an explanation for CIN3+ associated with an HPV –ve result?
- What is the HPV genotype profile for this population?
- What are the rates of type-specific persistence over 3 years and what are the outcomes associated with this in terms of abnormal cytology?
- What is the negative predictive value of HPV testing in terms of disease detected at 3 years?
- Related to the above, would HPV as an initial stand-alone screening test, followed by cytology, be superior to cytology followed by HPV triage?
- What would be women's choice if HPV were persistently +ve at 12 months?

Design

The ARTISTIC prospective randomised trial compared routine cytology (concealed arm) against routine cytology plus HPV testing (revealed arm) in primary screening, randomised in a concealed : revealed ratio of 1 : 3. The study was designed to be firmly embedded within the NHSCSP, so making the findings credible and applicable to women across the UK. The original trial target was to recruit 28,000 women aged 20 to 64 years who were undergoing routine cervical screening from participating GP surgeries or family planning clinics (FPCs) in Greater Manchester. Information regarding the trial was enclosed with invitations to attend for a routine smear, and information leaflets and consent forms were also available in GP surgeries and FPCs. Women could opt into the trial at the time of attending for their smear by giving written informed consent to randomisation. Women were then allocated to the arm in which the HPV result was revealed (study arm, recruitment target: 21,000 women) or concealed (control arm, recruitment target: 7000 women) in a 3 : 1 ratio respectively. Women were contacted immediately after consenting into the study to welcome them and inform them to which group they had been randomised. The trial intervention is summarised in *Figure 1*.

All samples were taken in LBC. The samples were taken in ThinPrep® (HOLOGIC), although a small proportion of subsequent samples in round 2 were taken in SurePath® (Becton Dickinson). An HPV test was performed on the cervical cells in the LBC sample as well as cytology screening. The LBC samples were processed at the Manchester Cytology Centre (MCC), and the HPV tests were performed at the Department of Virology, Manchester Royal Infirmary (MRI). Women would then receive their result letter, copied to their GP surgery or FPC. Women in the revealed arm who tested HPV +ve also received an HPV information leaflet (see Appendix 3). In the concealed arm all LBC samples were accompanied by an HPV test but the result was not disclosed to women or clinical staff.

For those women in the revealed arm whose baseline test results were –ve cytology and HPV

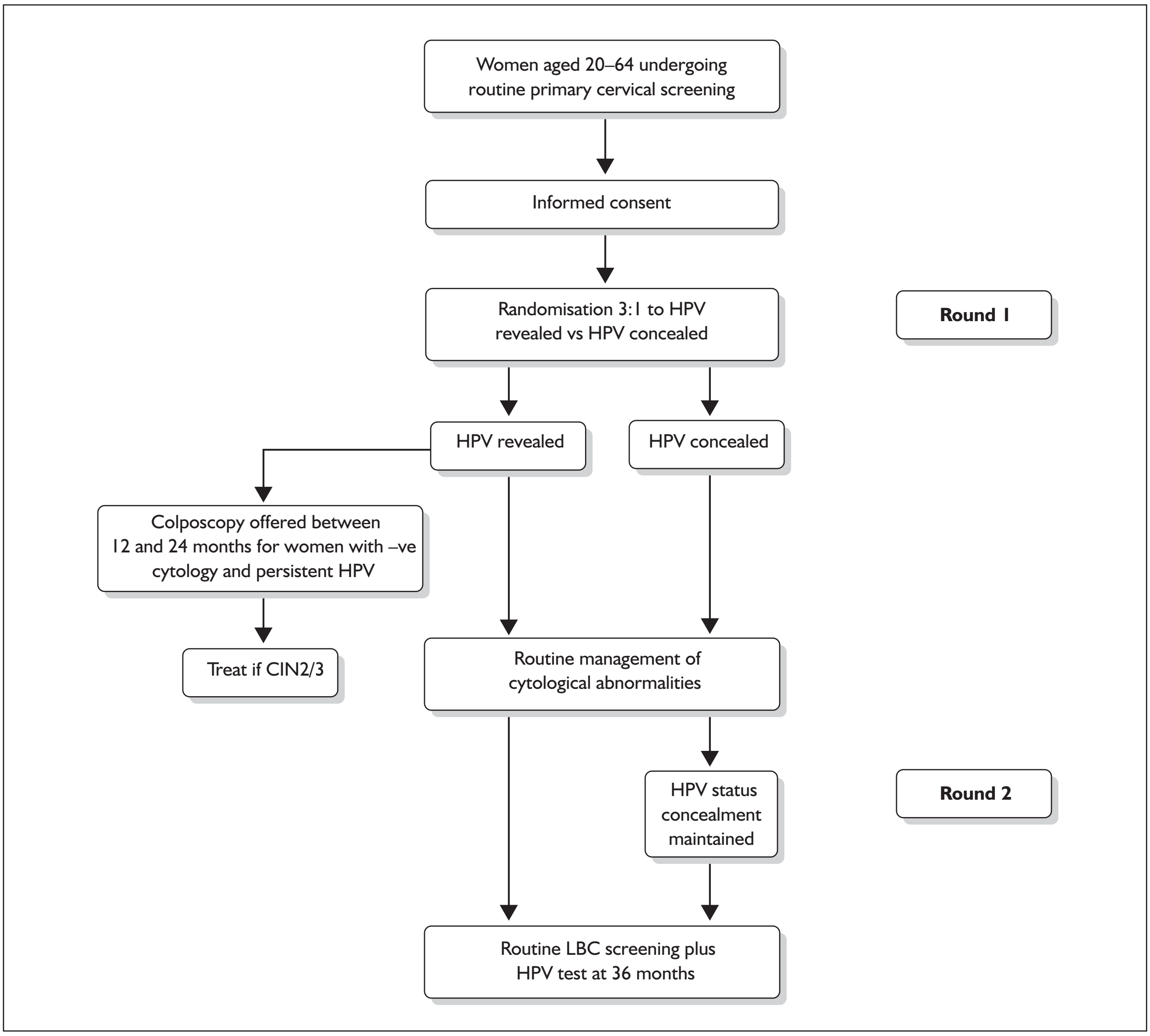

FIGURE 1 *Trial intervention.*

+ve, the HPV test was repeated at 12 months and a choice was offered if the test was HPV +ve again. Women could either undergo colposcopy or have a further HPV test at 24 months, and if still +ve would be offered colposcopy. This was to determine women's preference in the event of a future programme of HPV testing triaged by cytology.

Reading of cytology slides and samples

Cytology results were reported according to the laboratory routine using the British Society for Clinical Cytology (BSCC) classification (described in *Table 2*). A cytoscreener read the slides with abnormal slides checked by a biomedical scientist or cytopathologist. Rapid review of every negative or inadequate slide was performed before reports were authorised. Cytoscreeners were unaware of HPV test results.

Biopsies were also reported according to routine practice using classification according to agreed guidelines.[30] All pathology results were checked by a consultant pathologist. There was no central review of cytopathology or histopathology, and pathology was reported blind to HPV results.

Concealment

Staff reading cytology slides and biopsies were unaware of the allocation of the sample and concealment was maintained throughout the trial. Women in the concealed arm could request their HPV result if they insisted, but in practice only three women requested their HPV results.

TABLE 2 *Cytology classifications*

BSCC 1986	Bethesda System 2001	Definition[a]
Negative	Negative for intraepithelial lesion or malignancy	Normal cytology
Inadequate	Unsatisfactory for evaluation	Low-grade cytology
Borderline nuclear change (includes koilocytosis)	1. Atypical squamous cells of undetermined significance (ASC-US) ASC-H [cannot exclude high-grade squamous intraepithelial lesions (HSIL)] 2. Atypical endocervical/endometrial/ glandular cells: not otherwise specified or favour neoplastic	Low-grade cytology
Mild dyskaryosis	Low-grade squamous intraepithelial lesions (LSIL)	Low-grade cytology
Moderate dyskaryosis	HSIL	High-grade cytology
Severe dyskaryosis	HSIL	High-grade cytology
Severe dyskaryosis – ?invasive	Squamous cell carcinoma	High-grade cytology
Glandular neoplasia	1. Endocervical carcinoma in situ 2. Adenocarcinoma Endocervical Endometrial Extrauterine Not otherwise specified	

BSCC, British Society for Clinical Cytology.
a Low-grade cytology (positive predictive value for CIN2+ generally in the range of 15–20%); high-grade cytology (positive predictive value for CIN2+ generally in the range of 69–85%).

Management protocol

The protocol did not require significant deviation from national guidelines for the management of abnormal cytology samples. In the revealed arm women received their cytology and HPV test result and in certain cases management was dependent on the HPV result. Women were reminded about their next LBC test – either routine cytology or a follow-up HPV test – by letter, sent approximately 1 month before the due date. A reminder was then sent 2 weeks after the test was due. A final reminder was sent around 3 months later.

Women with inadequate cytology samples were retested and re-entered the trial with follow-up as appropriate. In both arms of the trial, women with moderate or severe dyskaryosis were referred for colposcopy and managed according to standard guidelines. Once a woman had been referred to colposcopy, the trial office ceased to send further recall letters to avoid discrepant management from that advised by the colposcopy clinic.

Colposcopy clinics were asked to send copies of all correspondence relating to the appointment to the trial office and all related cytology, HPV, colposcopy and histology results were recorded in the trial database. Women in the concealed arm with mild or borderline cytology had a second LBC test at 6 months. If dyskaryosis persisted a colposcopy referral was made and any CIN was monitored or treated according to local policy. If the second sample was negative or borderline, women were recalled for a third LBC test at 12 months. If this third test was abnormal then a referral for colposcopy was made, and if it was negative, the women were recalled for a fourth test at 24 months. Women in the revealed arm who had two consecutive borderline or worse results which were HPV +ve were referred for colposcopy.

The management protocol is summarised in *Figure 2*. Women who were initially cytology and revealed HPV –ve were managed exactly as in the control arm. Women in the revealed arm who tested cytology –ve and HPV +ve at baseline were invited to be retested for HPV only at 12 months. Most HPV infections are transient and persistence over 12 months or longer was chosen to give greater specificity for detection of CIN than a single HPV +ve result. If this second HPV test was +ve then the women would receive a result letter offering a choice between a colposcopy examination at their local clinic or a repeat HPV test at 24 months. It was explained that if a 24-month HPV test were +ve then a referral would be made for a colposcopy examination. A postage-paid envelope was included for women to return the form indicating their preference. Patient choice was offered to improve compliance and provide valuable information on women's reactions to being persistently HPV +ve. All women in the trial were recalled to have an LBC and HPV test 36 months

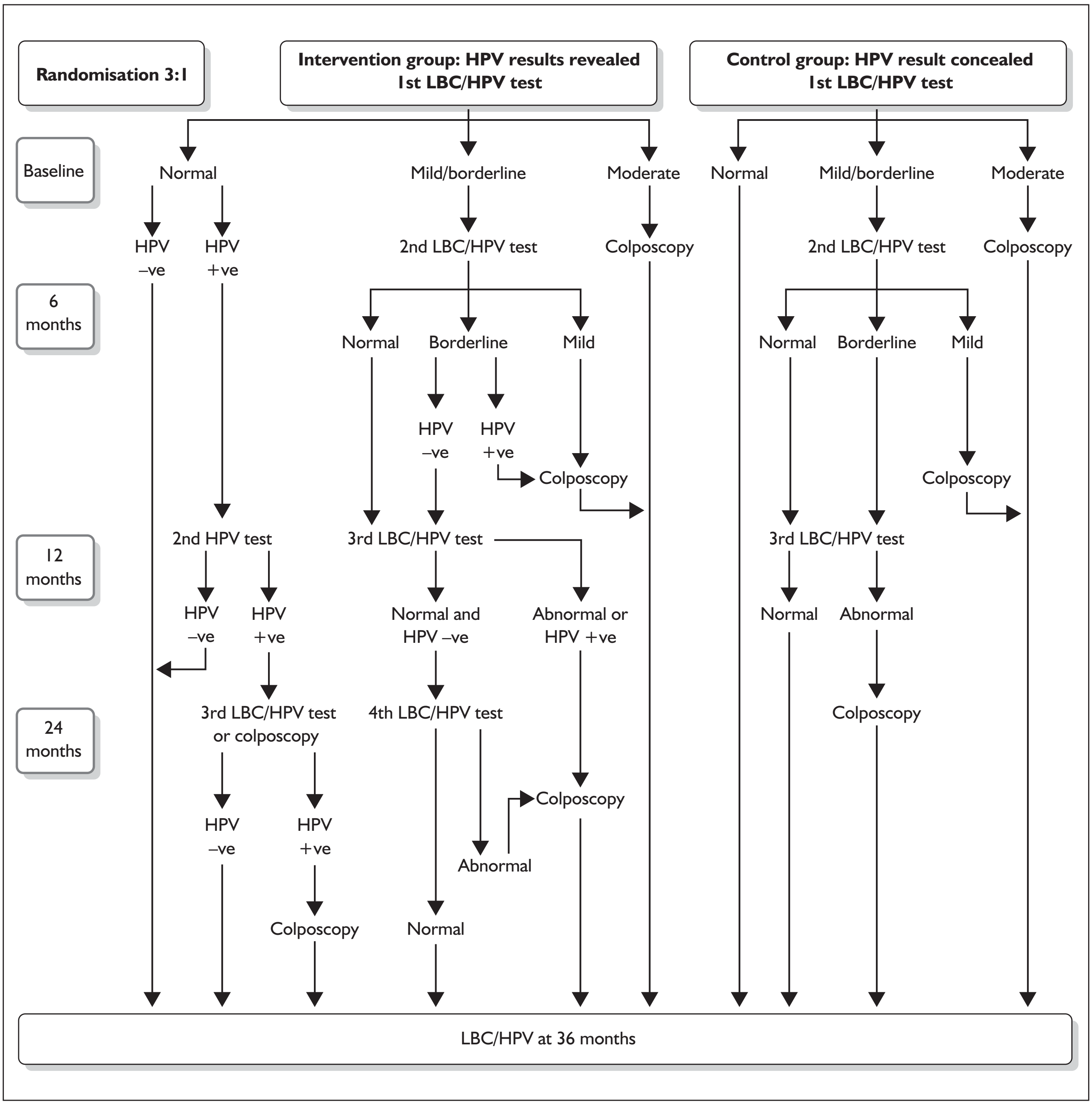

FIGURE 2** ARTISTIC trial protocol for the management of women with negative and abnormal cytology and HPV +ve and –ve tests, in the revealed arm. Referral to colposcopy varied depending on cytology history, some women were referred to colposcopy only after three consecutive borderline results or after a mild result followed by a borderline result. Reproduced with permission of Cancer Research UK from Kitchener H, Almonte M, Wheeler P, Desai M, Gilham C, Bailey A, et al. HPV testing in routine cervical screening: cross sectional data from the ARTISTIC trial.* Br J Cancer *2006;95***:56–61.*[31]

after round 1 and were followed up by cytological and histological record linkage. At 36 months, women in both arms were managed according to NHSCSP guidelines, with the exception of those who had borderline cytology; those women were referred to colposcopy after only two consecutive borderline results (rather than the usual three) to ascertain histology within the timescale of the trial.

Definitions of HPV, CIN and cancer diagnosis at recruitment and follow-up

Round 1

The round 1 (entry) sample was defined as the first cytologically adequate sample after randomisation that gave a satisfactory HPV result by HC2.

Round 2

The round 2 (first routine follow-up) sample was defined as the first cytologically adequate sample taken between 30 and 48 months after the date of the round 1 sample. We do not employ the term 'exit round' because women are continuing to be followed up in a third round, 6 years following recruitment to the study. Alternative analyses of CIN2 and CIN3+ (see *Table 15*) included women with round 2 samples 26–54 months after round 1, in order to reduce the number of excluded lesions.

Abnormal sample

An abnormal sample was defined as borderline or worse cytology, and/or HPV detected by HC2 for women in the revealed arm. Cytology is categorised in *Table 2*. Cytology +ve is consistently used to mean abnormal cytology of any degree.

Follow-up of abnormal round 1 samples

We considered periods of 6 months (i.e. < 6, 6–11.9, 12–17.9, etc.) to define time of second sample for the analysis of viral persistence in women who were recalled following a round 1 sample that was cytologically abnormal or HPV +ve.

HPV typing and HC2 cut-off point

The main analysis for ARTISTIC was carried out using the recommended cut-off value of ≥1 relative light unit/mean control (RLU/Co). In a separate analysis, we present the result of screening tests in round 1 using three additional cut-off points for the HC2 assay (2, 4 and 10 RLU/Co).

CIN1, CIN2 and CIN3

CIN1, CIN2 and CIN3 are worsening grades of CIN in terms of the likelihood of cancer developing and reduced likelihood of spontaneous regression. CIN3+ included CIN3, carcinoma in situ, cervical glandular intraepithelial neoplasia (CGIN), adenocarcinoma in situ, microinvasive carcinoma, invasive squamous carcinoma and adenocarcinoma. Incomplete excision or ablation is sometimes followed by recurrence. Women were therefore censored at CIN3+, so any later CIN2 or CIN3+ was excluded. In analyses of CIN2 women were censored at CIN2, so any later CIN2 was excluded. One CIN3 in round 2 in a woman with CIN2 in round 1 was excluded in the initial analysis but included in the alternative analysis in *Table 15*.

Disease outcomes

CIN2, CIN2+ (CIN2 or worse) and CIN3+ (CIN3 or worse) in round 1 were defined as the worst histology within 30 months of an *abnormal round 1 sample*, as there was sometimes a long interval between the first abnormal sample and eventual referral for colposcopy and subsequent histology. CIN2, CIN2+ and CIN3+ in round 2 were defined as worst histology within 30 months of a *cytologically abnormal round 2 sample*. CIN and cancer diagnosed as a result of histology following HPV detection in a cytologically –ve round 2 sample were ignored in the primary analyses to provide consistency in comparing the revealed and concealed arms.

HPV results

HPV detection (HC2 +ve) includes the 13 high-risk human papillomavirus (HR-HPV) types detected by the HC2 test. Results on HR-HPV types are presented for HPV16 alone, HPV16 and/or HPV18 (HPV16/18), and HPV16 and/or HPV18 and/or HPV31 and/or HPV33 and/or HPV35 (HPV 5 HR types).

Persistent HPV infection

A woman was considered to have a persistent HPV infection justifying referral for colposcopy in the revealed arm if she had:

- two consecutive HC2 +ve samples over a minimum of 12 months

- two HC2 +ve/line blot assay +ve specifically for HPV16, HPV16/18 or HPV 5 HR types (as defined above).

Analyses of HPV persistence
These were based on detection of HPV in round 1 and in the second sample. Two different definitions were used for second HPV samples:

- the first adequate sample after round 1
- the round 2 sample.

Sample size

The age distribution of the ARTISTIC study population was weighted to give adequate expected numbers of abnormal round 1 samples in each of four age groups (20–29, 30–39, 40–49 and 50–64 years). The weighting for the numbers to be stratified on the basis of age is based on a previous large cohort study in Manchester.[32] In the previous study cervical samples were obtained from 61,570 women recruited between 1987 and 1993 with subsequent cytology for up to 6 years. This provided a reliable basis for estimating patient numbers for the ARTISTIC study. A larger number of older women were recruited in ARTISTIC to achieve adequate numbers of women with abnormal results and sufficient HPV +ve women in each age group. The overall proportion of high-grade abnormal samples in the study population would therefore be expected to be less than in the normal population (1.8%). The HPV revealed arm is three times as large as the HPV concealed arm because a large reduction in the proportion of high-grade lesions detected in round 2 was expected in cytology –ve/HPV +ve patients on the revealed arm, and this ratio was chosen to give high power to detect this difference.

Cytological outcomes

Assuming 10% loss to follow-up by the next screening round, the study had a power of 96% ($2p < 0.05$) to detect a reduction from 8% to 2% in the prevalence of high-grade CIN at 36 months among women initially HPV +ve but cytologically –ve. The study would also have 90% power to detect an overall reduction of 40% between the two arms in the incidence of high-grade cytology and high-grade CIN at 36 months. This assumes a 1% rate in round 1 of moderate/severe dyskaryosis in the concealed arm. For the subgroup of patients who have an abnormal result and who are HPV +ve, a comparison will be made between subjects randomised to the revealed and concealed arms for high-grade cytological abnormalities at the 36 months rescreen although differences in management are unlikely to affect outcome, and this comparison is of less interest. The study had 80% power to show an overall reduction of 25% between the two arms in the incidence of low-grade cytology.

Setting and Ethics Committee approval

The trial was approved by the North West Multicentre Research Ethics Committee to recruit women from the Greater Manchester area, including Manchester, Wigan & Leigh, Salford & Trafford, and Stockport Health Authorities (ref: 00/8/30). The trial was conducted in 127 primary care practices and all FPCs in the four Health Authority areas listed above. The numbers of women recruited in each Health Authority are listed in *Table 4*.

Practice and GP recruitment

In early 2001, comprehensive general practice lists were obtained from the patient data departments of the four Health Authorities. Information about the trial was sent to the senior partner at the surgeries along with an invitation to attend an evening seminar on how they could participate in the study. The seminar would also provide an update on cervical screening. An event was arranged in each of the areas. Contact was made with screening co-ordinators within Manchester where links already existed. They suggested that due to the nature of cervical screening it may be more appropriate to target practice nurses to gain support for the study.

A series of meetings was arranged which coincided with the decision to employ LBC as the technique for taking samples, so we were able to promote the meetings as an opportunity to be trained and gain experience in this new technique. The event was Continuing Professional Development accredited. Marie Curie Cancer Care supported the initial LBC/ARTISTIC trial training sessions which had over 100 attendees from general practices, FPCs and colposcopy units. Further training was hosted by Practice Nurse forums and later cascaded to new staff either by those who had been on the Marie Curie Cancer Care-supported course or by research nurses on the trial.

Participation in the trial by practices was straightforward. Detailed information about the trial and a consent form were included in recall invitations sent out to women by Health Authority screening staff. Additional copies of paperwork were also sent out to practices. Women were given information about HPV with their invitation for screening, backed up if necessary with information by the sample taker. Once signed consent to take part in the trial was obtained, a cervical sample was taken according to NHSCSP guidance[33] and sent to either Stepping Hill Hospital cytology laboratory or MCC based at Central Manchester Health-care Trust (depending on where the woman was recruited), and then to the MRI Virology Department for HPV testing. A cytology request form and the completed patient consent form accompanied the cervical samples when they were sent for processing.

Regular meetings were held across all four Health Authorities throughout the 2-year recruitment phase keeping practices updated with recruitment figures and details of how the trial was progressing. GPs and FPCs received regular newsletters (3- to 6-monthly) with frequently asked questions, recruitment statistics, protocol reminders and trial updates.

Service support costs

The GPs and FPCs were given a reimbursement amounting to £10 for each woman recruited into the trial. Invoices were sent to the trial office on a 6-monthly basis. The target for the under-30 age group was reached more quickly than for the older age groups, therefore practices were asked to target recruitment of women aged 50–64 years. The recruitment reimbursement was increased from £10 to £15 in this age group and ceased for women under 30 years old.

Reimbursements also included postage and stationery (envelopes, paper, printing and photocopying) used to maintain contact with both women and sample takers.

Links with local screening co-ordinators

Regular meetings were held with screening co-ordinators in order to establish the trial. Local screening co-ordinators in Salford & Trafford and Manchester were involved in altering the recall dates for those women in the ARTISTIC study under 50 years of age and under routine recall from 5 years to 3 years, as the standard screening interval in these Health Authorities was still 5-yearly. This brought their recall in line with the trial protocol. Lists of women were sent to the co-ordinators who adjusted the date of recall to make it compatible with the study recall date so that women would receive their invitation letter from the trial office and the Health Authority at the same time, and subsequently be more likely to comply with the 3-year screening protocol. Permission was not given to bring forward the recall date for women over 50 years old, although the women did receive a 3-year invitation letter from the trial office.

Recruitment, consent and randomisation procedures

The study population was screened in over 127 general practices and FPCs which had agreed to participate in the trial. Of those women who were able to access the trial, and were offered the opportunity to participate, fewer than 5% refused.

All women consented to randomisation and separately, to storage of samples for further research. Women were assigned a unique trial number for identification purposes on the main Access 2000 trial and HPV databases. A consent form and a trial information sheet were produced for the study (see Appendices 4 and 5 respectively).

Allocation of women to HPV test revealed or HPV test concealed was in the ratio 3 : 1. Simple randomisation was used because blocking or minimisation is unnecessary to maintain balance in a large sample. For reasons of cost it was not feasible to use an independent randomisation service. Instead, randomisation was carried out by a research assistant independent of the study using a list prepared by one of the trial statisticians. Allocation was concealed from the practice nurse recruiting women into the study because allocation was made when the trial consent forms arrived at the trial centre. To achieve the desired age distribution the minimum age was increased from 20 to 30 when the recruitment target for women aged 20–29 had been reached, then to 40 when there were enough aged 30–39, and so on. Randomisation status of the women was concealed from the staff at the Cytology and Virology Laboratories.

Logistics of cytology and HPV testing

Figure 3 represents the pathway of the sample after its collection in primary care. At the outset of the trial there was no central transport or internal postal system that could deal with the sheer volume of written material involved in the study. Information sheets and consent forms had to be delivered by car by trial staff to practices and Health Authorities.

The introduction of LBC also led to transport issues; conventional samples could be routinely posted, but existing systems did not support the transportation of LBC samples. HPV testing was undertaken centrally at the MRI Virology Department. Cervical samples taken were read at the MCC and Stepping Hill Cytology Laboratory in Stockport. LBC samples had to be couriered from GP surgeries to either MCC or Stepping Hill Hospital. The samples from Stepping Hill Hospital were couriered to MCC for the slides to be prepared, then back to Stepping Hill for reading. All vials were retained at MCC and taken in batches to the MRI virology laboratory for HPV testing because it was on the same site.

Protocol amendments

- Following a complaint on behalf of a trial participant's partner midway through round 1, it was determined by the Ethics Committee that all women should be given at least 24 hours between receiving information regarding the trial and giving consent to participate, and the information leaflet was amended to be more explicit about HPV being sexually transmitted.
- GPs were asked to flag the records of women who defaulted HPV testing at 12 months to provide opportunistic encouragement to undergo repeat HPV testing.
- Women with borderline cytology were referred for colposcopy after two not three borderline results in round 2 of the trial to avoid undue delay in diagnosis.
- Ethical approval was granted to flag women participating in ARTISTIC in the NHS central register for automatic notification of incident cancers and death.

Since the ARTISTIC trial was implemented, there have been several national and local changes to the NHSCSP which have had an impact on the trial.

- At the time the trial began in 2001, NHSCSP guidelines recommended that women aged 20 to 64 should participate in cervical cancer screening every 3–5 years. In 2003, national guidelines were changed so that those women under 25 were no longer invited to attend cervical screening. Population-based data on the natural history of CIN in women screened in the English programme aged less than 25 years will therefore no longer be available. The ARTISTIC trial will provide data on long-term outcomes following HPV infection and CIN in 2575 women aged 20–24 years at recruitment.
- The roll-out of LBC to all General Practices and FPCs in the Greater Manchester region, and nationally, had two impacts on the trial. First, when the trial began the only practices and FPCs using LBC were those participating in the trial. This made it easy to identify which samples were in the trial and should therefore be HPV tested. LBC was more or less fully rolled-out in Greater Manchester by October 2005, which meant that the number of samples which could not be HPV tested as they had been mistakenly collected in 'conventional' cytology decreased dramatically, but it became more difficult to distinguish 'ARTISTIC' samples at the laboratories. To facilitate this process, letters were written to all surgeries to remind sample takers to flag the cytology request form as 'ARTISTIC', with lists of women recruited from their surgery. The roll-out of LBC to non-ARTISTIC practices also enabled samples from non-ARTISTIC practices to be HPV tested, for example, if a woman changed her GP or moved to a different Health Authority. In some cases we were able to perform HPV tests on samples from women who had moved out of the Greater Manchester area completely by asking the practice nurse to notify the local cytology laboratory to forward the sample to the Manchester Virology Laboratory. The roll-out of LBC also led to a number of samples being taken in SurePath medium, rather than ThinPrep.
- Referral to colposcopy after one mildly dyskaryotic cytology result instead of two began in Manchester, Salford & Trafford and Wigan & Leigh in January 2005. Stockport, however, continued to refer to colposcopy only after two results showing mild dyskaryosis.

Clinical samples

Cervical samples were collected using the Rovers® Cervex-brush® cervical sampler (Rovers Medical Devices). The sample was taken using the recommendation of the manufacturers of the ThinPrep system.

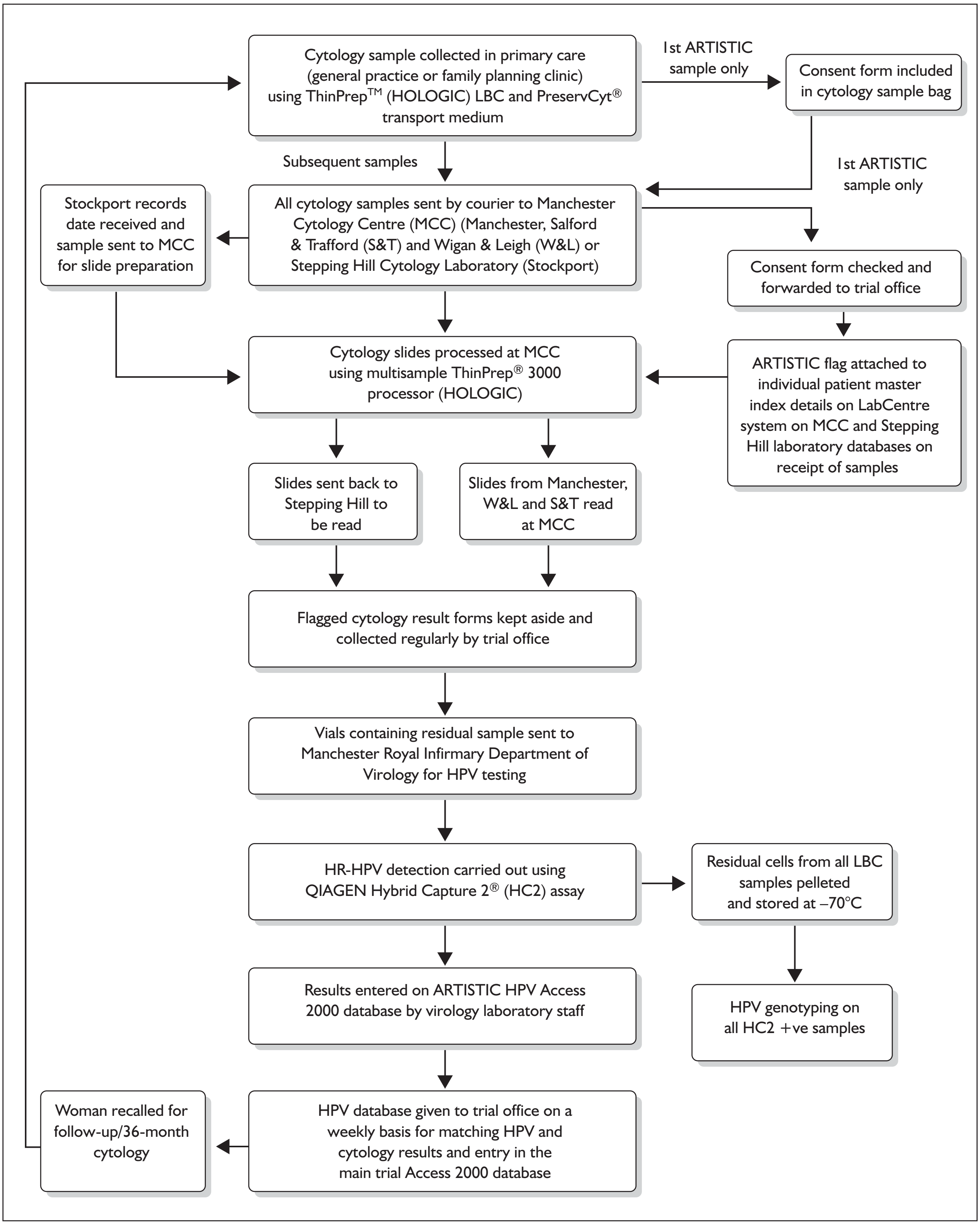

FIGURE 3 *Logistics of cytology and HPV testing.*

Cervical cell samples collected in ThinPrep and any in SurePath medium were transported at ambient temperature and stored at room temperature before being tested for HPV within 21 days. Transportation of the cervical cell samples complied with national regulations for the transport of pathological material.

Receipt of LBC samples in the virology laboratory

On receipt of samples in the virology laboratory, the sample vial and request form demographics were checked before labelling vials and request forms with a unique bar-coded identification number. All information was then manually added to an Access 2000 database.

Polymerase chain reaction conditions and protocols

For all polymerase chain reaction (PCR) protocols performed, the risk of cross-contamination was minimised by the use of a DNA-free room for preparation of PCR master mix and an extraction room for the extraction of DNA and for the addition of DNA to the master mix. Post-PCR analysis was carried out in a further separate room. Pipette tips with cotton plugs were used at all times and controls were added to each PCR run to ensure no contamination had occurred. Disposable gloves were worn and changed frequently. Laboratory coats were dedicated for use in specific rooms. Laboratory benches were cleaned following local guidelines.

Sample processing for the QIAGEN Hybrid Capture® 2 test

ThinPrep LBC samples

To ensure suitability for the HC2 test ThinPrep LBC samples were first processed using the HC2 Sample Conversion Kit according to the manufacturer's instructions. Any sample containing less than 4 ml of residue (from the original 20 ml) after the cytology slide was made was discarded because of insufficient volume. Following this initial treatment the sample was denatured to render any nucleic acid single stranded. Denatured samples were stored at –30°C for a maximum of 7 days before testing by the HC2 test.

SurePath LBC samples

After a cell enrichment process to prepare the cytology slides, the cell-enriched vial and the residual of the original SurePath material were pooled before processing the sample. Any sample containing less than 3 ml was discarded because of insufficient volume. Samples were processed using the HC2 Sample Conversion Kit according to the manufacturer's instructions. Denatured samples were stored at –30°C for a maximum of 7 days before testing by the HC2 assay.

Preparation of samples for archival storage

Cells from a further 4 ml of the ThinPrep LBC samples and 3 ml of the SurePath LBC samples (depending on sufficient residual material) were centrifuged and the supernatant was decanted. The pellets were resuspended in 800 μl phosphate-buffered saline and transferred to 2 ml vials for storage at –70°C before DNA extraction and subsequent HPV testing.

DNA extraction of storage samples

The DNA extraction for PCR-based assays was carried out using the Roche MagNA Pure automated system. Storage samples were thawed and 50 μl was added to a 32-sample well MagNA Pure tray. HPV16 +ve and –ve controls were included on each run. Nucleic acid from each sample was extracted using the automated MagNA Pure LC instrument (Roche Molecular Systems) in conjunction with the Total Nucleic Acid Extraction Kit (Roche MagNA Pure nucleic acid variable volume protocol). The purified total nucleic acid was eluted with a low-salt buffer to a final volume of 100 μl, which was transferred to a 2-ml vial for storage at –70°C.

High-risk HPV screening using the QIAGEN Hybrid Capture 2 test

Principle of assay

The QIAGEN HR-HPV DNA test uses HC2 technology which is a nucleic acid microplate hybridisation assay relying on signal amplification and detection of chemiluminescence. Following hybridisation with a probe containing complementary RNA sequences to 13 well recognised HR-HPV genotypes (HPV types 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59 and 68) the resultant RNA/DNA hybrid is captured onto the surface of a microtitre plate coated with antibodies specific for RNA/DNA hybrids. Immobilised hybrids are then reacted with alkaline-phosphatase-conjugated antibodies specific for RNA/DNA hybrids and detected with a chemiluminescent substrate which is cleaved by the action of alkaline phosphatase to produce light. The intensity of light emission denotes the presence or absence of target DNA in the sample.

Detection of HPV DNA using Hybrid Capture 2 test

Stored denatured LBC samples were equilibrated to room temperature before HR-HPV DNA detection using the QIAGEN HC2 assay according to the manufacturer's instructions. To ensure the most economical usage of kits only full microtitre plates (88 samples plus eight controls) were run. Results were read and calculated on the Digene Microplate Luminometer 2000 (DML 2000™) instrument using the HC2 software at the recommended RLU/Co ratio of ≥1.0. Those performing the HPV tests were blind to the corresponding cytology results. The HC2 testing was conducted by two experienced virology staff and they participated in an external quality assurance exercise.

High-risk HPV screening using the Roche AMPLICOR Microwell Plate Assay

During the ARTISTIC trial the opportunity arose to compare the HC2 test with the AMPLICOR test (Roche). There was a possibility that AMPLICOR would be more sensitive than the HC2 test and so there was a need to assess whether this might provide any clinical benefit. A comparison between HC2 and AMPLICOR was undertaken to determine whether one or the other test had greater utility in the setting of borderline cytology where the greatest need for effective triage exists. The AMPLICOR testing was performed on archived samples for which women had consented to further testing. None of the AMPLICOR results were acted on clinically. The original LBC samples had been spun down and resuspended in phosphate-buffered saline and stored at −70°C. Thawed samples were tested for β-globin as a test of DNA integrity. The results of the comparison between the tests is shown in Appendix 6, *Tables 64* and *65*.

The AMPLICOR test was also assessed in a real-time comparison with HC2 on the residual material from a group of 5020 ARTISTIC women during round 2 whose LBC specimen had been used for cytology and HC2. The results of this are also shown in Appendix 6, *Tables 66* and *67*.

Principle of AMPLICOR assay

The AMPLICOR test differs from the HC2 test by requiring a PCR step which simultaneously amplifies HPV target DNA and β-globin DNA. Amplification of HPV is dependent on a pool of biotinylated primers specific for the same 13 HR-HPV types detected by the HC2 test. Following amplification, the amplicon is denatured before being captured onto the surface of a microwell plate coated with either a pool of oligonucleotides specific for the 13 HR-HPV types or for the β-globin gene. The presence of immobilised amplicon is then detected by the addition of a streptavidin–horseradish peroxidase (SA-HRP) conjugate followed by a tetramethylbenzidene (TMB) conjugate. Any bound SA-HRP oxidises the TMB to form a coloured complex, the optical density (OD) of which can be read on an automated microwell plate reader.

Detection of high-risk HPV using the Roche AMPLICOR assay

The HPV DNA was amplified from a 50-μl volume of extracted sample DNA using the Roche AMPLICOR HPV amplification mix according to the manufacturer's protocol. After amplification and subsequent denaturation amplified HPV and β-globin product were detected according to the manufacturer's protocol. Samples were deemed positive if the HPV OD was ≥0.2 whereas samples giving an HPV OD < 0.2 and a positive β-globin signal were considered negative. Those samples giving a negative HPV signal and a negative β-globin signal were considered inhibitory or unsuitable for PCR.

HPV genotyping by prototype line blot assay

PCR amplification

The prototype line blot assay (LBA) used biotinylated PGMY primers[34] to target HPV-specific nucleotide sequences within the polymorphic L1 region of the HPV genome. A pool of primers was used to amplify DNA from 37 mucogenital HPV types.[35] In addition, primers that target a portion of the human β-globin gene were incorporated into the PCR mix to coamplify this gene, which acts as a control for sample adequacy. Following amplification under standard PCR conditions the product was denatured to render it single stranded before performing the detection stage.

PCR product detection

Denatured PCR product was added to wells containing hybridisation buffer and the line blot typing strips, which are precoated with specific HPV and β-globin probe lines. The biotin-labelled amplicon will only hybridise to those probe lines containing matching sequences. Following the hybridisation reaction the typing strip was washed stringently to remove any unbound material before the addition of SA-HRP, which binds to the biotinylated amplicon. After further washing a substrate solution containing TMB was added to each strip. Any bound SA-HRP catalyses the oxidation of TMB to form a blue complex which precipitates at the probe positions where hybridisation has occurred. The genotyping strip was then read visually by comparing the pattern of blue lines to the Line Blot reference guide.

HPV genotyping using the Roche Linear Array Assay

The Linear Array (LA) assay (Roche) is the improved commercialised version of the LBA used throughout this work. With minor modifications this assay is essentially similar to the LBA. A comparison between the LA and the LBA was carried out using samples that tested HC2-positive and/or AMPLICOR-positive within the group of 5020 ARTISTIC women during round 2. All linear array assays were carried out according to the manufacturer's instructions. The results of the comparison between the tests are shown in Appendix 6, *Figure 19*.

Changes to HPV testing protocol

Certain changes in technology and various practical considerations necessitated a number of variations from the original protocol regarding the virological testing of samples.

- All HC2-positive samples have been retested using the Roche prototype LBA rather than using an in-house GP5+/6+ consensus primer system.
- As a result of the unexpectedly high prevalence of HPV in the study population and the subsequent increased cost and time pressures in genotyping all positive samples, it has not been possible to test 10% of the HC2 –ve/cytology –ve samples using a consensus primer PCR-based assay.
- Inter-laboratory testing over the whole of the 5-year study was not possible because of the paucity of suitable collaborating laboratories. We did, however, participate in the 12-month external quality assurance scheme operated by Professor Heather Cubie to monitor the performance of the LBC/HPV pilot sites.[36] No quality problems were identified by this scheme. At all other times continued quality was monitored by the use of internal kit controls.
- Analysis of samples taken from cases of women with CIN3+ who were HPV –ve has been undertaken by the use of the Roche LBA.
- The HC2 assay is designed to detect integrated as well as episomal HPV sequences, therefore it was considered unlikely that investigation of these CIN2+ HC2 –ve cases using 14 type-specific primer pairs targeting the E7 open reading frame would prove productive.

Procedure for data collection

As women were flagged in both cytology laboratories participating in the trial (MRI and Stepping Hill, Stockport), a summary report containing NHS numbers as identifiers and cytology and histology results was sent every 3 months to the epidemiology/statistics office at the London School of Hygiene and Tropical Medicine (LSHTM), where these data were collated using NHS numbers and those coming from the HPV testing laboratory and the central ARTISTIC trial office using trial identification numbers. The final database contained trial numbers, NHS numbers, dates of birth and randomisation as personal identifiers, as well as, cytology, HPV testing and histology sample numbers with corresponding date of collection and results. These data were kept in a STATA,[37] file which was later used for analysis. Sources of information used in the trial are summarised in *Figure 4*.

Development of the database

Data were recorded using MICROSOFT ACCESS 2000.[38] Participants were identified on the database by a unique trial number (1–25078). This was verified by a 10-digit NHS number. Participants' demographic information (date of birth, address, first, last and previous names, comments, registered GP details, clinic/practice venue) and all cytology, HPV results and sample dates were recorded.

The Virology Laboratory kept a separate MICROSOFT ACCESS 2000 database of samples that were flagged for HPV testing as part of the trial. The virology database detailed the woman's trial number, laboratory identification number, name, date of birth, NHS number and HPV result. Any samples which came to the virology laboratory from the cytology laboratories in the ARTISTIC study for HPV testing that were not recognised as being part of the trial were included in a separate table of unidentified women, this helped to avoid samples being lost as a result of errors in information recorded on the cytology request form, such as the wrong date of birth, or a change of surname.

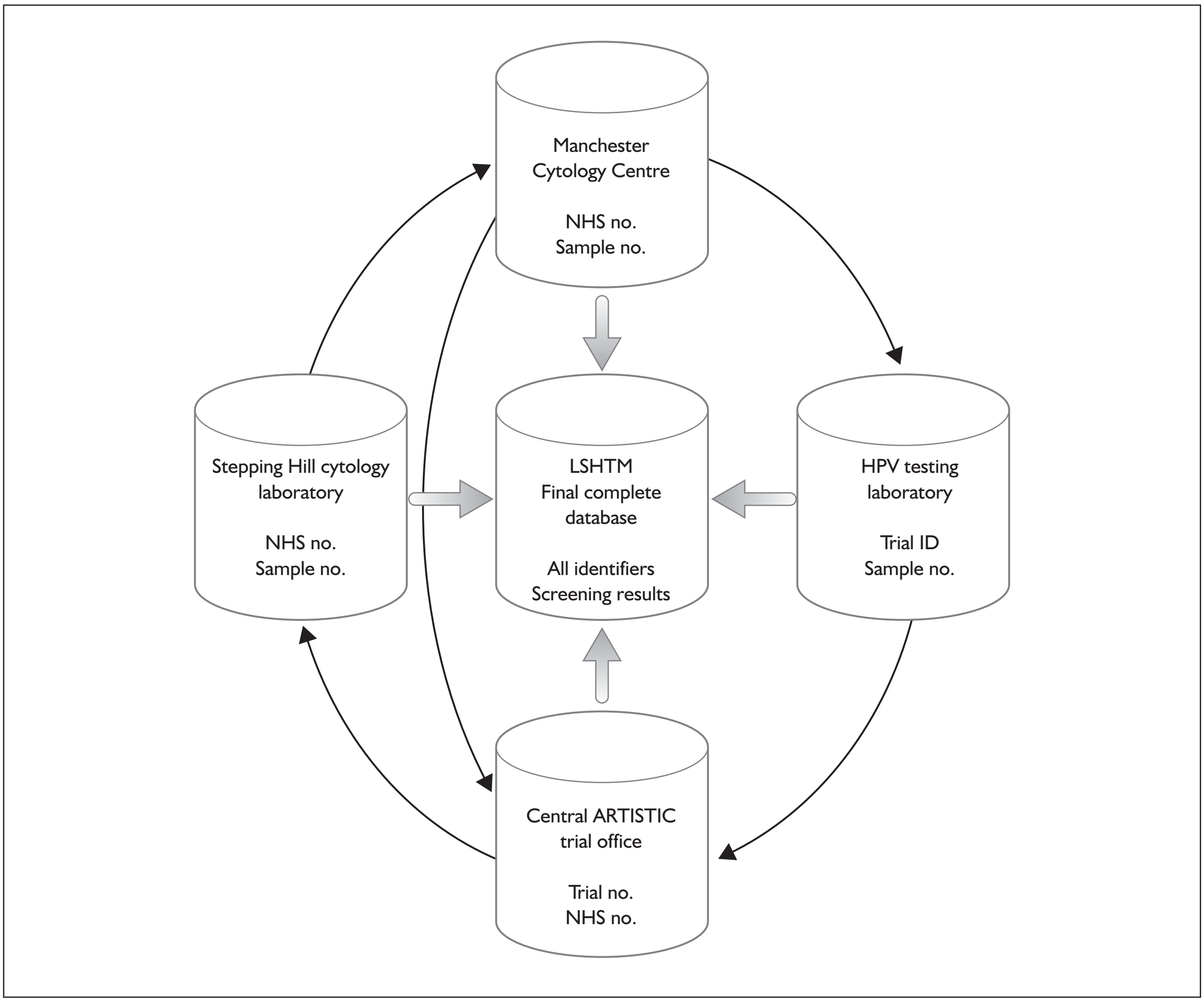

FIGURE 4 *Sources of information used in the trial. LSHTM, London School of Hygiene and Tropical Medicine.*

This database was passed on to the trial office on a regular basis to link copies of flagged cytology reports with HPV results, and enter this information on the main trial database.

Recording data/colposcopy data

On receipt of a consent form, demographic details were entered on the trial database and women were assigned trial numbers consecutively as their details were entered on the database. Copies of flagged cytology results were collected on a regular basis and matched to the woman's record on the database by performing a search on the 'date of birth' or 'NHS number' variable. Demographic details were updated if those on the cytology form differed from those on the database, after verification using NHS Open Exeter or by contacting the surgery.

The trial office received copies of correspondence from colposcopy clinics in Greater Manchester relating to colposcopy appointments, these were entered on the database in a subform, detailing the hospital, cytology and HPV result, biopsy result, treatment and the results of any follow-up tests as appropriate.

An audit of the colposcopy data was carried out to ensure that records were complete. The trial co-ordinator obtained an honorary research contract to access patient files at the colposcopy clinics, to confirm the number of attendances and events.

'Missing' data

By comparing data gathered in the central ARTISTIC trial office and at the LSHTM, some screening results were discovered to be missing in either database. The trial co-ordinator carried out a manual search using NHS Open Exeter to complete these missing screening records.

All women in the trial have been flagged on the NHS central cancer registry for cancer incidence and mortality, to obtain complete information in the long-term for missing data of which we are currently unaware.

Statistical analysis

Statistical plan

Statistical analysis of the primary outcome, CIN3+ detected in the screening round 2, was based on a test of proportions with confidence intervals of the difference. An intention-to-treat estimate of the effect of the intervention was determined using numbers randomised as the denominator. This assumes that all subjects without a follow-up screen are negative for CIN2/3+, and may be thought of as a measure of effectiveness of screening. An efficacy estimate was obtained by using the numbers screened in round 2 as the denominator. An efficacy estimate across both screening rounds was estimated by combining the estimate of the proportion of CIN3+ or CIN2+ for round 1 with the efficacy estimate for round 2.

Inclusion criteria: women were included if they:

- were aged 20–64 years attending the NHS screening programme in Greater Manchester (Manchester, Salford & Trafford, Stockport and Wigan)
- had an adequate round 1 sample defined as the first sample after randomisation that was cytologically adequate and gave a satisfactory HPV result by HC2.

Women were invited for their next routine LBC test 3 years after round 1 (round 2), but there was considerable variation in the actual interval. Women with no cytology result in the 30- to 48-month interval were initially excluded from analyses of results in round 2. A further analysis using a round 2 interval of between 26 and 54 months allowed fewer exclusions of second-screening round lesions.

The analysis of treatment policy was based on intention to treat. Women were therefore classified as HPV test revealed or HPV test concealed according to random allocation, irrespective of management. The primary outcome, i.e. the outcome of paramount importance was CIN3+ identified in round 2. Although CIN2+ represents the lesions that are treated, CIN3+ is widely accepted as the true cancer precursor and is the prime target for screening.

Economic analysis

Introduction

The main objective of the economic evaluation alongside the ARTISTIC trial was to assess the cost-effectiveness of HPV testing in addition to LBC when compared with a cervical screening programme using LBC only. Secondary objectives included subgroup analyses to identify characteristics of screened women that render HPV testing more cost-effective than if HPV testing were applied to all women. Further scenarios were developed and modelled to explore the cost-effectiveness of alternative approaches to the use of HPV testing within the NHSCSP.

Measuring costs

The cost analysis was carried out from the NHS and personal social services perspective. All costs refer to 2006. The trial data capture methods recorded cost-generating events incurred by women from the point of recruitment to their end point in the study. The key cost-generating events according to the protocol were:

- cervical screening at recruitment and 36 months for all women, and, selectively, repeat screening at 6, 12 and 24 months
- colposcopic examinations, biopsies and treatments for CIN
- histopathology analysis of biopsied material
- gynaecological treatments for severe CIN or cervical cancer.

Unit costs were estimated for these cost-generating events and attributed to the women experiencing the events in order to estimate total costs. Unit costs were derived from observational studies, most undertaken specifically for ARTISTIC, and existing tariffs and contracts, and from published sources.[39] Staff costs reflected the new pay system for NHS staff.[40]

The NHSCSP operates a comprehensive failsafe system to minimise the risk of women failing to be screened or managed appropriately. Within local cervical screening programmes (CSPs), the Exeter call/recall computer system generates letters reminding non-responders to attend for routine smears, and letters for women with abnormal smear results who have defaulted or who have had an inadequate smear result. Cytology laboratories have their own failsafe systems for checking that an appropriate referral has been made for women whose test result requires investigation by colposcopy (especially test results of severe dyskaryosis indicative of invasive cancer or glandular neoplasia that must be referred urgently). Failsafe arrangements in colposcopy clinics issue reminder letters to women who default from appointments and notification letters to their GP or other responsible clinician. However, costs were not prepared for the different components of this integrated system.

Cervical screening costs

General practice/community clinic costs

The unit cost for obtaining a cervical sample using the LBC technique covered the time for taking the sample by a doctor or nurse, the cost of the materials and transportation of the vial containing the sample to a cytology laboratory. Evidence from the primary care surveys undertaken in the English pilot study of LBC use[41] was used to derive the staff time required for taking an LBC cervical sample.

Cytology laboratory costs

The unit cost of an LBC cytology test covered: the costs of ThinPrep materials (equipment and consumables) for processing the LBC sample; staff time for processing the sample and staff time for reading the slide.

When deriving unit costs for the LBC processors and associated consumables, estimates were based on an assumption that the ThinPrep LBC technology had been introduced throughout the NHSCSP. The NHSCSP is co-ordinated through a system of regional Quality Assurance Reference Centres (QARCs), which cover a number of subregions. Cytology laboratories are situated in acute hospitals located in towns and cities across the regions. In 2004–5 there were nine QARCs with 28 subregions and 140 cytology laboratories, of which 117 (84%) had an annual workload of 40,000 slides or less. The total workload was 4.02 million slides.[42]

HOLOGIC manufactures two types of ThinPrep machines for processing cervical samples and producing slides: the T2000 machine and the T3000 machine. The optimum capacity per year is around 60,000 for a T3000, and 40,000 samples for a T2000, which is less automated. Activities associated with the processing machines are normally performed by medical laboratory assistants. The Central Manchester Laboratory, where the ARTISTIC samples were processed, had both a T3000 machine and a T2000 machine. The T3000 machine was used for the majority of trial samples.

A model was developed to identify the optimal laboratory configurations for installing T2000 and T3000 machines within QARCs, taking account of equipment contracts, labour costs for operating the machines (mid-scale salary of a medical laboratory assistant), and any transport costs between laboratories should centralisation of processing activities occur. Yearly contract prices for leasing T3000 and T2000 machines (inclusive of consumables) and staff costs for operating the machines were entered in the model, and mileage allowances for distances within groups of laboratories to cover the spoke-to-hub transfer of vials, and the hub-to-spoke transfer of slides were included.[43] As the NHS contract price structure was supplied in confidence, costs could not be reported in disaggregated form. The main parameters of the model that determined the total annual cost for England in 2005–6 were: duration of contract, number of T2000 processors and number of T3000 processors. Labour costs for medical laboratory assistants were adjusted according to the type of processors installed and annual workload.

To estimate the durations of time required for reading and reporting LBC slides, self-timing surveys were undertaken by cytoscreeners, including medical staff, in the two laboratories.[44] During 2001, 10 staff members in the Manchester laboratory and four in the Stockport laboratory were trained to read LBC slides: they included five cytoscreeners, five biomedical scientists and four senior doctors (cytopathologists). These staff participated in three timings surveys during 2001–2, when they recorded the time taken for examining and reporting individual slides. Staff who operated the ThinPrep processing machine also filled in survey forms, and observational fieldwork was carried out. Costings for the Thin Prep resources were obtained from the laboratories and the equipment supplier.

HPV testing costs

After the LBC samples were processed for cytology, vials were sent almost daily in batches of up to 50 to the Department of Virology in the MRI, where the QIAGEN HC2 primary screening technology had been acquired for the trial. Analysis of the samples was a multistage process requiring the input of a laboratory technician at various stages. A self-timing survey was carried out by the technician midway through the recruitment period. The manufacturer supplied costs for the HC2 testing kits according to various assumptions over usage levels, and the Virology Department provided other associated costs (consumables, staff costs).

Colposcopy costs

To inform the process of attributing unit costs to the colposcopic management of women, timing surveys were carried out in four hospital colposcopy clinics participating in the ARTISTIC trial and in a clinic in the North East region. The surveys identified four types of attendances with differing mean durations: diagnostic colposcopy with a biopsy taken (usually punch biopsies); colposcopic treatment [usually large loop excision of the transformation zone (LLETZ)]; surveillance colposcopy with, or without, a cervical sample; and a cervical sample only. The cervical samples were frequently taken using the SurePath LBC technique. Unit costs for the different types of attendances in the ARTISTIC colposcopy dataset were derived from unit costs supplied by the finance departments of two NHS Trusts in Greater Manchester that administered colposcopy clinics, and from published costs for SurePath cytology.

Biopsied samples of cervical tissue were examined in the histopathology laboratories of the hospitals where the colposcopy clinics were located. Observational fieldwork confirmed that punch biopsy samples were processed and reported on more quickly than larger samples of excised tissue resulting from a LLETZ or cone biopsy. Histology laboratory costs were also supplied by the two NHS Trusts.

Gynaecological treatments

Day case or 24-hour admissions for a cervical procedure performed under general anaesthetic (such as a cone biopsy), and inpatient admissions for hysterectomies were identified in the ARTISTIC colposcopy dataset. NHS tariffs were applied to these admissions.

Measuring health benefits

The purpose of ARTISTIC's TTO postal survey was to provide women's valuations of health states following cervical screening involving HPV testing. The health states (i.e. scenarios) corresponded to the states in the Markov model intended to establish cost-effectiveness. The valuations would be used to generate QALYs for cost–utility analyses of cervical screening programmes. Research ethics approval was obtained. Questionnaires were sent to almost 1600 ARTISTIC women whose cytology and HPV results were –ve in both round 1 and round 2 of the trial, and more than half of the questionnaires were completed.

Utility scores were generated for five health states, but they were not incorporated in a Markov model as originally intended, because of the similarity in the clinical results for two arms of the trial. It is for this reason that an account of the TTO survey is not presented in this report, but more information is available at http://brunel.ac.uk/about/acad/herg.

Synthesis of costs and benefits

Observed within-trial cost-effectiveness

We proposed to analyse and compare the costs for the two trial arms according to the protocol [*scenario 1*]:

- the first round alone (that is, over 30 months from recruitment)
- the full trial (that is, rounds 1 and 2 combined covering 48 months from recruitment)

on an 'intention to treat' basis according to randomisation.

Alternative configurations of the national screening programme

As one of the purposes of the trial was to inform the NHSCSP of the potential roles that could be adopted for HPV testing, three alternative scenarios for introducing HPV testing alongside cytological screening would be explored in the cost analyses:

- primary screening with LBC, followed by HPV testing as a triage for women with a borderline or mild dykaryosis report; the original LBC sample would be used for HPV testing. [*scenario 2*]
- primary screening with an HPV test followed by LBC as a triage for women with an HPV +ve result [*scenario 3a*]; the initial sample for HPV testing would be taken with a dedicated HPV cervical sampler developed by QIAGEN and women would return to their GP or FPC to have a second cytology sample taken with an LBC cervical sampler
- primary screening with an HPV test, followed by LBC as a triage for women with a +ve test result [*scenario 3b*]; the cytological examination

would be performed on the original sample, which was taken with an LBC cervical sampler.

The management of those women who are triaged in these scenarios would be in accordance with the protocol for an evaluation for the implementation of HPV testing in NHS sentinel sites and from expert opinion. The reason for considering two variations of the third scenario is that commercially there are different types of cervical samplers available, in particular, the LBC sampler used in the trial (provided by ThinPrep) and a sampler developed by QIAGEN specifically for HPV testing. The QIAGEN sampler could be advantageous in screening programmes where high volumes of HPV tests are performed, because the medium in the vials would not have to be 'denatured' before being analysed (*scenario 3a*). Those women triaged for cytological analysis would, however, need to be resampled using an LBC cervical sampler.

Modelling beyond the trial end point

Although there was an intention in the trial protocol, which was originally developed in 1998–99, to undertake Markov modelling beyond the end point of the trial to determine the impact that HPV testing could have on life-years gained, the feasibility of completing the modelling for this report depended upon the clinical results, and in particular, the performance of HPV testing in identifying additional cases of CIN2 or CIN3+. For the clinical analyses presented in this report, 54 months is the maximum duration of follow-up for women recruited in the trial, but many women had not yet been followed up for this length of time. Moreover, the emerging clinical results for round 2 indicated an unexpectedly low incidence of high-grade pathology. As the trial progresses through a third round of screening, that is 72 months after recruitment, the observed incidence rates of CIN2+ for the two screening techniques (LBC versus HPV testing) should be sufficiently reliable for modelling purposes.

A range of sensitivity analyses were carried out to explore the effects of key variables on the overall cost results, such as HPV test cut-off levels, unit costs for the colposcopy-related events and LBC inadequate rates for the NHSCSP.

Protocol amendments

TTO survey methods

It was originally intended that interviews for the TTO survey would be conducted with a sample of 200 women aged 20–64 years from outside the trial, and who were invited for cervical screening. This proposal was reassessed in year 4 following the publication of a systematic review of TTO methodologies,[45,46] which indicated that: a large population sample was needed to enable stratification, because demographic characteristics tend to influence TTO results; and the survey should cover women who were already familiar with HPV testing to minimise the likelihood of the respondents becoming 'zero-traders' (unwilling to trade years of life in exchange for improvements in health). Consequently, women in the ARTISTIC trial became the sample population for a large-scale postal survey.

Implementation of LBC in primary care screening

National policy developments between 2000 and 2003 over the use of LBC in cervical screening affected the fieldwork programme for measuring costs outlined in the original protocol. The National Institute for Clinical Excellence (NICE), after considering reports from three national pilots of LBC implementation,[41,47,48] and a systematic review[49] advised in October 2003, that LBC techniques be introduced across the cervical screening programmes for England and Wales.[11] Implementation of the guidance was mandatory, and a timescale of 5 years was set to complete the retraining of laboratory staff involved with cervical cytology and primary care sample takers, and the installation of equipment in laboratories. Rationalisation of pathology services and some centralisation of LBC processing was anticipated.[11]

Observational fieldwork in general practices to assess the impact of screening women for HPV testing was not carried out because, by adopting the LBC method, only a single cervical sample was needed from which material for HPV testing could be extracted. Moreover, in a postal survey of LBC-trained sample takers in 120 practices involved in the English LBC pilot study, 82% of respondents felt that the consultation time when taking samples with LBC was no different or slightly quicker when compared with conventional smears.[50]

National postal surveys of virology, cytology and histology laboratories to assess the generalisability of costs derived from local fieldwork were not carried out because laboratory services were being reconfigured in response to the NICE guidance on adopting LBC and the wider national policy for modernising pathology services.[51] However, national data on cytology and virology laboratories were available through framework contracts signed by the supply chain (Purchasing and Supply Agency) and from the NHS Cancer Screening Programme's databases relating to the conversion to LBC.

Finally, in 2004, the NHSCSP issued revised guidelines[52] on referral to colposcopy after one mildly dyskaryotic sample – the guidance previously advised referral after two samples. To assess the impact of the referral guidance, a questionnaire on the management of women and clinic appointment strategies was circulated to all 178 colposcopy services in England under the auspices of the British Society for Colposcopy and Cervical Pathology and the NHSCSP.[53] In view of these activities, a national survey for the ARTISTIC trial was not carried out.

Psychological analysis

Samples of consecutive women aged 20–64 years with negative or mildly abnormal cytology who had been recruited into the trial were sent a booklet of questionnaires by post approximately 2 weeks after they had received the results of their baseline cytology. Women in the revealed arm received the results of their HPV test with their baseline cytology result, and women in the concealed arm were informed only of the cytology result. Two information leaflets were distributed to women who were eligible to enter the study, which outlined the purpose of the study and provided specific information regarding HPV. The leaflets explained that HPV infection was relatively common in women including the statement 'Up to 70% of women have this infection in their cervix at some point in their life but in most cases this clears itself up.' Helpline telephone numbers were available for women who required further information before or during the study.

Questionnaire measures

The *General Health Questionnaire* (GHQ-28)[54] measures generalised psychological distress 'over the past few weeks'. A cut-off score GHQ ≥4 was employed to estimate the numbers of probable cases of affective disorder in the sample.

The *Spielberger State–Trait Anxiety Inventory* (STAI)[55] assesses two domains: state anxiety levels 'right now, that is, at this moment' (STATE) and trait anxiety 'how you generally feel' (TRAIT). GHQ and STAI higher mean scores indicate greater levels of general psychological distress and state and trait anxiety respectively.

The *Sexual Rating Scale* (SRS)[56] determines sexual satisfaction with the woman's current partner, and the participants were instructed to complete the SRS only 'if they had a current partner'. These are rescaled as percentage scores (0–100%) generated from the SRS data, with higher scores indicating greater levels of sexual satisfaction in their current relationship.

Initially, the questionnaire data were collected in face-to-face interviews ($n = 106$) but postal delivery was subsequently adopted by the investigators because of time and economic costs. Non-responders were posted repeat questionnaires approximately 2 weeks after the initial mailing, and women who returned all four questionnaires completely blank were coded as non-responders. Those participants who completed at least one of the four questionnaires were classified as responders.

Statistical methods

Sample size and sampling

The primary comparison specified in the study protocol was of GHQ caseness between the HPV revealed and the HPV concealed arms for women who were HPV +ve but cytology –ve. Therefore the baseline for calculating power is the GHQ caseness rate in the general population, among whom the prevalence of such psychiatric morbidity (GHQ ≥5) varies from 4% to 11% with an average of about 7%.[25] Comparison was made between subjects who are HPV +ve (revealed)/cytology –ve and HPV +ve/cytology –ve in the concealed arm for GHQ caseness. Because of the smaller cohort in the concealed arm, we would need to use unequal sampling to obtain sufficient numbers. Using a 1 : 2 sampling ratio would require 470 completed responses in the revealed arm and 235 in the concealed arm, and the study would have 80% power to detect a difference of 7% versus 14% in the numbers of GHQ cases (GHQ ≥4) with a two-sided 5% significance level. The planned sample size of the main ARTISTIC trial was very much larger; therefore, stratified sampling was used with sampling fractions differing according to baseline HPV status, baseline cytology and allocation group. This ensured that actual numbers sampled in each arm were approximately in proportion to the randomisation ratio.

The same comparison between HPV –ve and HPV +ve was also made among women in the revealed arm who had negative cytology. Comparing a sample of 470 in the HPV –ve (revealed)/cytology

–ve group against the 470 women in the HPV +ve/cytology –ve group would give a power of 93% to detect the difference between 7% and 14%.

For subjects with mild dyskaryosis/borderline cytology the same two comparisons made would be: (1) between all affected subjects in the concealed arm and those in the revealed arm who are HPV +ve and (2) between those who are revealed as HPV +ve as compared with those who are HPV –ve.

Early data from a patient choice trial[27] detected a GHQ-28 caseness rate of over 20% in women who present with recurrent mildly dyskaryotic/borderline cytology. With 200 subjects in each of these three groups the study will have a power of 89% to detect a difference between 25% and 40% in caseness with a 0.05 two-sided significance level.

Statistical analysis

The primary statistical analysis was a logistic regression model for GHQ caseness including covariates for the intervention group, initial screening test results and age decade. Secondary analysis compared the questionnaire scores using analysis of covariance with the same covariates. Analyses were carried out using the statistical package STATA,[37] weighting data by the sampling fraction from the main trial in which this study is nested. GHQ and STAI-STATE measures were positively skewed, so for these measures, confidence intervals based on the non-parametric bootstrap[57] are presented.

Chapter 3
Results

Clinical results

The CONSORT diagram (*Figure 5*) shows that of 25,078 women who consented to randomisation, 568 were excluded from the analyses because 222 were outside the screening age range and 346 had inadequate tests or missing results. All round 1 analyses are restricted to the remaining 24,510 randomised women (18,386 allocated to the revealed arm, 6124 to the concealed arm) aged 20–64 years who had both adequate cytology and HPV tests in round 1.

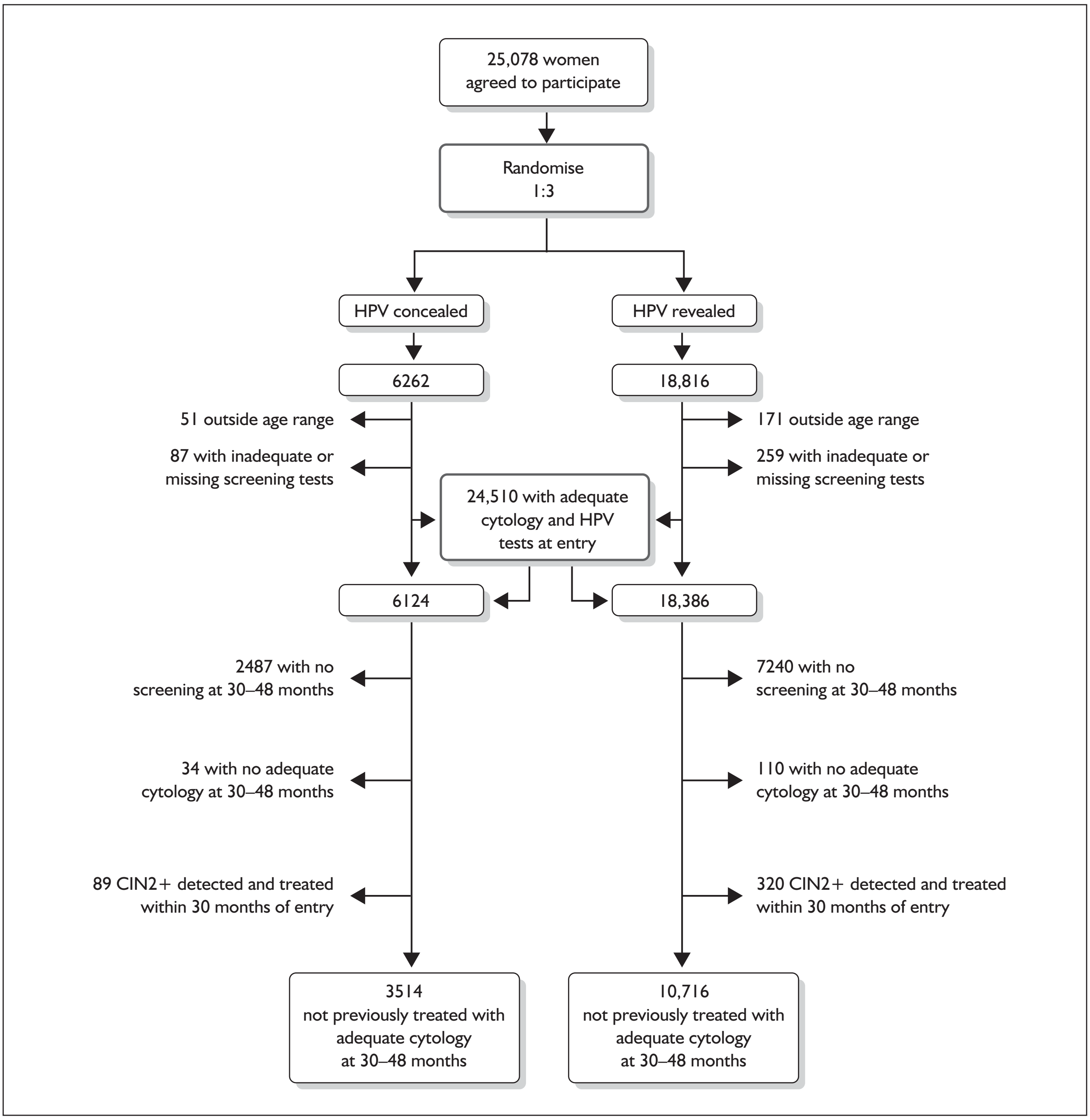

***FIGURE 5** CONSORT diagram of the ARTISTIC trial for the 30–48 months definition of round 2.*

Round 2 results are based on 14,230 (58.1%) of those women who did not have CIN2+ histology in round 1 and had an adequate cytology result in round 2. This was defined as the first cytologically adequate test between 30 and 48 months following round 1, taken before 1 May 2007. A further 553 (2.3%) women were followed up 30–48 months after round 1, but of these, 409 had CIN2+ in round 1, and 144 had no adequate round 2 cytology result. Round 2 analyses are therefore based on 10,716 of 18,386 women in round 1 (59.4%) in the revealed arm, and 3514 of 6124 in round 1 (57.4%) in the concealed arm.

Round 2 exclusions

Eleven subsequent CIN2 cases (11 revealed, 0 concealed) and six CIN3+ cases (five revealed, one concealed) were ignored because the woman's round 2 sample was cytologically negative. This convention is necessary to give uniform round 2 follow-up between the arms of the trial, because HPV results were ignored in the concealed arm. In addition, 12 CIN2 cases (seven revealed, five concealed) and 14 CIN3+ cases (10 revealed, four concealed) were excluded because there was no preceding round 2 sample. Six of these 12 excluded CIN2 cases and all 14 excluded CIN3+ cases are included in the alternative analyses (*Table 15*) in which round 2 is defined as the first adequate cytology result between 26 and 54 months after round 1. Details of all excluded CIN2 and CIN3+ cases are given in *Table 3*. To minimise exclusion of CIN3+ cases in this alternative analysis an abnormal cytology result on the date of histology was assumed for three CIN3+ cases diagnosed 29, 31 and 35 months after round 1 with no abnormal smear record.

Accrual

Women entered the study between July 2001 and October 2003 as shown in *Figure 6*. Accrual was steady, slowing only a little after recruitment of women below 30 years old was stopped. *Figure 7* shows the rate of return for round 2 cytology samples. Between July 2004 and April 2007, 14,639 women entered round 2 with adequate cytology, representing almost 60% of the original cohort. Of these women, 1325 did not have an HPV test. There was no difference between the proportions who attended round 2 from the two arms.

The accrual from each Health Authority is shown in *Table 4*. The routine recall policy varied among Health Authorities before the 2005 national guidance on 3-year and 5-year follow-up, although invitations were sent from the trial office to all women at 3 years. Health Authority recall dates for women in the trial were altered in 2005 to bring them in line with the trial protocol (discussed in more detail in Chapter 2, Links with screening co-ordinators).

Cytology, HPV and histology data from round 1

Table 5 shows the characteristics in round 1 of those women who did and did not attend for round 2 screening. A higher proportion of older women attended for screening in round 2 (66% aged 40–64, 43% aged 20–29). This was reflected in the round 1 HPV +ve rates for those who did and did not attend for round 2 screening; 12.6% versus 19.7% respectively. There was however no difference in either baseline age or HPV rates between the arms in round 2 indicating that the pattern of adherence to round 2 did not introduce bias.

Of the 25,078 samples collected in round 1374 (1.5%) were inadequate for cytology and 141 (0.6%) were insufficient for HPV testing. The cytology results are tabulated against the HPV results in *Table 6*. Overall there was a cytology –ve rate of 87.2%, 7.3% of smears showed borderline changes, 3.6% mild dyskaryosis, 1.1% moderate dyskaryosis and 0.8% severe dyskaryosis. This latter proportion, 1.9% moderate and severe dyskaryosis combined is almost identical to the calculation (1.8% moderate/severe) made before the trial. It can be seen that the proportions of cytological abnormality are almost identical between the arms. The cytologically negative women who were HPV +ve represented the only real difference between the arms in terms of potential disease detection, as women in the revealed arm were offered colposcopy if the HPV tests were persistently positive over 12–24 months. There were 1675 such women accounting for 9.1% of the revealed arm.

Overall 3813 (15.6%) women were HPV +ve, while women with negative cytology had an HPV rate of 10.4%. Women who were HPV +ve had an abnormal cytology rate of 14.6% borderline; 16.1% mild dyskaryosis and 10.9% moderate or worse. HPV +ve rates rose as the grade of cytological abnormality increased; borderline, mild, moderate and severe dyskaryosis had HPV +ve rates of 31%, 70%, 86% and 96% respectively.

TABLE 3 *CIN3+ and CIN2 cases excluded in round 1 and in round 2 under original and/or alternative rules*[a]

		Status under original rules	**Status under alternative rules**
R	**C**	**Round 2: 30–48 months after round 1**	**Round 2: 26–54 months after round 1**
No. CIN3[b]			
1	0	Excluded in round 2: no cytology between 30 and 48 months, histology at 35 months	Included in round 2: negative round 2 cytology at 52 months after histology. Abnormal round 2 cytology assumed at histology date (35 months)
0	1	Excluded in round 1: negative round 1 cytology, histology at 29 months	Excluded in round 1 but included in round 2: abnormal round 2 cytology assumed at histology date (29 months)
3	0	Excluded in round 2: CIN3 after CIN2 in round 1	Excluded in round 2: CIN3 after CIN2 in round 1
5	1	Excluded in round 2: negative round 2 cytology between 30 and 48 months	Excluded in round 2: negative round 2 cytology between 30 and 48 months
1	0	Included in round 2: abnormal round 2 cytology at 36 months, histology at 59 months	Excluded in round 2: negative round 2 cytology at 29 months and histology 30.2 months after round 2 cytology
2	0	Excluded in round 2: CIN3 after CIN3 in round 1	Excluded in round 2: CIN3 after CIN3 in round 1
0	1	Excluded in round 2: no cytology between 30 and 48 months	Included in round 2: abnormal round 2 cytology at 28 months, histology at 32 months
0	1	Excluded in round 1: negative round 1 cytology, histology at 27 months	Excluded in round 1 but included in round 2: abnormal round 2 cytology at 27 months, histology at 27 months
6	1	Excluded in round 2: no cytology between 30 and 48 months	Included in round 2: abnormal round 2 cytology between 48 and 54 months, histology between 50 and 61 months
No. CIN2[c]			
1	0	Excluded in round 1: negative round 1 cytology, histology at 15 months	Excluded in round 1: negative round 1 cytology, histology at 15 months
11	0	Excluded in round 2: negative round 2 cytology between 30 and 48 months	Excluded in round 2: negative round 2 cytology between 30 and 48 months
1	0	Included in round 2: abnormal round 2 cytology at 35 months, histology at 40 months	Excluded in round 2: negative round 2 cytology at 26 months, histology at 40 months
1	0	Excluded in round 2: negative round 2 cytology at 45 months after histology at 35 months	Excluded in round 2: negative round 2 cytology at 45 months after histology at 35 months
3	2	Excluded in round 2: no round 2 cytology between 30 and 48 months	Excluded in round 2: no round 2 cytology between 26 and 54 months
0	1	Excluded in round 2: CIN2 after CIN3 in round 1	Excluded in round 2: CIN2 after CIN3 in round 1
3	0	Excluded in round 2: CIN2 after CIN2 in round 1	Excluded in round 2: CIN2 after CIN2 in round 1
0	1	Excluded in round 2: no cytology between 30 and 48 months, histology at 31 months	Included in round 2: abnormal round 2 cytology at 28 months, histology at 31 months
3	1	Excluded in round 2: no cytology between 30 and 48 months	Included in round 2: abnormal round 2 cytology between 48 and 54 months, histology between 54 and 66 months
0	1	Excluded in round 2: negative round 2 cytology at 33 months after histology at 30 months	Included in round 2: abnormal cytology at 29 months, histology at 30 months

R, revealed arm; C, concealed arm.

a Alternative definitions: (1) Round 2: First adequate cytology 26–54 months instead of 30–48 months after round 1. (2) Abnormal round 2 cytology on date of histology assumed for two CIN3 cases diagnosed at 29 and 35 months after round 1. (3) Five CIN3 at round 2 with CIN2+ in round 1 excluded. Four CIN2 at round 2 with CIN2+ in round 1 excluded.

b CIN3+ cases: two excluded in round 1 and 20 excluded in round 2 under original rules; 12 excluded in round 2 under alternative rules, including one extra exclusion.

c CIN2 cases: one excluded in round 1. 27 excluded in round 2 under original rules, 22 excluded in round 2 under alternative rules, including one extra exclusion.

***FIGURE 6** Accrual to trial between July 2001 and October 2003.*

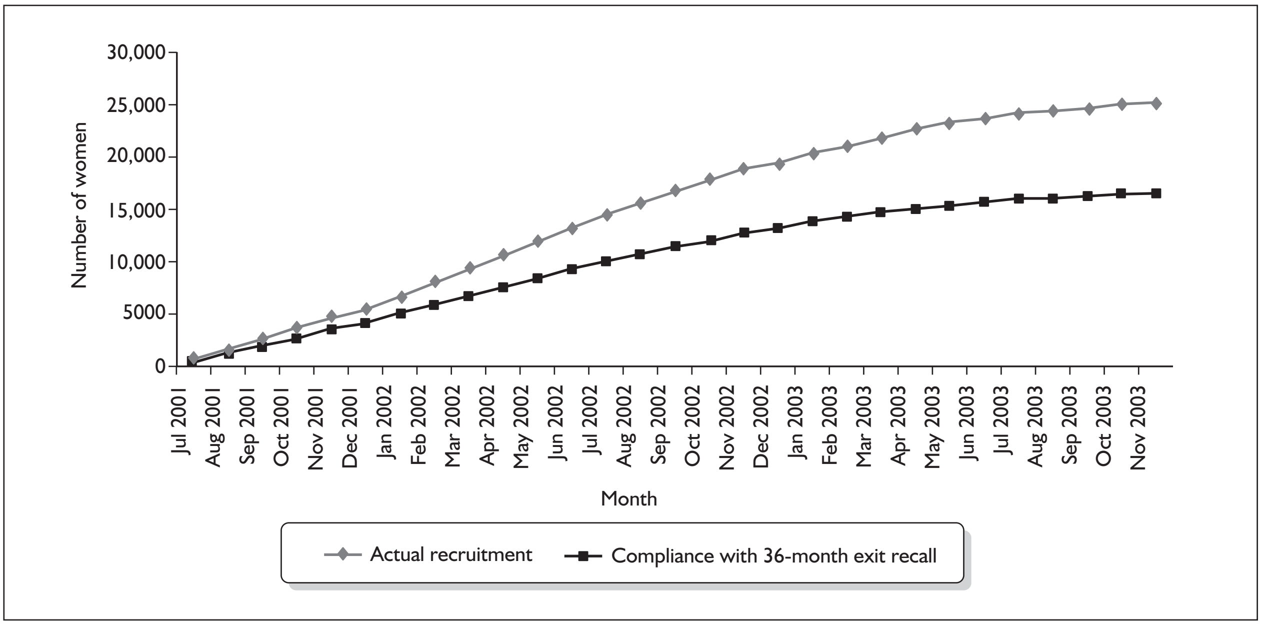

***FIGURE 7** Accrual and follow-up curves of women returning for cervical samples in round 2 by original month of accrual.*

***TABLE 4** Number of women recruited in each Health Authority*

Health Authority	Number of women recruited
Ashton, Wigan & Leigh	4097
Manchester	6721
Salford & Trafford	6459
Stockport	7801
All Health Authorities	25,078

TABLE 5 *Characteristics in round 1 of women with and without screening in round 2[a] by randomisation*

	Revealed arm				Concealed arm				All women in the trial			
	With second screening		Without second screening		With second screening		Without second screening		With second screening		Without second screening	
	No.	%	No.	%	No.	%	No.	%	No.	%	No.	%
Age (years)												
20–24	797	7.4	1136	14.8	257	7.3	385	14.8	1054	7.4	1521	14.8
25–29	882	8.2	1064	13.9	292	8.3	353	13.5	1174	8.3	1417	13.8
30–39	3233	30.2	2492	32.5	1058	30.1	831	31.8	4291	30.1	3323	32.3
40–49	2987	27.9	1614	21.0	955	27.2	561	21.5	3942	27.7	2175	21.2
50–64	2817	26.3	1364	17.8	952	27.1	480	18.4	3769	26.5	1844	17.9
Cytology												
negative	9556	89.2	6486	84.6	3110	88.5	2228	85.4	12,666	89.0	8714	84.8
borderline/mild	1085	10.1	901	11.7	385	11.0	296	11.3	1470	10.3	1197	11.6
moderate+	75	0.7	283	3.7	19	0.5	86	3.3	94	0.7	369	3.6
HPV testing												
negative	9382	87.6	6144	80.1	3059	87.1	2112	80.9	12,441	87.4	8256	80.3
positive	1334	12.4	1526	19.9	455	12.9	498	19.1	1789	12.6	2024	19.7

a Excluding women with CIN2+ lesions detected and treated within 30 months of round 1. See table of exclusions (*Table 3*).

The striking relationship between HPV infection and age is shown in *Figure 8*. The HPV +ve rates fall from 40% in women aged 20–24 to less than half (18.5%) in women aged 30–34, down to just 6% in women aged over 55 years.

The relationship between cytology, HPV status and age is shown in *Table 7*. If the moderate and severe dyskaryosis rates are combined the values are 112/2575 (4.3%) and 103/2591 (3.9%) in women aged 20–24 and 25–29 years respectively, falling to 223/13,731 (1.62%) in women aged 30–49 and 25/5613 (0.45%) in women aged 50–64. This fall in abnormal cytology is largely the result of the falling rates of HPV infection, because among HPV +ve women the rates of high-grade cytology remained steady with advancing age; 203/1749 (11.6%) and 197/1697 (11.6%) for age 20–29 and 30–49 respectively. There was however a fall in HPV +ve women aged 50–64, 17/367 (4.3%).

Figure 9 depicts graphically the relationship between age and cytology and the rate of HPV infection. It is clear that rates of HPV infection in negative cytology, as well as in borderline and mild dyskaryosis are very age dependent. In moderate dyskaryosis the effect of age appears lessened and almost disappears with severe dyskaryosis. This reflects the very high association with CIN3 in severe dyskaryosis whatever the age. In younger women a high proportion of mild abnormalities merely reflects HPV infection.

The histological data from round 1 are shown by age and grade of cytology for both HPV +ve and HPV –ve women in *Table 8*. In total there were 313 CIN3+ lesions and 586 CIN2+ (273 CIN2). Only nine CIN3+ lesions were detected in women aged 50 years or more and all of these occurred in association with HPV +ve/high-grade cytology. Only 10 CIN2 lesions occurred in women aged 50 years or more and only three of these occurred in association with HPV +ve/high-grade cytology.

Among the 313 women with CIN3+, 91 (29.1%) were detected in women with low-grade cytology and 212 (67.7%) in women with high-grade cytology. For CIN2+ the proportions were 225/586 (38.4%) and 329/586 (56.1%) respectively. When histological outcomes in women with abnormal cytology were analysed by initial HPV status (by HC2), 93.3% of CIN2+ and 97% of CIN3+ were detected in HPV +ve women. The proportion of women with moderate and severe dyskaryosis overall is 50 times greater in HPV +ve women (10.9%) compared with HPV–ve women (0.22%).

The same data by randomisation are shown in Appendix 6 (*Table 58*: Revealed arm and *Table 59*: Concealed arm), and corresponding data for round 2 in both arms together (*Table 60*).

A total of 313 cases of CIN3+ and 273 of CIN2 were diagnosed in round 1. There were no significant differences in proportions between the arms. Only 28 CIN2 and nine CIN3+ lesions were detected in the HPV –ve group, as against 245 CIN2 and 304 CIN3+ in the HPV +ve group. The latter included 22 CIN2 and 10 CIN3+ lesions in women in the revealed arm with negative cytology

TABLE 6 *Screening results for HC2 and LBC for the revealed and concealed arms in round 1*

	Revealed arm			Concealed arm			All women in the trial		
Cytology	**HPV –ve**	**HPV +ve**	**Subtotal**	**HPV –ve**	**HPV +ve**	**Subtotal**	**HPV –ve**	**HPV +ve**	**Subtotal**
Negative	14,367	1675	16,042	4787	551	5338	19,154	2226	21,380
	(92.5%)	(58.6%)	(87.3%)	(92.6%)	(57.8%)	(87.2%)	(92.6%)	(58.4%)	(87.2%)
Borderline	923	420	1343	309	137	446	1232	557	1789
	(5.9%)	(14.7%)	(7.3%)	(6.0%)	(14.4%)	(7.3%)	(5.9%)	(14.6%)	(7.3%)
Mild	196	447	643	69	166	235	265	613	878
	(1.3%)	(15.6%)	(3.5%)	(1.3%)	(17.4%)	(3.8%)	(1.3%)	(16.1%)	(3.6%)
Moderate	34	170	204	4	63	67	38	233	271
	(0.2%)	(5.9%)	(1.1%)	(0.1%)	(6.6%)	(1.1%)	(0.2%)	(6.1%)	(1.1%)
Severe+	6	148	154	2	36	38	8	184	192
	(0.1%)	(5.2%)	(0.8%)	(0.04%)	(3.8%)	(0.6%)	(0.04%)	(4.8%)	(0.8%)
Total	15,526	2860	18,386	5171	953	6124	20,697	3813	24,510
	(100%)	(100%)	(100%)	(100%)	(100%)	(100%)	(100%)	(100%)	(100%)

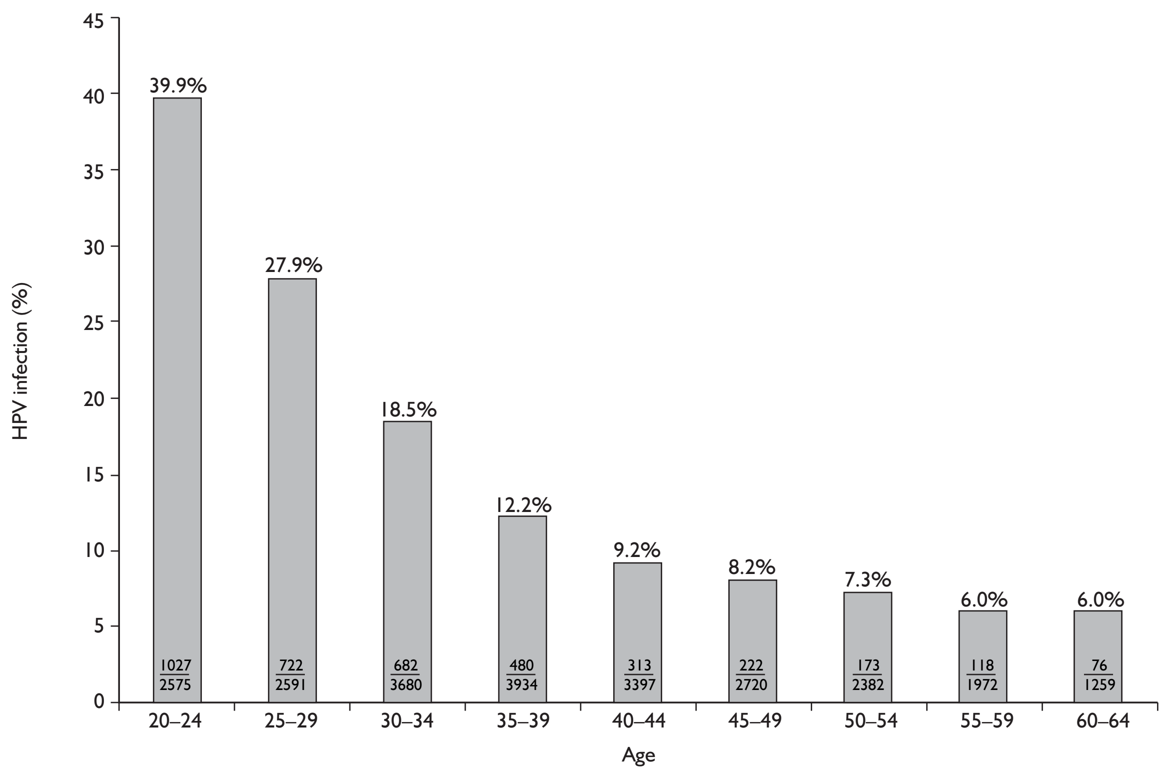

FIGURE 8** Prevalence of high-risk HPV (HR-HPV) by Hybrid Capture 2 (HC2) according to age quinquennia. Reproduced with permission of Cancer Research UK from Kitchener H, Almonte M, Wheeler P, Desai M, Gilham C, Bailey A,* et al. *HPV testing in routine cervical screening: cross sectional data from the ARTISTIC trial.* Br J Cancer *2006;95***:56–61.*[31]

who were referred for colposcopy because they had persistent HPV infection.

The 12 cancers included in the CIN3+ category of lesions are summarised in *Table 9*. Eight of the nine cancers detected in round 1 were HPV +ve with moderate or worse cytology (severe dyskaryosis in six cases, moderate in one and glandular neoplasia in one). The remaining round 1 case, an adenocarcinoma, was HPV –ve with borderline cytology. Two of the three cancers detected in round 2 had negative cytology at both round 1 and round 2, and one was also HPV –ve in round 1. This was an adenocarcinoma that may have occurred high in the cervical canal and was perhaps inadequately sampled. The third round 2 cancer had borderline cytology in both round 1 and round 2. This woman was also HPV –ve in round 1, and had no HPV test in round 2.

Cytology, HPV and histology data in round 2

A total of 14,639 women had an adequate cytology result in round 2, representing 60% of the original cohort. HPV and cytology results for round 2 of screening are shown by randomisation in *Table 10* and by age in round 1 in *Table 11*. Comparison against the corresponding round 1 results (*Tables 6* and *7*) shows a remarkable and unexpected reduction in cytological abnormality in both arms, the cytology –ve rate rising from 87.2% in round 1 to 95.1% in round 2. The borderline and mild dyskaryosis rates more than halved from round 1 to round 2, from 7.3% to 3.1% and from 3.6% to 1.5% respectively. The reductions in the moderate and severe dyskaryosis rates were even greater, from 1.1% to 0.2% and from 0.8% to 0.1% respectively.

As shown in *Table 12*, these low rates of cytological abnormality in round 2 led to a much lower number of colposcopies. Overall, 1925 women had one or more colposcopy clinic consultations. Eighty per cent of the colposcopies were performed in the revealed arm in both rounds 1 and 2 (a first colposcopy within 30 months of a round 1 sample was classified as being in round 1).

The numbers of CIN3+ and CIN2 lesions detected amongst all 24,510 women in round 1

TABLE 7 Rates of HPV positivity by age and grade of cytological abnormality in round 1

Cytology grade	20–24	25–29	30–39	40–49	50–64	All ages
Negative	***(1928)***	***(2085)***	***(6611)***	***(5480)***	***(5275)***	***(21,380)***
HPV +ve	26.9% (518)	18.1% (377)	10.3% (679)	6.3% (345)	5.7% (307)	10.4% (2226)
HPV –ve	73.1% (1411)	81.9% (1708)	89.7% (5932)	93.7% (5135)	94.3% (4968)	89.6% (19,154)
Borderline	***(281)***	***(241)***	***(591)***	***(428)***	***(248)***	***(1789)***
HPV +ve	62.9% (174)	47.7% (115)	42.1% (175)	15.9% (68)	10.1% (25)	31.1% (557)
HPV –ve	37.1% (107)	52.3% (126)	57.9% (416)	84.1% (360)	89.9% (223)	68.9% (1232)
Mild	(253)	(162)	(258)	(140)	(65)	(878)
HPV +ve	90.1% (228)	82.7% (134)	63.6% (164)	49/3% (69)	27.7% (18)	69.9% (613)
HPV –ve	9.9% (25)	17.3% (28)	36.4% (94)	50.7% (71)	72.3% (47)	30.1% (265)
Moderate	***(73)***	***(60)***	***(84)***	***(38)***	***(16)***	***(271)***
HPV +ve	93.1% (68)	90% (54)	86.5% (77)	65.8% (25)	56.2% (9)	86% (233)
HPV –ve	6.9% (5)	10% (6)	13.5% (7)	34.2% (13)	43.8% (7)	14% (38)
Severe	***(39)***	***(43)***	***(70)***	***(31)***	***(9)***	***(192)***
HPV +ve	100% (39)	98% (42)	95.7% (67)	90.3% (28)	98% (8)	95.8% (184)
HPV –ve	0% (0)	2% (1)	4.3% (3)	9.7% (3)	11% (1)	4.2% (8)
All grades	(2575)	(2591)	(7614)	(6117)	(5613)	
HPV +ve	39.9% (1027)	27.9% (722)	15.3% (1162)	8.7% (535)	6.5% (367)	
HPV –ve	60.1% (1548)	72.1% (1869)	84.7% (6452)	91.3% (5582)	93.5% (5246)	

Numbers in category are given in parentheses.

and in 14,230 women in round 2 are shown by randomised arm and by cytology and HPV status in round 1 in *Table 13a*. The low prevalence of cytological abnormality is reflected in the low numbers of CIN2 and CIN3+ lesions identified in round 2 as shown in *Table 13b*. This unexpectedly low incidence rate of high-grade histology means that the trial has low power to detect the reduction in incidence of CIN3+ in the revealed arm, which was the primary outcome at the end point of the trial.

Primary outcome

Differences in CIN2 and CIN3+ rates between the randomised arms are shown in *Table 14* for all women (upper part) and for those who were HPV +ve but cytologically –ve in round 1 (lower part). When a comparison is made between the two arms the overall CIN3+ rate in round 2 by intention to treat was 0.34% in the concealed arm and 0.18% in the revealed arm. This represents a 48% reduction, but the numbers are too low to show a statistically significant difference ($p = 0.09$). When the two rounds are combined the overall detection rates in the two arms of the trial were similar for CIN2+ (2.83% concealed, 2.91% revealed) and for CIN3+ (1.65% concealed, 1.45% revealed), the small number of additional CIN3+ lesions identified in the revealed arm in round 1 being counterbalanced by the additional cases in round 2 in the concealed arm.

High-grade histology in round 1 and round 2: amended definition of round 2 sample to reduce exclusions

There was a need to define time limits for round 2 for the purpose of the data analysis for this report, hence the 30–48 months definition. As the trial progressed, it became apparent that this resulted in a number of excluded cases which fell outside the definitions of both round 1 and round 2. Because of the need to exclude as few cases as possible in a per protocol analysis, a further definition of round 2 was adopted covering months 26–54. The

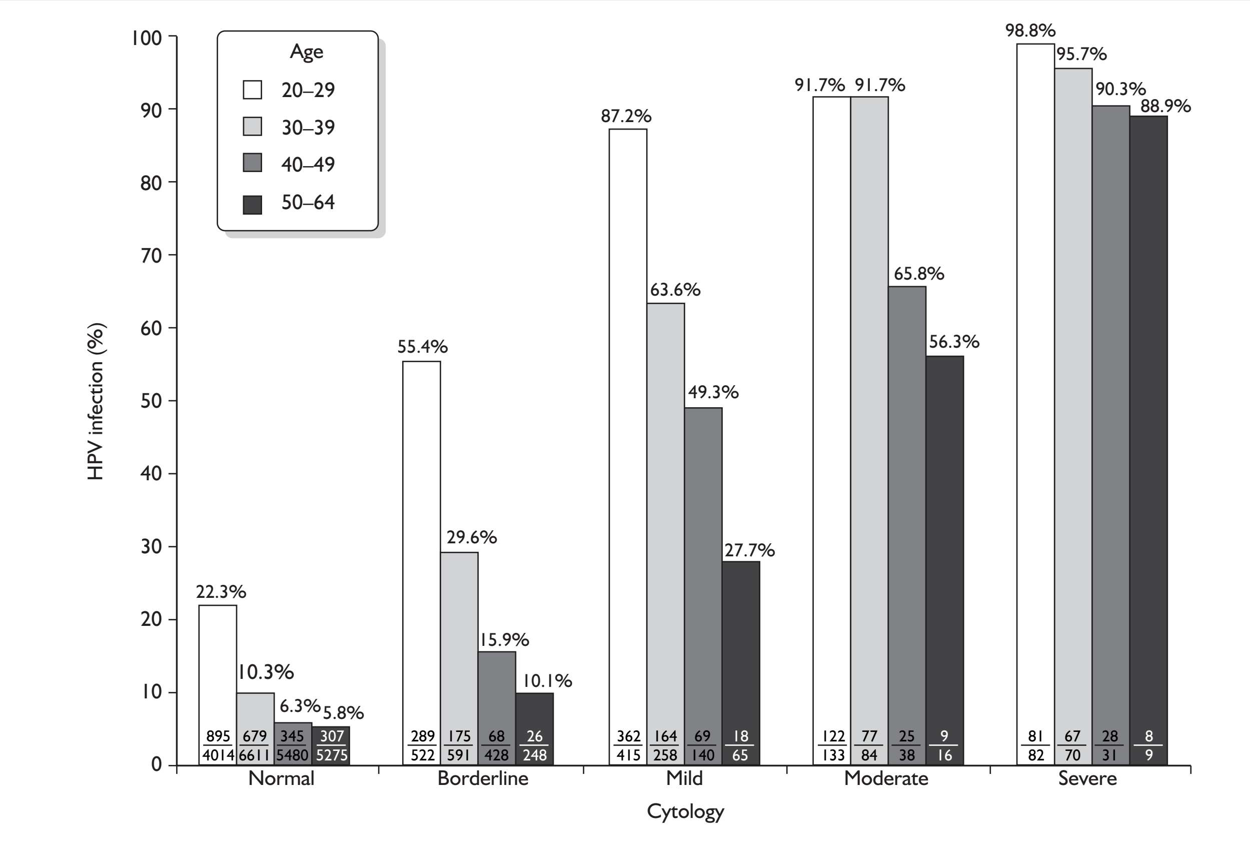

FIGURE 9 *Prevalence of high-risk HPV (HR-HPV) by Hybrid Capture 2 (HC2) and cytology grade within different age bands. Reproduced with permission of Cancer Research UK from Kitchener H, Almonte M, Wheeler P, Desai M, Gilham C, Bailey A,* et al. *HPV testing in routine cervical screening: cross sectional data from the ARTISTIC trial.* Br J Cancer *2006;***95***:56–61.*[31]

TABLE 8 *Age, CIN2 and CIN3+*[a] *by cytological grade and HPV +ve and HPV –ve women in round 1 in both arms*

	Cytology negative			**Borderline/Mild**			**Moderate+**		
Age in round 1	**No.**	**CIN2**	**CIN3**	**No.**	**CIN2**	**CIN3**	**No.**	**CIN2**	**CIN3**
HPV +ve									
20–24	518	7	5	402	33	34	107	34	43
25–29	377	8	–	249	28	23	96	30	50
30–39	679	5	4	339	38	24	144	31	77
40–49	345	–	1	137	11	5	53	13	29
50–64	307	2	–	43	2	–	17	3	9
All ages	2226	22	10	1170	112	86	417	111	208
HPV –ve									
20–24	1411	–	–	132	5	1	5	1	1
25–29	1708	–	–	154	3	2	7	1	–
30–39	5932	–	–	510	8	–	10	2	3
40–49	5135	–	–	431	3	2	16	2	–
50–64	4968	–	–	270	3	–	8	–	–
All ages	19,154	–	–	1497	22	5	46	6	4

a Including six invasive carcinomas and two adenocarcinomas.

TABLE 9 *Cancer cases detected in the ARTISTIC trial*

					Round 1 screening tests results		Round 2 screening tests results	
No.	**Randomisation**	**Age in round 1**	**Type of cancer**	**Screening round of diagnosis**	**Cytology**	**HPV test**	**Cytology**	**HPV test**
1	Concealed	27.1	Microinvasive	First	Severe	Positive	Negative	Negative
2	Revealed	41.7	Invasive carcinoma	First	Severe	Positive		
3	Revealed	35.6	Invasive carcinoma	Second[a]	Negative	Positive	Negative	Positive
4	Revealed	53.6	Invasive carcinoma	Second	Borderline	Negative	Borderline	Not done
5	Revealed	36.6	Invasive carcinoma	First	Severe	Positive		
6	Concealed	38.7	Invasive carcinoma	First	Severe	Positive	Negative	
7	Concealed	41.1	Invasive carcinoma	First	Moderate	Positive		
8	Revealed	36.6	Invasive carcinoma	First	Severe	Positive		
9	Revealed	42.7	Invasive carcinoma	First	Possible invasion	Positive		
10	Revealed	28.4	Adenocarcinoma	Second[a]	Negative	Negative	Negative	Positive
11	Concealed	41.0	Adenocarcinoma	First	Glandular neoplasia	Positive		
12	Revealed	45.6	Adenocarcinoma	First	Borderline	Negative		

a Cases occurred after a negative second screening smear and were excluded from analysis.

TABLE 10 *Screening results for HC2 and LBC for the revealed and concealed arms in round 2*

	Revealed arm			Concealed arm			All women with round 2 screening			
Cytology	**HPV –ve**	**HPV +ve**	**Subtotal**	**HPV –ve**	**HPV +ve**	**Subtotal**	**HPV –ve**	**HPV +ve**	**HPV missing[a]**	**Total**
Negative	8952	647	9599	2897	211	3108	11,849	858	1220	13,927
	(97.6%)	(74.1%)	(95.5%)	(97.4%)	(72.8%)	(95.2%)	(97.5%)	(73.8%)	*(92.1%)*	(95.1%)
Borderline	182	103	285	72	34	106	254	137	57	448
	(2.0%)	(11.8%)	(2.8%)	(2.4%)	(11.7%)	(3.2%)	(2.1%)	(11.8%)	*(4.3%)*	(3.1%)
Mild	39	95	134	6	36	42	45	131	39	215
	(0.4%)	(10.9%)	(1.3%)	(0.2%)	(12.4%)	(1.3%)	(0.4%)	(11.3%)	*(2.9%)*	(1.5%)
Moderate	–	17	17	–	6	6	–	23	6	29
	–	(1.9%)	(0.2%)	–	(2.1%)	(0.2%)	–	(2.0%)	*(0.5%)*	(0.2%)
Severe+	2	11	13	1	3	4	3	14	3	20
	(0.02%)	(1.3%)	(0.1%)	(0.03%)	(1.0%)	(0.1%)	(0.03%)	(1.2%)	*(0.2%)*	(0.1%)
Total	9175	873	10,048	2976	290	3266	12,151	1163	1325	14,639
	(100%)	(100%)	(100%)	(100%)	(100%)	(100%)	(100%)	(100%)	*(100%)*	(100%)

a Women with adequate cytology in round 2 but no HPV test on their second screening.

results are shown in *Table 15* and there is a separate CONSORT diagram to accompany this (*Figure 10*). The differences between the arms in round 2 for CIN3+ (0.21% revealed, 0.41% concealed) and for CIN2+ (0.49% revealed, 0.80% concealed) both become statistically significant ($p = 0.05$ and $p = 0.03$ respectively), but there remains no difference between the arms where rounds 1 and 2 are summed. Round 2 cases of CIN2+ whose round 2 sample was cytology –ve were excluded to avoid bias between the arms (see round 2 exclusions in *Table 3*).

In addition to the more stringent per protocol analysis, an analysis on the basis of 'intention to treat' is presented in *Table 16*. This includes every initial CIN2+ and CIN3+ for every randomised woman over round 1 and 2.

Decline in cytological abnormality and histological disease from round 1 to round 2

Several factors independent of LBC may have contributed to the marked decline in disease rates from round 1 to round 2. These include:

- Women were about 3 years older in round 2, and disease rates drop sharply with age in younger women.
- Women screened in round 2, whose last routine smear was the round 1 sample taken approximately 3 years earlier, are at lower risk than the cross-section recruited in the trial, many of whom had not been screened within 3 years of recruitment.
- Histological follow-up of abnormal cytology in round 2 is still incomplete for some women.

Any change in the CIN2+ diagnosis rate in women with abnormal cytology can be assessed by calculating cumulative (Kaplan–Meier) CIN2+ rates. These are similar up to 12 months following abnormal cytology in round 1 and round 2: moderate or worse 68% [95% confidence interval (95% CI) 63% to 72%) in round 1, 60% (95% CI 46% to 74%) in round 2; borderline/mild 4.3% (95% CI 3.6% to 5.2%) in round 1, 5.4% (95% CI 3.9% to 7.5%) in round 2. Age-specific HPV prevalence rates in women with negative cytology were also similar in round 1 and in round 2 in women aged up to 40, although slightly higher above age 40 (respective HPV rates in round 1 in women with negative cytology at age 20–24, 25–29, 30–39, 40–49 and 50–64 were 27%, 18%, 10%, 6% and 6%, compared with 25%, 19%, 9%, 6%, 4% and 3% in round 2).

The contribution of the biases listed above to the extraordinary decline in disease rates during the ARTISTIC trial can be adjusted for by comparing cytological abnormality rates in round 1 and round 2, adjusting for current age in round 1 and at follow-up (round 2), and restricting the round 1

TABLE 11 *Rates of HPV positivity by age and grade of cytological abnormality in round 2*

Cytology grade	20–24	25–29	30–39	40–49	50–64	All ages
Negative	1020	1151	4181	3854	3721	13,927
HPV +ve	18.8% (192)	11% (127)	6.3% (263)	4.1% (156)	3.2% (120)	6.2% (858)
HPV –ve	63.6% (649)	74% (852)	84.2% (3519)	89.1% (3435)	91.2% (3394)	85.1% (11,849)
HPV missing	17.6% (179)	15% (172)	9.5% (399)	6.8% (263)	5.6% (207)	8.7% (1220)
Borderline	72	71	161	96	48	448
HPV +ve	55.5% (40)	38% (27)	26.2% (42)	16.6% (16)	25% (12)	30.5% (137)
HPV –ve	26.3% (19)	43.7% (31)	63.9% (103)	72.9% (70)	64.6% (31)	56.7% (254)
HPV missing	18.2% (13)	18.3% (13)	9.9% (16)	10.5% (10)	10.4% (5)	12.8% (57)
Mild	56	37	74	39	9	215
HPV +ve	75% (42)	67.6% (25)	56.8% (42)	48.7% (19)	33.3% (3)	60.9% (131)
HPV –ve	7.1% (4)	16.2% (6)	22.9% (17)	33.3% (13)	55.5% (5)	20.9% (45)
HPV missing	17.9% (10)	16.2% (6)	20.3% (15)	17.8% (7)	11.2% (1)	18.2% (39)
Moderate	11	10	5	2	1	29
HPV +ve	72.7% (8)	80% (8)	100% (5)	100% (2)	0% (0)	79.3% (23)
HPV –ve	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)	0% (0)
HPV missing	27.3% (3)	20% (2)	0% (0)	0% (0)	100% (1)	20.7% (6)
Severe	3	3	8	2	2	20
HPV +ve	100% (3)	100% (3)	62.5% (5)	50% (1)	0% (0)	70% (14)
HPV –ve	0% (0)	0% (0)	12.5% (1)	50% (1)	50% (1)	15% (3)
HPV missing	0% (0)	0% (0)	25% (2)	0% (0)	50% (1)	15% (3)
All grades	1162	1274	4429	3993	3781	14639
HPV +ve	24.5% (285)	15.1% (192)	8.1% (357)	4.9% (194)	3.6% (135)	7.9% (1163)
HPV –ve	57.8% (672)	69.8% (889)	82.2% (3640)	88.1% (3519)	90.7% (3431)	83% (12,151)
HPV missing	17.7% (205)	15.1% (193)	9.7% (432)	7% (280)	5.7% (215)	9.1% (1325)

TABLE 12 *Numbers of women who underwent colposcopy in rounds 1 and 2; (concealed : revealed randomised 1 : 3)*

Women who underwent colposcopy	Frequency	%
Round 1		
Concealed	320	20.4
Revealed	1247	79.6
Total	1567	100.0
Round 2		
Concealed	74	20.7
Revealed	284	79.3
Total	358	100.0

analysis to women whose previous smear was 30–48 months earlier and cytologically negative. This logistic multiple regression gives an adjusted odds ratio for round 2 against round 1 of 0.45 (95% CI 0.37 to 0.56) for borderline/mild and 0.21 (95% CI 0.10 to 0.43) for moderate or worse cytology.

A further explanation for this dramatic change is that a high proportion of cytological abnormality, particularly high-grade disease, which was detected by LBC in round 1 was missed by the preceding conventional smear test. This was unexpected because recent studies suggest similar sensitivity for these tests.[58]

There are two factors which may have had an important influence on the performance of LBC.

TABLE 13a *Number of CIN2 and CIN3+ cases in rounds 1 and 2 by randomisation and screening test results in round 1*

		HPV in round 1	Cytology in round 1	Concealed n (%)	Revealed n (%)	Both arms n (%)
Round 1[a]	CIN2 within 30 months of abnormal round 1 cytology	+ve	Negative	0/551 (0)	22/1675 (1.3)	22/2226 (1.0)
			≥Borderline	48/402 (11.9)	175/1185 (14.8)	223/1587 (14.1)
		–ve	Negative	0/4,787 (0)	0/14,367 (0)	0/19,154 (0)
			≥Borderline	5/384 (1.3)	23/1159 (2.0)	28/1543 (1.8)
	CIN3+ within 30 months of abnormal round 1 cytology	+ve	Negative	0/551 (0)	10/1675 (0.6)	10/2226 (0.4)
			≥Borderline	78/402 (19.4)	216/1185 (18.2)	294/1587 (18.5)
		–ve	Negative	0/4,787 (0)	0/14,367 (0)	0/19,154 (0)
			≥Borderline	2/384 (0.5)	7/1159 (0.6)	9/1543 (0.6)

TABLE 13b *Number of CIN2 and CIN3+ cases in round 2 by randomisation and screening test results in round 2 [26–54 definition of round 2]*

		HPV in round 2	Cytology in round 2	Concealed n (%)	Revealed n (%)	Both arms n (%)
Round 2[b]	Round 2 – CIN2 within 30 months of abnormal round 2 cytology	+ve	Negative	0/224 (0)	0/683 (0)	0/907 (0)
			≥Borderline	12/92 (13.0)	23/249 (9.2)	35/341 (10.3)
		–ve	Negative	0/3,064 (0)	0/9,334 (0)	0/12,398 (0)
			≥Borderline	0/76 (0)	4/235 (1.7)	4/311 (1.3)
		Not done	Negative	0/368 (0)	0/1,084 (0)	0/1,452 (0)
			≥Borderline	3/42 (7.1)	5/91 (5.5)	8/133 (6.0)
	Round 2 – CIN3+ within 30 months of abnormal round 2 cytology	+ve	Negative	0/224 (0)	0/683 (0)	0/907 (0)
			≥Borderline	13/92 (14.1)	23/249 (9.2)	36/341 (10.6)
		–ve	Negative	0/3,064 (0)	0/9,334 (0)	0/12,398 (0)
			≥Borderline	1/76 (1.3)	0/235 (0)	1/311 (0.3)
		Not done	Negative	0/368 (0)	0/1,084 (0)	0/1452 (0)
			≥Borderline	2/42 (4.8)	2/91 (2.2)	4/133 (3.0)

a Denominators in each cell represent the number of women in the trial.
b Denominators in each cell represent the number of women who had round 2 screening and were not previously treated for CIN2+ lesions.

The first of these was the rigorous training which required medical and non-medical laboratory staff to complete a formal curriculum before being able to read slides independently. Non-medical staff had to read 400 unmarked and 20 test slides and medical staff 200 unmarked and 20 test slides. All staff had to achieve 95% sensitivity identifying high-grade slides and had to achieve an 80% pass mark for the test slides. In other countries, training was often provided by the manufacturer and consisted of 3–5 days of lectures and viewing slides.

The second factor may have been the high rate of low-grade abnormality in round 1 comprising 7.3% borderline and 3.5% mild dyskaryosis. In fact, the cytological abnormality rate was 16.8% in the first 6 months of recruitment and the age adjusted odds ratio (95% CI) in round 1 for any abnormality fell in successive 6-month periods from 1.0 (reference) to 0.75 (0.68 to 0.82), 0.71 (0.64 to 0.79), 0.60 (0.53 to 0.69) and 0.61 (0.49 to 0.76). This resulted in a colposcopy rate of 5.2% in the concealed arm and 6.8% in the revealed arm, the extra cases in the revealed arm being the result of cytology –ve/HPV +ve women. This relatively high colposcopy rate will have contributed to a high detection rate of CIN2+ and CIN3+. This will have had an impact on the incidence of disease in round 2.

TABLE 14 *High-grade disease[a] in rounds 1, 2 and overall, by randomisation arm*

	HPV revealed		HPV concealed		
	No.	Prevalence (95% CI)	No.	Prevalence (95% CI)	*p*-value
All women in the study					
Round 1					
No. randomised	*18,386*		*6124*		
CIN2	220	1.20% (1.04 to 1.36)	53	0.87% (0.65 to 1.13)	0.03
CIN3+	233	1.27% (1.11 to 1.44)	80	1.31% (1.04 to 1.62)	> 0.1
CIN2+	453	2.46% (2.24 to 2.70)	133	2.17% (1.82 to 2.57)	> 0.1
Round 2					
No. of women in round 2	*10,716*		*3514*		
CIN2	30	0.28% (0.18 to 0.39)	12	0.34% (0.17 to 0.59)	> 0.1
CIN3+	19	0.18% (0.11 to 0.27)	12	0.34% (0.17 to 0.59)	0.09
CIN2+	49	0.46% (0.34 to 0.60)	24	0.68% (0.44 to 1.01)	0.10
Round 1 + Round 2[b]					
CIN2	250	1.48% (1.30 to 1.67)	65	1.21% (0.93 to 1.54)	> 0.1
CIN3+	252	1.45% (1.28 to 1.64)	92	1.65% (1.33 to 2.02)	> 0.1
CIN2+	502	2.91% (2.66 to 3.17)	157	2.83% (2.41 to 3.30)	> 0.1
Women with cytology –ve and HPV +ve test at entry					
Round 1					
No. randomised	*1675*		*551*		
CIN2	22	1.31% (0.82 to 1.98)	0	0%	
CIN3+	10	0.60% (0.29 to 1.10)	0	0%	
CIN2+	32	1.91% (1.31 to 2.69)	0	0%	
Round 2					
No. of women in round 2	*989*		*326*		
CIN2	11	1.11% (0.55 to 1.98)	7	2.15% (0.87 to 4.37)	> 0.1
CIN3+	8	0.80% (0.35 to 1.59)	6	1.84% (0.68 to 3.96)	> 0.1
CIN2+	19	1.92% (1.16 to 2.98)	13	3.99% (2.14 to 6.72)	0.06
Round 1 + Round 2[b]					
CIN2	33	2.41% (1.65 to 3.34)	7	2.15% (0.87 to 4.37)	> 0.1
CIN3+	18	1.40% (0.83 to 2.20)	6	1.84% (0.68 to 3.96)	> 0.1
CIN2+	51	3.80% (2.83 to 4.95)	13	3.99% (2.14 to 6.72)	> 0.1

95% CI, 95% confidence interval.
a Round 2: First adequate cytology 30–48 months after entry.
b Round 1 + round 2 prevalence = $1-(1-p_1)(1-p_2)$ where p_1 is prevalence in round 1 and p_2 is prevalence in round 2.

Management preferences of women after two HPV +ve (cytology –ve) results

Of the 1675 women in the revealed arm who tested cytology –ve and HPV +ve, 1040 (62%) had returned for a first repeat HPV test within 30 months (*Figure 11*). Out of 1040 such women tested, 439 again tested HPV +ve (42.2%), of whom 427 responded to the letter offering either a colposcopy or a repeat HPV test at 24 months. Colposcopy was preferred by the majority of women (61.8%), all of whom attended. A further HPV test before round 2 was chosen by 163 women

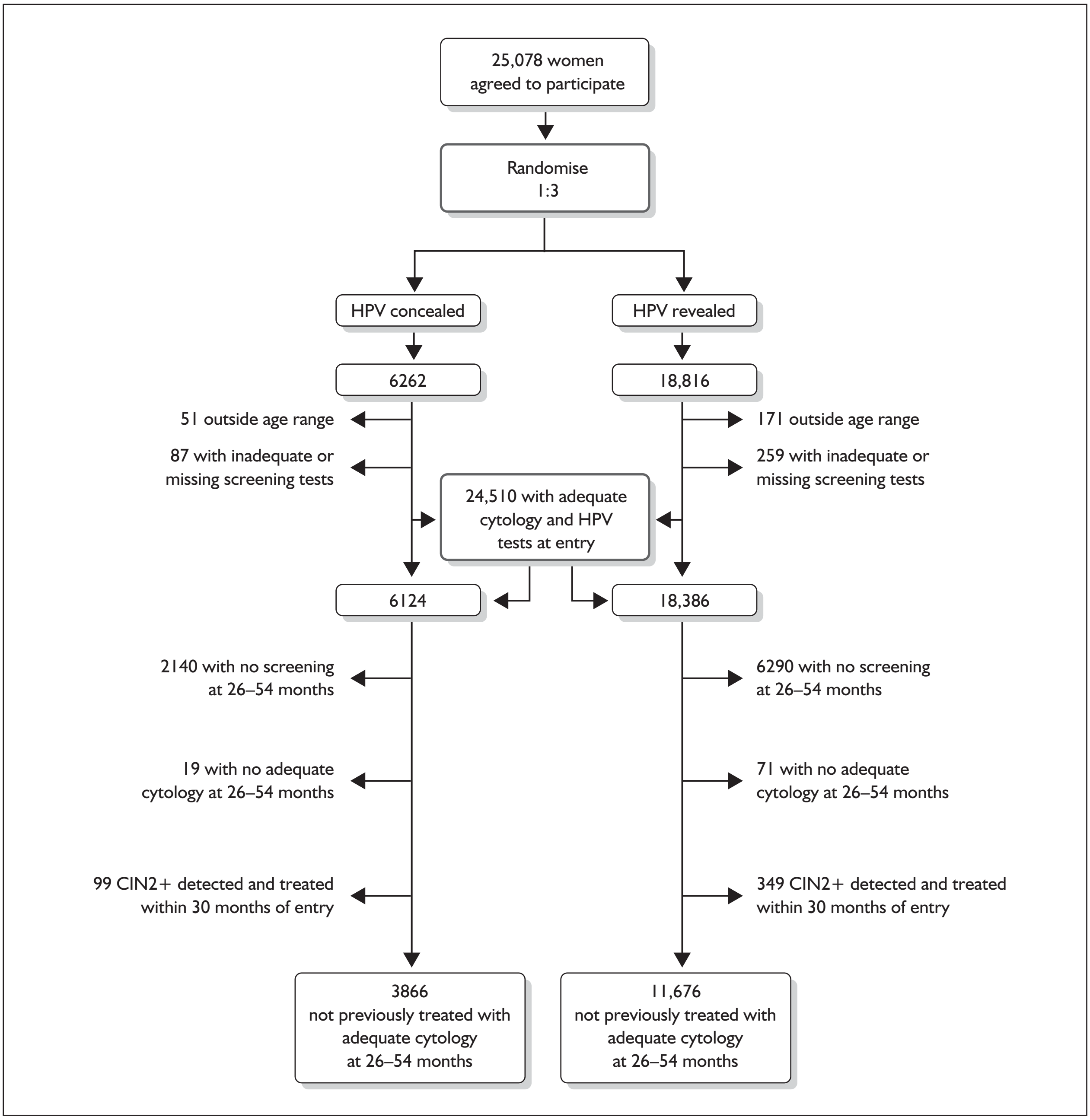

FIGURE 10 *CONSORT diagram of the ARTISTIC trial for round 2 definition of 26–54 months.*

(39.2%). Only 50 of these 163 attended again for HPV testing before round 2, and a further 72 were retested at their next (round 2) routine recall. Twenty-seven (54%) of the 50 women who returned tested HPV +ve for a third time and were referred for colposcopy by the trial office.

The effect of patient choice in the revealed arm

As a result of choosing colposcopy if persistently HPV +ve at 12 months and referral for colposcopy if still HPV +ve at 24 months, 10 CIN3+ and 32 CIN2+ were detected. A further one CIN3+ and

TABLE 15 High-grade disease[a] in rounds 1, 2 and overall, by randomisation arm

	HPV revealed		HPV concealed		
	No.	Prevalence (95% CI)	No.	Prevalence (95% CI)	p-value
All women in the study					
Round 1					
No. randomised	*18,386*		*6124*		
CIN2	220	1.20% (1.04 to 1.36)	53	0.87% (0.65 to 1.13)	0.03
CIN3+	233	1.27% (1.11 to 1.44)	80	1.31% (1.04 to 1.62)	> 0.1
CIN2+	453	2.46% (2.24 to 2.70)	133	2.17% (1.82 to 2.57)	> 0.1
Round 2					
No. of women in round 2	*11,676*		*3866*		
CIN2	32	0.27% (0.19 to 0.39)	15	0.39% (0.22 to 0.64)	> 0.1
CIN3+	25	0.21% (0.14 to 0.32)	16	0.41% (0.24 to 0.67)	0.05
CIN2+	57	0.49% (0.37 to 0.63)	31	0.80% (0.55 to 1.14)	0.03
Round 1 + Round 2[b]					
CIN2	252	1.47% (1.29 to 1.66)	68	1.25% (0.97 to 1.58)	> 0.1
CIN3+	258	1.48% (1.31 to 1.67)	96	1.71% (1.38 to 2.08)	> 0.1
CIN2+	510	2.94% (2.69 to 3.20)	164	2.96% (2.53 to 3.44)	> 0.1
Women with cytology –ve and HPV +ve test at entry					
Round 1					
No. randomised	*1675*		*551*		
CIN2	22	1.31% (0.82 to 1.98)	0		
CIN3+	10	0.60% (0.29 to 1.10)	0		
CIN2+	32	1.91% (1.31 to 2.69)	0		
Round 2					
No. of women in round 2	*988*		*326*		
CIN2	12	1.21% (0.63 to 2.11)	7	2.15% (0.87 to 4.37)	> 0.1
CIN3+	12	1.21% (0.63 to 2.11)	7	2.15% (0.87 to 4.37)	> 0.1
CIN2+	24	2.43% (1.56 to 3.59)	14	4.29% (2.37 to 7.10)	0.09
Round 1 + Round 2[b]					
CIN2	34	2.51% (1.74 to 3.49)	7	2.15% (0.87 to 4.37)	> 0.1
CIN3+	22	1.80% (1.13 to 2.71)	7	2.15% (0.87 to 4.37)	> 0.1
CIN2+	56	4.29% (3.26 to 5.54)	14	4.29% (2.37 to 7.10)	> 0.1

95% CI, 95% confidence interval.

a Round 2: First adequate cytology 26–54 months after entry. Abnormal round 2 cytology on date of histology assumed for two CIN3 cases diagnosed 29 and 35 months after entry. Three CIN3 at round 2 with CIN2 in round 1 excluded. One CIN2 case (revealed arm) excluded from round 1 because of negative cytology. Twelve CIN2s, three CIN3s and two cancers (revealed) and a further CIN3 from the concealed arm were excluded from round 2 because of negative cytology in round 2 (see *Table 2*).

b Round 1 + round 2 prevalence = $1-(1-p_1)(1-p_2)$ where p_1 is prevalence in round 1 and p_2 is prevalence in round 2.

TABLE 16 *Numbers of all CIN2+ and CIN3+ detected amongst all randomised women over both rounds*[a]

	Revealed arm	Concealed arm	
CIN3+	266 (1.45%)	97 (1.58%)	Diff. –0.13% 95% CI –0.52% to 30%, $p = 0.44$
CIN2+	533 (2.9%)	167 (2.73%)	Diff. 0.17% 95% CI –0.32% to 0.63%, $p = 0.48$
No. women randomised	18,386	6124	

a Excludes only round 2 lesions in women who had had a round 1 lesion, i.e. either treatment failure or untreated.

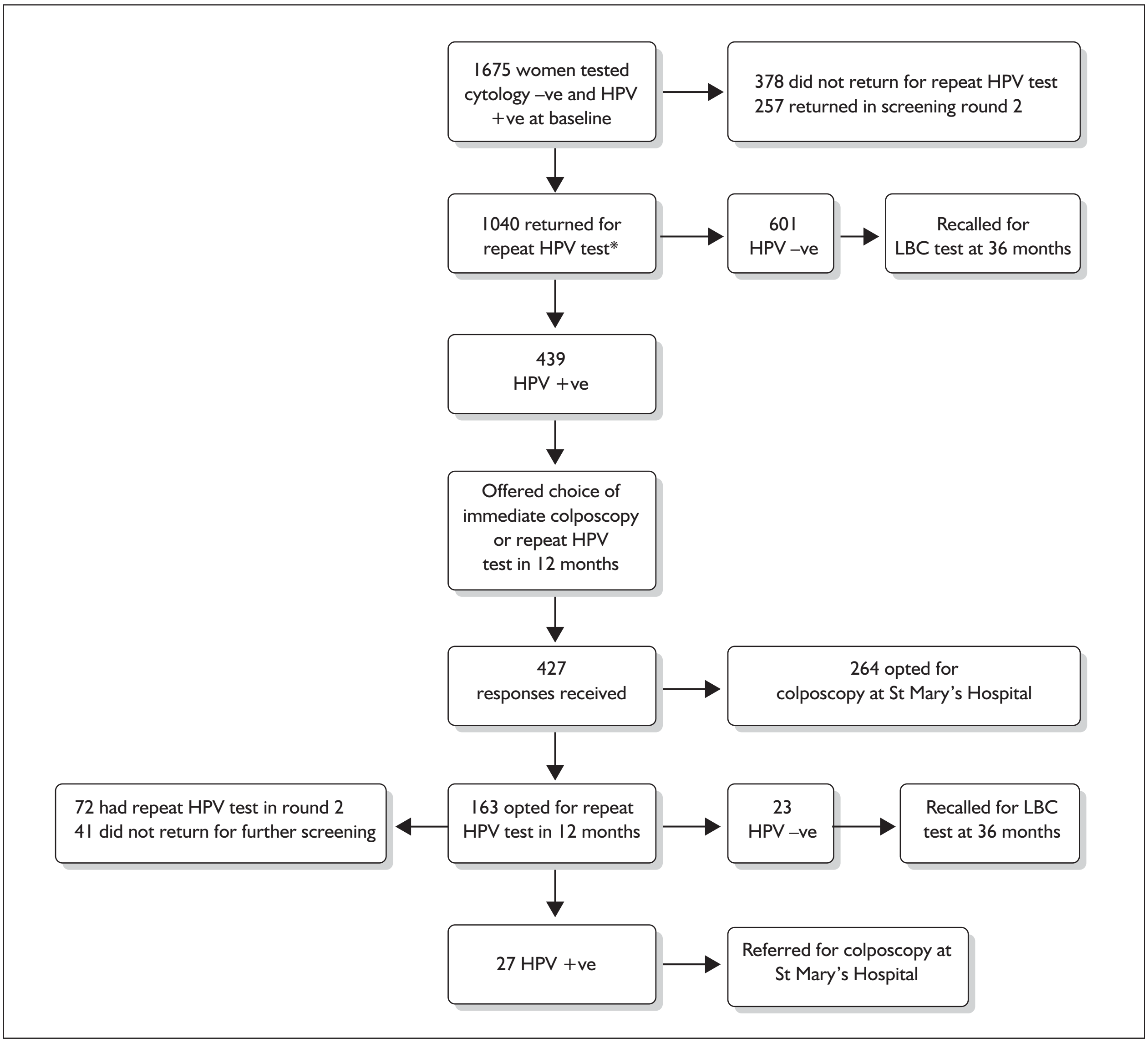

FIGURE 11 *Flow of women who were cytology –ve/HPV +ve in the revealed arm in round 1. *Includes all women who returned for a second HPV test up to 30 months since the first one.*

eight CIN2+ were detected in round 2 amongst women who chose to be retested at 24 months, and a remaining 11 CIN3+ and 16 CIN2+ were diagnosed as a result of being rescreened in round 2.

Performance of HPV as a stand-alone test with cytology reserved for HPV +ve women

Because cytology combined with HPV testing did not appear more effective than cytology alone it is important to consider HPV testing as an initial sole test, cytology being reserved for HPV +ve women. The key data in this context are the lesions that would have been missed by HPV testing alone. For this purpose, all of the lesions detected in ARTISTIC have been mapped through rounds 1 and 2 according to initial HPV test results. As *Figure 12* shows, in round 1 there were nine CIN3+ and 37 CIN2+ in the HPV –ve group of 20,697 women, compared with 304 and 549 respectively for the HPV +ve group of 3813 women. Therefore 97% of CIN3+ and 94% of CIN2+ were detected in the HPV +ve group.

Figure 12 allows comparison of lesions missed by an HPV test and by initial cytology. Compared with combined testing, HPV initial testing would therefore have missed nine CIN3+ and 37 CIN2+ compared with 10 CIN3+ and 32 CIN2+, which would have been missed by initial cytology. These figures are almost identical.

The bottom half of *Figure 12* and *Figures 13* and *14* provide cytology and HPV data in round 1 on women with a diagnosis of CIN2+ and CIN3+ in round 2. In 12,441 women who had been HPV –ve in round 1 and were rescreened, there were only 10 CIN3+ (0.08%) and 22 CIN2+ (0.18%) cases in round 2. Rates were about twice as high among 12,666 women who had been cytology –ve in round 1, among whom there were 22 CIN3+ (0.17%) and 50 CIN2+ (0.39%) cases in round 2. In contrast, there were 21 CIN3+ (1.2%) and 51 CIN2+ (2.9%) cases in 1789 women screened in round 2 who had been HPV +ve in round 1.

To demonstrate screening outcomes following an initial HPV screen, the cytology and histology results in round 2 are also shown for women who had been HPV +ve (*Figure 12*) and HPV –ve (*Figure 13*) in round 1.

With respect to cytological outcomes, it is noteworthy that in women who were HPV +ve in round 1 the total rate of cytological abnormalities in round 2 was almost as high as it was in round 1. These were 1587/3813 (41.6%) in round 1 and 170/497 (35.5%) in round 2. With respect to high-grade cytology only, there were 417/3813 (10.9%) in round 1 but only 37/1789 (2%) in round 2 (*Figure 12*). This confirms the effect of sensitive screening in round 1 for high-grade disease; the impact was far less for low-grade abnormalities, many of which clearly represent little more than HPV infection.

Using all of the data from the revealed arm it was possible to calculate the relative sensitivity and specificity for CIN2+ detection under different screening policies based on 220 CIN2 and 233 CIN3+ lesions detected in the whole revealed arm in round 1. These are shown in *Table 69* in Appendix 6.

Sensitivity of combined and separate cytology and HPV testing in the detection of CIN2/3 when backed up by routine colposcopy

A concurrent colposcopic study conducted locally, but outside the trial (Flynn M, *et al.*, unpublished data) involved 557 women (aged 20–64) who were routinely screened in a single primary care practice in Greater Manchester using the same tests (HC2 and ThinPrep) as in ARTISTIC but these women all consented to undergo colposcopy, and in the event of any colposcopic abnormality, a biopsy was performed. The standard use of colposcopy was to ascertain, within the limits of sensitivity of colposcopy/biopsy, the presence of any underlying disease which might not be detected, particularly in cytology –ve/HPV –ve women for whom no colposcopy was performed in ARTISTIC. Sixty-nine women (12.4%) underwent biopsy, and as can be seen in *Table 17*, 444 women (78%) were cytology –ve/HPV –ve. Of these women, none were found to have CIN, confirming the very high negative predictive value of this combination.

In a total of 490 HPV –ve women, 46 of whom had some cytology abnormality, none had CIN2+. Of 473 cytology –ve women, only one woman had CIN2. There were two cases of CIN3 and one of CIN2, all of whom were HPV +ve.

Optimal cut-off for a +ve Hybrid Capture 2 test

HC2 allows for a range of cut-off values because of the semiquantitative nature of the assay. We

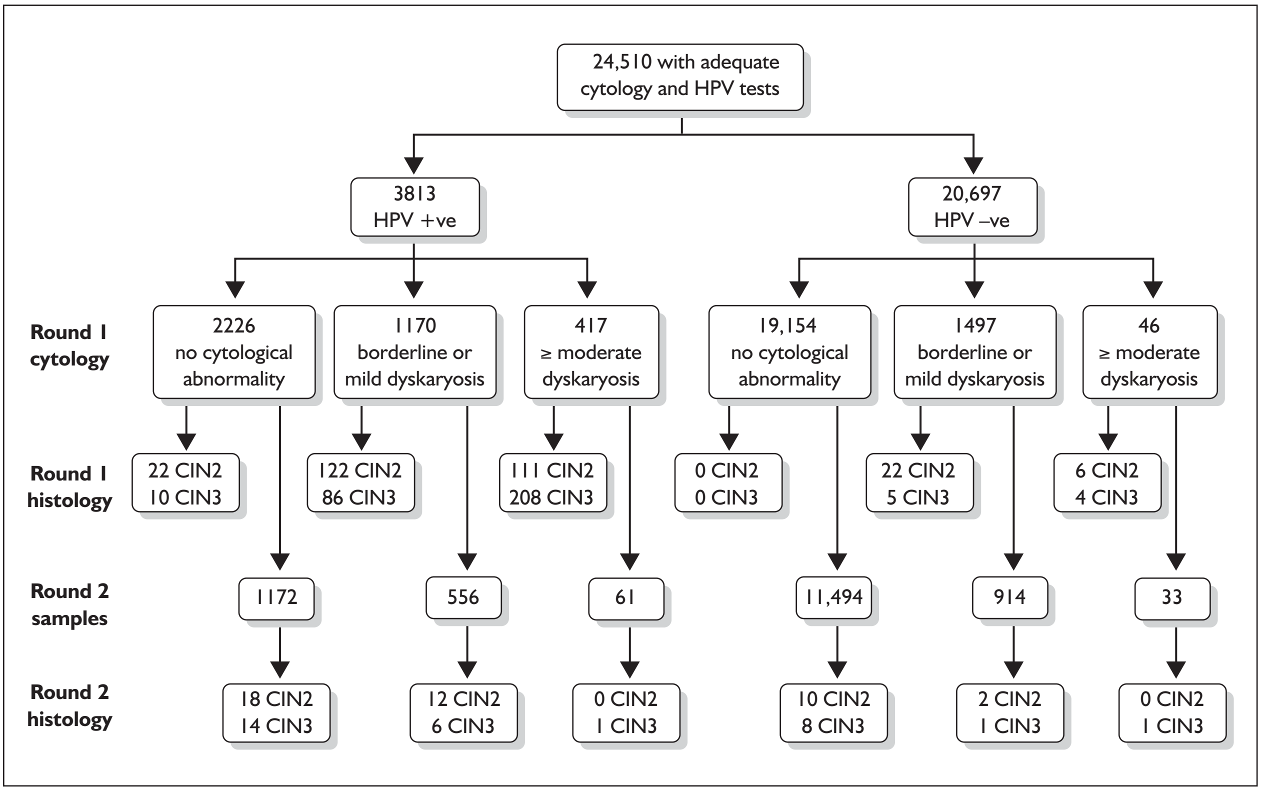

FIGURE 12 *Number of CIN2 and CIN3 or worse histological lesions detected in rounds 1 and 2 by cytology and HPV status in round 1. Numbers in boxes refer to women who came back for screening in round 2 who were not previously diagnosed with CIN2 or CIN3+ in round 1 and 11 extra CIN3 cases (nine in the revealed arm and two in the concealed arm) listed in* Table 3.

employed the manufacturer's recommended threshold for a +ve HC2 test result of ≥1 RLU/Co in the trial, but the large size of the study allows analysis of different cut-offs and resultant cytological and histological outcomes in terms of sensitivity and specificity.

Cytology and histology in round 1 by different HC2 cut-off points

As *Table 18* shows, the round 1 prevalence of HPV with a cut-off of 1 RLU/Co was 15.6% for the whole study population and 10.4%, 43.9% and 90.1% for negative, borderline/mild dyskaryosis and moderate/severe dyskaryosis respectively. All HPV +ve results yielded 516 CIN2+ lesions in women with abnormal cytology. There were 32 of these among cytology –ve/HPV +ve women. Changing the cut-off to 2 RLU/Co and 4 RLU/Co would have reduced the number of CIN2+ detected in women who had abnormal cytology to 507 and 497 respectively, with non-detection of one and five CIN3+ respectively.

If colposcopy was performed for borderline/mild dyskaryosis in HPV +ve women as well as for moderate/worse, the changes in cut-off to 2 or 4 RLU/Co, there would have been 87 and 143 fewer procedures respectively. Additional cut-offs are shown in Appendix 6 (*Tables 61* and *62*). If there were a strategy of colposcopy for cytology –ve/HPV +ve women who remained HPV +ve at 12 months, around 25% would require colposcopy. In that event the number of HPV +ve/cytology –ve women would have been cut in round 1 by 526 and 854 for cut-offs of 2 RLU/Co and 4 RLU/Co respectively. Raising the cut-off to 2 RLU therefore would result in 613 fewer positives, over 200 fewer colposcopies with the loss of only four CIN3+ and 10 CIN2, representing just 2.5% of CIN2+.

Comparison between HC2 and AMPLICOR for (1) borderline and (2) routine screening samples as well as clinical outcomes is shown in Appendix 6 (*Tables 64–67*).

In terms of current cytology screening with HPV testing to triage borderline/mild dyskaryosis, a change in cut-off from 1 RLU/Co to 2 RLU/Co would have resulted in 83 fewer colposcopies for this category of cytology with a loss of six CIN2+ including two CIN3+ lesions. The positive predictive value for CIN2+ following colposcopy

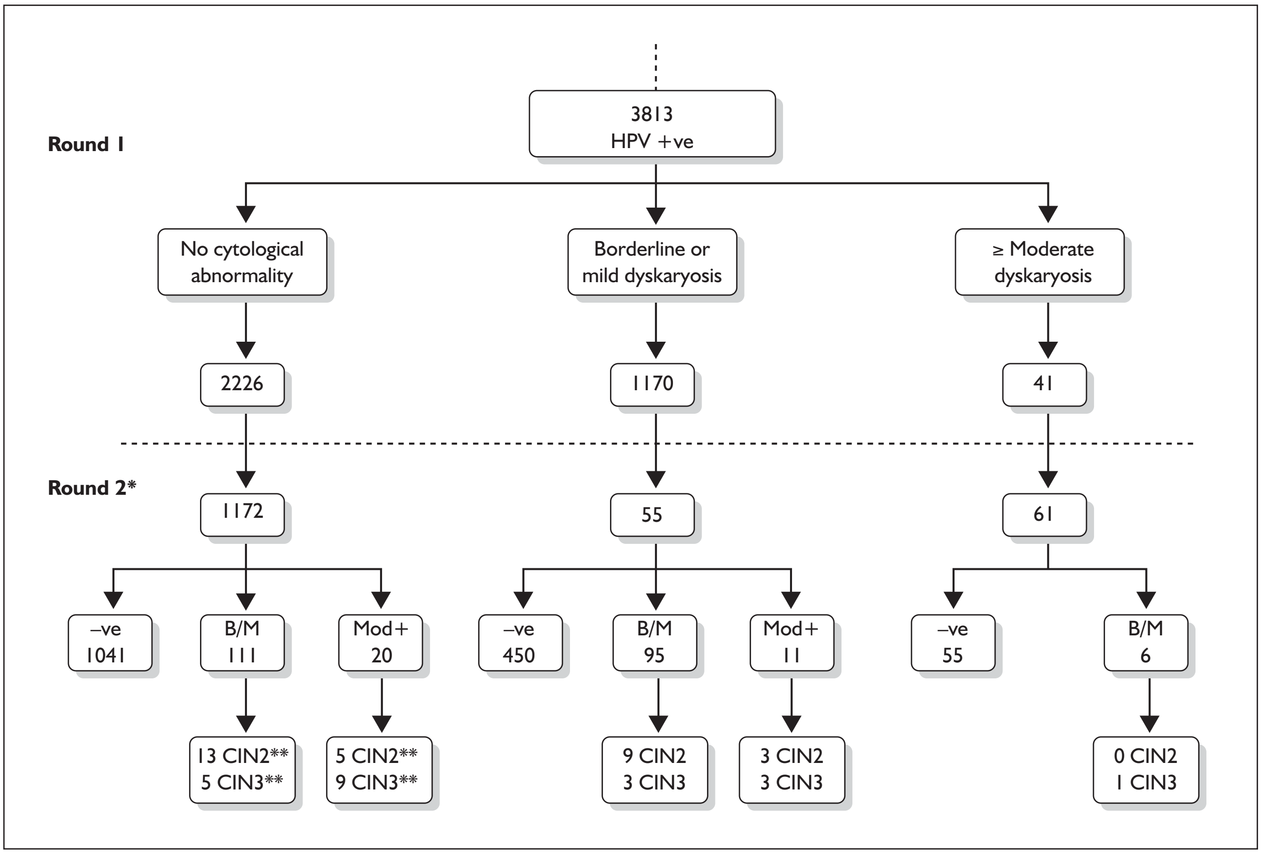

FIGURE 13 *Number of CIN2 and CIN3 or worse histological lesions detected in round 2 in women HPV +ve in round 1. *Numbers in boxes refer to women who came back for screening in round 2 who were not previously diagnosed with CIN2 or CIN3+ in round 1. **Number of cases in the revealed arm: seven CIN2 and two CIN3+ in women with borderline/mild (B/M) cytology in round 2, and four CIN2 and six CIN3+ in women with moderate or worse (Mod+) cytology in round 2.*

would have risen from 16.9% to 17.7%. Increasing the cut-off to 4 RLU/Co or greater would result in non-detection of a further four CIN2+ and one CIN3+ lesions and would avoid 49 more colposcopies, but the positive predictive value would only increase to 18.1%.

Modelled outcomes for different screening scenarios based on ARTISTIC data shown in *Figures 11–14* are shown in *Table 19*. All four strategies would identify similar rates of CIN3+. In terms of CIN2+ there would be a reduced number of lesions in the cytology to HPV triage because of a significant number of HPV –ve CIN2. Standard management involves fewer colposcopies than a primary HPV screen but requires many repeat cytology samples. Primary cytology triaged by HPV testing involves even fewer colposcopies but would have identified 12 (4%) fewer CIN3+ lesions.

The same strategy using colposcopy for HPV screening triaged by LBC has been costed and the data are presented in *Table 48* with a cut-off of 1 RLU/Co and of 2 RLU/Co.

Data are shown in Appendix 6 (*Table 69*) which indicate that the strategy of repeat HPV testing in women who are initially HPV +ve and cytology –ve achieves a higher sensitivity but in women below 30 years specificity is lower.

Explanation for CIN3 associated with an HC2 –ve result at baseline

There were nine women who were HC2 –ve at baseline and who subsequently developed CIN3. Typing data on residual material from these women found that three contained HPV16, one contained HPV6, four were LBA negative and one had insufficient sample for testing. Roche AMPLICOR results were available for eight of the samples (one had insufficient sample) of which three tested AMPLICOR positive (*Table 20*). Possible reasons for the failure of the HC2 assay to detect HPV in these samples may include sensitivity issues or the fact that this assay does not control for DNA integrity or sample adequacy.

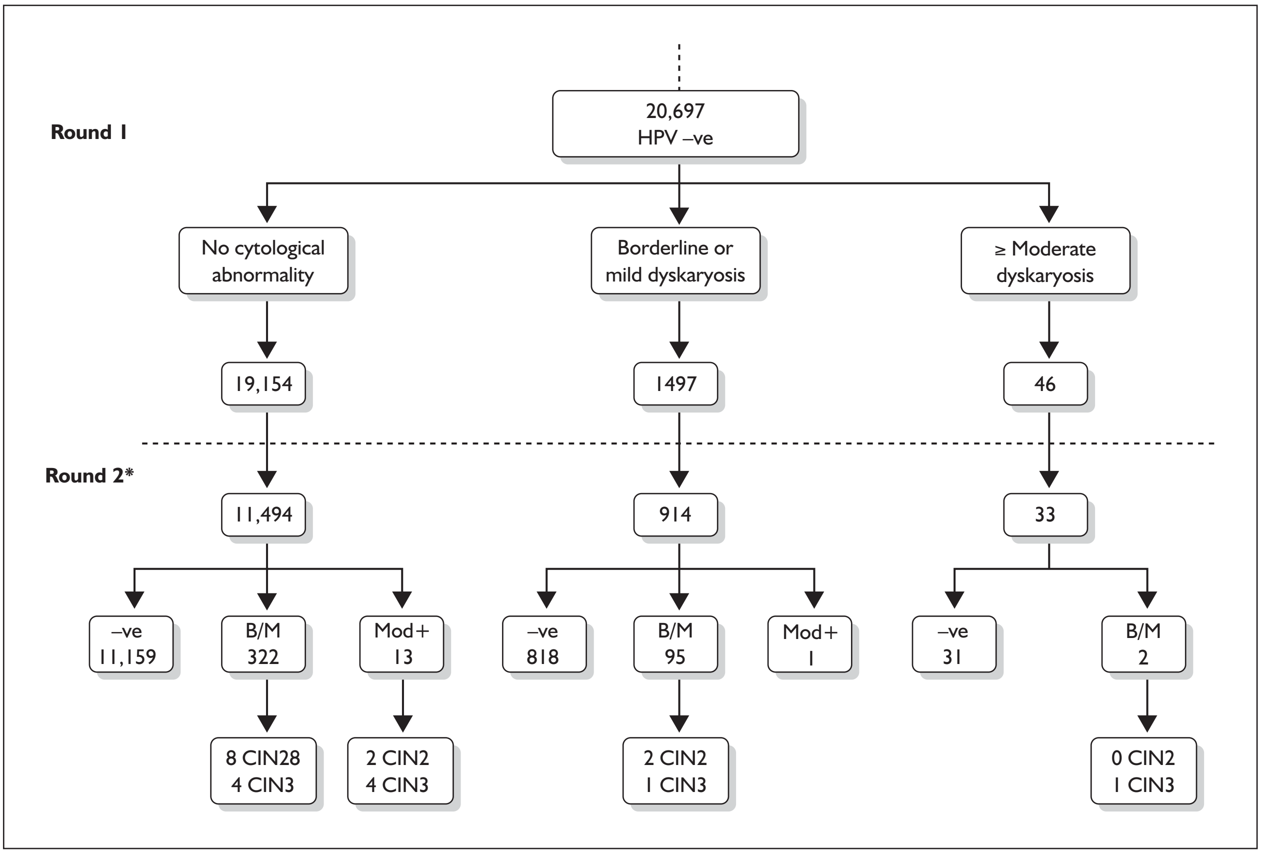

FIGURE 14 *Number of CIN2 and CIN3+ lesions in round 2 in women with HPV –ve test in round 1. * Numbers in boxes refer to women who came back for screening in round 2 who were not previously diagnosed with CIN2 or CIN3+ in round 1. B/M, borderline or mild; Mod+, moderate or worse.*

TABLE 17 *Colposcopic and histological outcomes in 557 women aged 20–64 years who underwent routine primary cervical screening all of whom underwent colposcopy[a]*

		HPV		
		Negative	**Positive**	**Total**
Cytology –ve	CIN2	0	1	1
	< CIN/HPV	41	6	47
	WNL[b] ± Biopsy negative	403	22	425
	Total	444	29	473
Cytology borderline+	CIN3	0	2	2
	CIN2	0	1	1
	CIN1	1	4	5
	< CIN/HPV	7	13	20
	WNL[b] ± Biopsy negative	38	18	56
	Total	46	38	84

a Sixty-nine of the women (12.4%) underwent a biopsy.
b Colposcopic appearance within normal limits (WNL).

TABLE 18 Cytology and histology in round 1 by different HC2 cut-off points

Cut-off point	1 RLU		2 RLU		4 RLU		10 RLU	
HC2	–ve	+ve	–ve	+ve	–ve	+ve	–ve	+ve
Cytology in round 1								
–ve	19,154	2226	19,680	1700	20,008	1372	20,362	1018
Borderline/Mild	1497	1170	1580	1087	1629	1038	1718	949
Moderate/worse	46	417	50	413	57	406	72	391
All women	20,697	3813	21,310	3200	21,694	2816	22,152	2358
Histology by cytology in round 1								
–ve								
CIN2	–	22	4	18	4	18	7	15
CIN3+	–	10	1	9	3	7	3	7
Borderline/Mild								
CIN2	22	112	26	108	29	105	35	99
CIN3+	5	86	7	84	8	83	11	80
Moderate/worse								
CIN2	6	110	8	108	10	106	14	102
CIN3+	4	208	5	207	9	203	17	195
CIN2+ in round 1	37	548	51	534	63	522	87	498

TABLE 19 Modelled outcomes of different screening scenarios based on HC2, cytology and histology data from the ARTISTIC trial cohort

Estimated number of colposcopies for:	Standard management[a]	Cytology + HPV triage for borderline/mild	Referral for HPV +ve/LBC triage[b] (HC2 1 RLU/Co)	Referral for HPV +ve/LBC triage[b] (HC2 2 RLU/Co)
Borderline/mild	460/878	1087	1170	1087
Moderate/severe	463/792	463	417	413
Negative cytology	–	–	556	425
Total	1791	1550	2143	1925
Proportion of screened women	7.3%	6.3%	8.7%	7.9%
CIN2+ detected[c]	553	507	548	534
CIN3+ detected	303	291	304	300

a Assumes colposcopy for mild, moderate and severe dyskaryosis and estimated 25% referral for repeated borderline.
b Assumes referral for any cytological abnormality (borderline+), or for 12 months repeated HC2 +ve women with negative cytology which is estimated as 25% of this group.
c Excludes CIN2+ detected in cytology –ve/HPV +ve women.

TABLE 20 *Additional testing on HC2 –ve women who subsequently developed CIN3*

HC2 (RLU/Co ≥1)	AMPLICOR test (OD ≥0.2)	Prototype line blot assay	Baseline cytology grade
Negative	Negative	Negative	mild
Negative	Positive	type 16	severe
Negative	Negative	Negative	borderline
Negative	Negative	type 6	severe
Negative	Positive	type 16	moderate
Negative	Insufficient	Insufficient	borderline
Negative	Positive	type 16	moderate
Negative	Negative	Negative	borderline
Negative	Negative	Negative	borderline

HPV genotype profile in the screened population

Total population

A total of 24,510 eligible women had satisfactory cytology and HPV results by HC2 in round 1. Samples from 3813 women (15.6% of all eligible women) were HPV +ve by HC2, but 40 (1.0%) of these either gave –ve results for β-globin gene amplification and were reported as inhibitory or were of insufficient volume for further testing. These 40 are excluded from analyses of type-specific HPV persistence (*Tables 24–28*), and all results are based on the remaining 24,470 women. Cross-reactivity with low-risk types or high-risk types not included in the HC2 probe mix was observed in 417 (11.1%) HC2 +ve samples. A broad range of HPV type cross-reactivity occurred. This was particularly noticeable for HPV types 53, 66 and 70, which were frequently detected. A further 772 (20.5%) HC2 +ve samples did not hybridise to any of the LBA probes. These 1189 are classified as HC2 +ve but HR-HPV –ve. The remaining 2584 HC2 +ve samples (68.5%) were +ve by LBA for one or more of the 13 high-risk types included in the HC2 HR probe mix. Of those HC2 +ve samples giving a low RLU/Co value between 1 and 3, 26.7% contained an HC2 high-risk type; 16.2% cross-reacted with other types and 57.1% failed to type. Corresponding figures of those HC2 +ve samples giving a high RLU/Co value ≥100 were 91.9%, 4.8% and 3.3% respectively. In total, 50% of HC2 +ve/LBA –ve samples had an RLU/Co value between 1 and 2.11. On testing a subset of 102 HC2 +ve/LBA –ve samples by GP5+/6+ PCR, 39.2% were found to be HPV +ve. Multiple HR-HPV types were detected in 680 (18.0% of HC2 +ve samples) and infection with a single HR-HPV type was detected in 1904 (50.5%).

The HC2 +ve/LBA –ve samples are not simply ‘background noise’ because they include 28/549 (5.1%) CIN2+ and 24/549 (4.4%) CIN2+ detected in round 1, with a cut-off of ≥1 RLU/Co and 2 RLU/Co respectively.

Typing

Cytology by HPV status is shown in *Table 21* for women aged 20–29, 30–64 and overall. Summing the number of different HR-HPV types detected in each woman for the denominator, the proportion of all detected infections that were due to each HPV type did not vary greatly with age. Below age 30, 24.0% (499/2077) of HR-HPV infections were due to HPV16, compared with 21.3% (306/1435) at age 30–64 ($p = 0.06$). The corresponding proportions were 6.3% and 3.7% for HPV33 ($p = 0.001$), 2.4% and 4.1% for HPV35 ($p = 0.003$) and 4.5% and 6.7% for HPV45 ($p = 0.005$). No other type showed significant variation with age.

When prevalence of different HPV types was considered in 1904 women with a single type infection, types 16, 31 and 33 were more prevalent in high-grade than negative cytology.

Prevalence

The proportion of women with a single HR-HPV type who had moderate or worse cytology (right-hand side of *Table 21*) was 26% for HPV16, between 12% and 19% for HPV types 18, 31, 33 and 58, 7% to 9% for types 35, 45, 51 and 52, and less than 5% for types 39, 56, 59 and 68. The proportion with borderline or mild cytology ranged from 23% to 42% for the different high-risk types. Similar data for HPV16, HPV18 and other HR HPV types collectively are shown in Appendix 6, *Table 63*.

TABLE 21 *Cytology by HPV status. Results by age (20–29, 30–64), overall, and in 1904 women with a single HPV type*

	20–29 years			30–64 years			All ages				1904 women with a single HPV infection		
HPV type	**Neg**	**B/M**	**Mod+**	**Neg**	**B/M**	**Mod+**	**Neg**	**B/M**	**Mod+**	**Total**	**Neg**	**B/M**	**Mpd+**
16	184	202	113	136	75	95	320 (39.8%)	277 (34.4%)	208 (25.8%)	805 (100%)	235 (45.5%)	146 (28.3%)	135 (26.2%)
18	93	74	24	67	41	20	160 (50.2%)	115 (36.1%)	44 (13.8%)	319 (100%)	96 (56.1%)	53 (31.0%)	22 (12.9%)
31	83	67	35	62	46	33	145 (44.5%)	113 (34.7%)	68 (20.9%)	326 (100%)	97 (53.3%)	53 (29.1%)	32 (17.6%)
33	45	58	27	21	22	10	66 (36.1%)	80 (43.7%)	37 (20.2%)	183 (100%)	32 (41.6%)	31 (40.3%)	14 (18.2%)
35	23	20	6	28	25	6	51 (47.2%)	45 (41.7%)	12 (11.1%)	108 (100%)	31 (52.5%)	23 (39.0%)	5 (8.5%)
39	67	71	21	56	38	13	123 (46.2%)	109 (41.0%)	34 (12.8%)	266 (100%)	78 (60.5%)	46 (35.7%)	5 (3.9%)
45	47	33	14	58	28	10	105 (55.3%)	61 (32.1%)	24 (12.6%)	190 (100%)	59 (64.8%)	24 (26.4%)	8 (8.8%)
51	70	99	20	63	40	13	133 (43.6%)	139 (45.6%)	33 (10.8%)	305 (100%)	83 (50.6%)	69 (42.1%)	12 (7.3%)
52	96	88	27	82	57	17	178 (48.5%)	145 (39.5%)	44 (12.0%)	367 (100%)	105 (56.1%)	68 (36.4%)	14 (7.5%)
56	43	46	9	40	38	6	83 (45.6%)	84 (46.2%)	15 (8.2%)	182 (100%)	48 (53.3%)	38 (42.2%)	4 (4.4%)
58	40	45	12	32	24	15	72 (42.9%)	69 (41.1%)	27 (16.1%)	168 (100%)	49 (57.6%)	24 (28.2%)	12 (14.1%)
59	69	44	12	46	20	8	115 (57.8%)	64 (32.2%)	20 (10.1%)	199 (100%)	74 (69.8%)	27 (25.5%)	5 (4.7%)
68	27	19	4	27	13	4	54 (57.4%)	32 (34.0%)	8 (8.5%)	94 (100%)	34 (72.3%)	11 (23.4%)	2 (4.3%)
16 and/or 18	265	260	129	198	111	114	463 (39.8%)	371 (34.4%)	243 (22.6%)	1077 (100%)	–	–	–
Any HR-HPV	651	556	197	619	362	199	1270 (43.0%)	918 (35.5%)	396 (15.3%)	2584 (100%)	–	–	–
HC2+ no HR-HPV	236	88	5	704	147	9	940 (49.1%)	235 (19.8%)	14 (1.2%)	1189 (100%)	–	–	–
HC2 –ve	3119	286	12	16,035	1211	34	19,154 (79.1%)	1497 (7.2%)	46 (0.22%)	20,697 (100%)	–	–	–
All women	4006	930	214	17,358	1720	242	21,364 (92.5%)	2650 (10.8%)	456 (1.9%)	24,470 (100%)	1021	613	270
No. of HR-HPVs detected	887	866	324	718	467	250	1605	1333	574	3512	1021	613	270

B/M, borderline or mild; Mod+, moderate or worse.

The proportion of different grades of cytology positive for HPV types 16, 18, 31, 45 and 52 is shown in *Figure 15*. This demonstrates graphically the increasing prevalence with cytology grade.

Prevalence rates for each HR-HPV type are shown in *Table 22*, both overall and by age group. HPV16 was the commonest genotype at all ages (overall prevalence 3.3%), followed by HPV52 (1.5%), HPV18 and HPV31 (both 1.3%), HPV51 (1.2%) and HPV39 (1.1%). There was a marked decline in the prevalence of HR-HPV with age, both overall (27.3% below age 30, 6.1% at age 30 or over) and for each HPV type, but less so for HC2 +ve samples in which no HR-HPV was detected (6.4% of women aged under 30, 4.5% at age 30–64).

HPV prevalence rates by age group and cytology are shown in *Table 23* for HPV16, HPV18 without HPV16, and for other HR-HPVs combined. Below age 30 a high proportion of infected women carried two or more different HR-HPV types (44% of women with HPV16, 50% with HPV18 but not HPV16, 24% of all women with other HR-HPVs). Multiple infection was less common at age 30–64 (23% of women with HPV16, 20% with HPV18, 14% of women with other HR-HPVs). The proportion with moderate dyskaryosis or worse was 15.3% (396/2584) in women with any HR-HPV infection, 1.2% for HC2 +ves with no HR-HPV, and 0.22% for HC2 –ve women. The risk of moderate or worse cytology was highest in women infected with HPV16 irrespective of the presence of other HPVs (26.2% for HPV16 alone, 25.3% together with other HR-HPVs).

Of the CIN2+ lesions found before round 2, 108/329 (33%) and 83/225 (37%) respectively, were identified in high-grade and low-grade cytological abnormalities, which were HR-HPV +ve but types 16/18 –ve.

Viral persistence

Detection of persistent HPV infection is important because it confers a high risk of developing high grade CIN. True persistence implies type-specific persistence but in terms of clinical utility it is also relevant to assess the effect of a persistent HC2 +ve result.

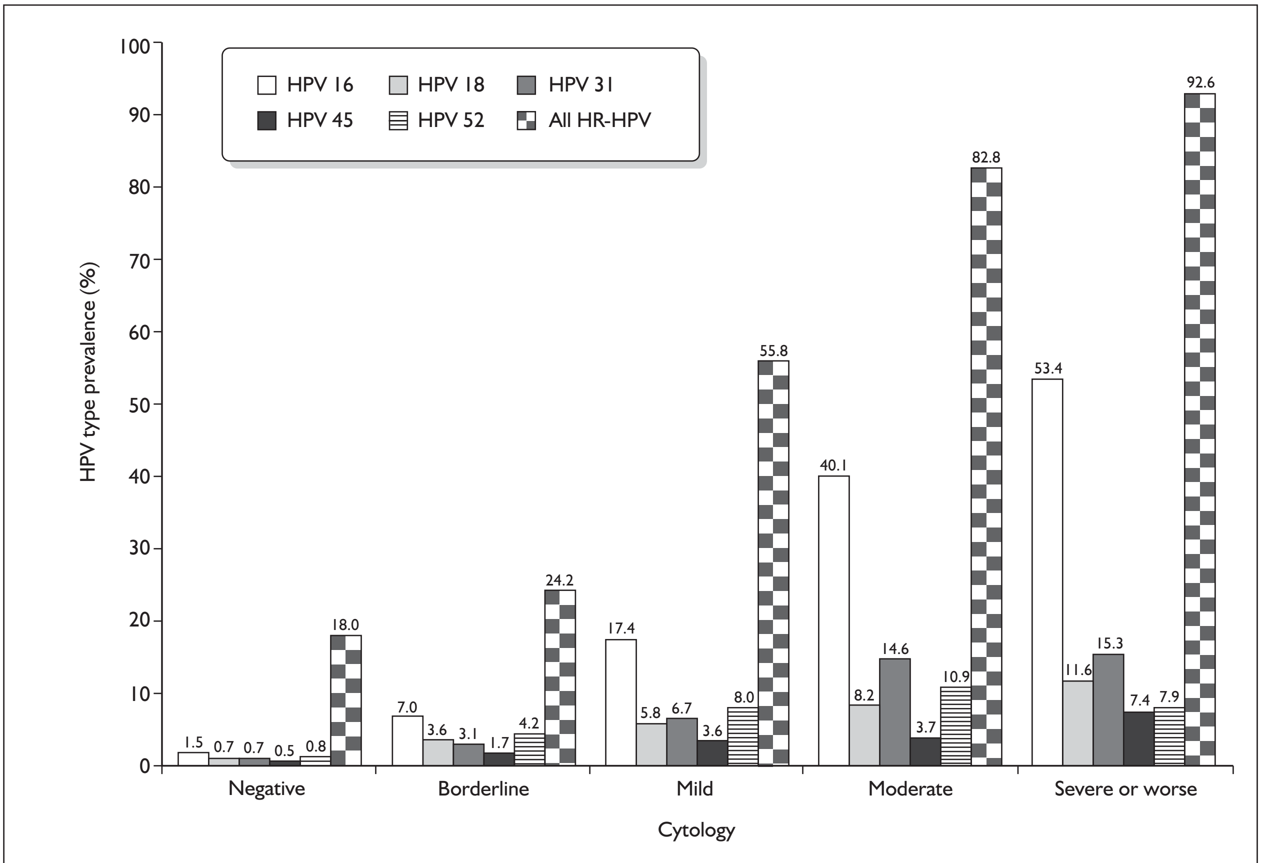

FIGURE 15 *Prevalence rates for four of the commonest five HPV types and HPV45 by cytological grade. Reproduced with permission of Cancer Research UK from Sargent A, Bailey A, Almonte M, Turner A, Thomson C, Peto J,* et al. *Prevalence of type-specific HPV infection by age and grade of cervical cytology: data from the ARTISTIC trial.* Br J Cancer *2008;***98***:1704–9.*

TABLE 22 *Prevalence of high-risk HPVs overall and as a proportion of HR-HPV +ve women, by age group*

Type	20–29 years			30–39 years			40–49 years			50–64 years			All ages		
	n	% of all women	% of HR-HPV+ women	*n*	% of all women	% of HR-HPV+ women	*n*	% of all women	% of HR-HPV+ women	*n*	% of all women	% of HR-HPV+ women	*n*	% of all women	% of HR-HPV+ women
16	499	(9.7)	35.5	207	(2.7)	26.6	62	(1.0)	23.9	37	(0.7)	26.1	805	(3.3)	31.2
18	191	(3.7)	13.6	89	(1.2)	11.4	20	(0.3)	7.7	19	(0.3)	13.4	319	(1.3)	12.3
31	185	(3.6)	13.2	102	(1.3)	13.1	27	(0.4)	10.4	12	(0.2)	8.5	326	(1.3)	12.6
33	130	(2.5)	9.3	41	(0.5)	5.3	10	(0.2)	3.9	2	(0.04)	1.4	183	(0.7)	7.1
35	49	(1.0)	3.5	39	(0.5)	5.0	17	(0.3)	6.6	3	(0.1)	2.1	108	(0.4)	4.2
39	159	(3.1)	11.3	75	(1.0)	9.6	17	(0.3)	6.6	15	(0.3)	10.6	266	(1.1)	10.3
45	94	(1.8)	6.7	58	(0.8)	7.4	20	(0.3)	7.7	18	(0.3)	12.7	190	(0.8)	7.4
51	189	(3.7)	13.5	73	(1.0)	9.4	26	(0.4)	10.0	17	(0.3)	12.0	305	(1.2)	11.8
52	211	(4.1)	15.0	106	(1.4)	13.6	39	(0.6)	15.1	11	(0.2)	7.8	367	(1.5)	14.2
56	98	(1.9)	7.0	58	(0.8)	7.4	13	(0.2)	5.0	13	(0.2)	9.2	182	(0.7)	7.0
58	97	(1.9)	6.9	46	(0.6)	5.9	18	(0.3)	7.0	7	(0.1)	4.9	168	(0.7)	6.5
59	125	(2.4)	8.9	40	(0.5)	5.1	23	(0.4)	8.9	11	(0.2)	7.8	199	(0.8)	7.7
68	50	(1.0)	3.6	30	(0.4)	3.9	8	(0.1)	3.1	6	(0.1)	4.2	94	(0.4)	3.6
16 and/or 18	654	(12.7)	46.6	289	(3.8)	37.1	80	(1.3)	30.9	54	(0.96)	38.0	1077	(4.4)	41.7
Any HR-HPV	1404	(27.3)	100	779	(10.3)	100	259	(4.2)	100	142	(2.5)	100	2584	(10.6)	100
HC2+ no HR-HPV	329	(6.4)	–	368	(4.8)	–	270	(4.4)	–	222	(4.0)	–	1189	(4.9)	–
HC2 –ve	3417	(66.4)	–	6452	(84.9)	–	5582	(91.3)	–	5246	(93.5)	–	20,697	(84.6)	–
All women	5150	(100)	–	7599	(100)	–	6111	(100)	–	5610	(100)	–	24,470	(100)	–

Reproduced with permission of Cancer Research UK from Sargent A, Bailey A, Almonte M, Turner A, Thomson C, Peto J, *et al*. Prevalence of type-specific HPV infection by age and grade of cervical cytology: data from the ARTISTIC trial. *Br J Cancer* 2008;**98**:1704–9.

TABLE 23 *Prevalence of single and multiple infections with HPV16, HPV18 and other high-risk HPV types by age group and cytology result; data are* n *(%)*

		HPV16		HPV18, not HPV16		HPV16 and/or 18			HC2 +ve		
	No. of women	Single HR-HPV	Multiple HR-HPV	Single HR-HPV	Multiple HR-HPV	No other HR	Other HR	HR-HPV, not 16/18	HR-HPV	No HR HPV	HC2 –ve
Age											
20–29	5150	280 (5.4)	219 (4.3)	77 (1.5)	78 (1.5)	374 (7.3)	280 (5.4)	750 (14.6)	1404 (27.3)	329 (6.4)	3417 (66.3)
30–39	7599	158 (2.1)	49 (0.6)	65 (0.9)	17 (0.2)	225 (3.0)	64 (0.8)	490 (6.5)	779 (10.3)	368 (4.8)	6452 (84.9)
40–49	6111	51 (0.8)	11 (0.2)	15 (0.2)	3 (0.1)	68 (1.1)	12 (0.2)	179 (2.9)	259 (4.2)	270 (4.4)	5582 (91.3)
50–64	5610	27 (0.5)	10 (0.2)	14 (0.2)	3 (0.05)	43 (0.8)	11 (0.2)	88 (1.6)	142 (2.5)	222 (4.0)	5246 (93.5)
Cytology											
–ve	21,364	235 (1.1)	85 (0.4)	96 (0.5)	47 (0.2)	340 (1.6)	123 (0.6)	807 (3.8)	1270 (6.0)	940 (4.4)	19,154 (89.7)
B/M	2650	146 (5.5)	131 (4.9)	53 (2.0)	41 (1.6)	210 (7.9)	161 (6.1)	547 (20.6)	918 (34.6)	235 (8.9)	1497 (56.5)
Mod+	456	135 (29.6)	73 (16.0)	22 (4.8)	13 (2.9)	160 (35.1)	83 (18.2)	153 (33.6)	396 (86.8)	14 (3.1)	46 (10.1)
Total	24,470	516 (2.1)	289 (1.2)	171 (0.7)	101 (0.4)	710 (2.9)	367 (1.5)	1507 (6.2)	2584 (10.6)	1189 (4.9)	20,697 (84.6)

–ve, negative; B/M, borderline or mild; Mod+, moderate or worse.

The prognostic significance of persistent as opposed to cleared infection has already been referred to. ARTISTIC provided an opportunity to examine the effect of HPV persistence and clearance between rounds 1 and 2 in terms of screening outcomes. Persistence data are presented as HC2, HC2/LBA+ and type-specific persistence. HC2 persistence does not represent evidence of a true persistent infection because one type could have been replaced by another type, but in terms of clinical utility it represents persistence of the positive standard HPV screening test result as the means of risk assessment. HC2/LBA+ excludes possible false-positive HPV results because a type has been detected and type-specific persistence provides the clearest evidence of a truly persistent infection by a specific oncogenic type. HC2 alone would be the most sensitive measure of HPV persistence, and type-specific persistence the most specific.

Table 24 shows HPV persistence in women with all cytology grades in round 1 over a range of intervals up to 48 months after round 1. The results beyond 6 months are hardly affected by clinical intervention. Treatment of CIN clears HPV in the majority of cases, but these results are based on the next HPV result after round 1, which would precede treatment except in women with high-grade cytology in round 1, most of whom would be treated within 6 months. Persistence rates are similar irrespective of the measure of HPV positivity, including HC2 with or without confirmation by LBA and various type-restricted analyses including HPV16 detection, declining from over 80% within 6 months to about 40% at 18–24 months and remaining around 20–30% from 2 to 4 years.

Type-specific persistence rates are shown in Appendix 6, *Table 68*. These data are complicated by the fact that multiple infections are included but there were no major type-specific differences in persistence rates among the 13 high-risk types represented in the HC2 test.

Table 25 suggests similar HPV persistence rates in cytology –ve women in the concealed arm in whom there was no treatment intervention before round 2, but numbers are small for type-specific/restricted analyses.

The overall results (both arms combined) for HPV persistence in round 2 are shown in *Table 26*. This shows HPV persistence at 30–48 months of 28%, by HC2 but substantially lower rates for type-specific/restricted persistence of around 10–17%.

The impact of HPV persistence on cytology in round 2, in terms of odds ratios, is shown in *Table 27* excluding those who had been treated in round 1. Abnormal cytology rates (borderline +) are consistently around 40% for women with persistence. The round 2 abnormality rate is only 4.8% in woman who had become HC2 –ve, but substantially higher (11–15%) in those who had become negative by the other more specific but less sensitive measures of HPV. It is therefore clear that women who have persistent HPV infection over 3 years are at considerable risk of developing an abnormality. When the results are compared between the arms, there are no striking differences (*Table 28*).

Economic results

The economic evaluation concentrated on performing cost analyses to observe whether there were significant differences in screening and managing the women in the concealed and revealed arms. Age-related comparisons and age-adjustments were made where appropriate.

Cost analyses

For the cost analyses, resource-use events experienced by all 24,510 women in the trial were identified in the trial data sets and costed accordingly. The items of resources used by individual women covered the protocol-driven events and additional events of relevance, such as follow-up cervical cytology tests arranged by GPs for women who were negative in round 1, or colposcopy clinic follow-up visits for surveillance. The cost analyses generated a mean cost per woman, according to trial arm, for the trial itself and for other scenarios with alternative screening policies.

Unit costs

Primary care costs

These costs apply to the resources involved in screening women in general practice surgeries or community clinics where cervical samples were taken for cytological examination and/or HPV testing. The two main resource components were: administration, inclusive of postal invitations to attend for screening; and staff costs for screening consultations. Administration costs were obtained

TABLE 24 *HPV testing and typing results in round 1 and next adequate HPV sample*

		Time (months) to second sample										
Round 1	**Second sample**	**<6**	**6–11.9**	**12–17.9**	**18–23.9**	**24–29.9**	**30–35.9**	**36–41.9**	**42–47.9**	**48+**	**No second sample**	**Total**
HC2+	HC2+	363	487	296	64	29	59	79	39	45		1461
	HC2–	66	391	352	81	53	159	200	95	116		1513
	No. tested	429	878	648	145	82	218	279	134	161	839	3813
	Persistence (%)	84.6	55.5	45.7	44.1	35.4	27.1	28.3	29.1	28.0		49.1
HC2+/LBA+	HC2+/LBA+	300	371	200	47	19	36	50	25	18		1066
	HC2 other	57	220	213	57	48	102	111	64	95		967
	No typed	357	591	413	104	67	138	161	89	113	551	2584
	Persistence (%)	84.0	62.8	48.4	45.2	28.4	26.1	31.1	28.1	15.9		52.4
HPV16+	HPV16+	124	110	51	10	5	10	16	6	4		336
	Other	19	78	61	15	18	37	39	22	30		319
	No. tested	143	188	112	25	23	47	55	28	34	150	805
	Persistence (%)	86.7	58.5	45.5	40.0	21.7	21.3	29.1	21.4	11.8		51.3
HPV16+/18+[a]	HPV16+/18+	147	138	54	11	6	12	16	6	5		395
	Other	29	111	96	25	28	49	54	31	39		462
	No typed	176	249	150	36	34	61	70	37	44	220	1077
	Persistence (%)	83.5	55.4	36.0	30.6	17.7	19.7	22.9	16.2	11.4		46.1
HPV5types+[b]	HPV 5 types+	218	215	95	20	11	23	23	12	8		625
	Other	38	148	133	35	32	79	80	42	63		650
	No typed	256	363	228	55	43	102	103	54	71	315	1590
	Persistence (%)	85.2	59.2	41.7	36.4	25.6	22.6	22.3	22.2	11.3		49.0

a HPV16+/18+ = HPV16+ and/or HPV18+.
b HPV5types+ = HPV16+ and/or HPV18+ and/or HPV31+ and/or HPV33+ and/or HPV45+.

TABLE 25 *HPV testing and typing results in round 1 and next adequate HPV sample – women in the concealed arm with negative cytology in round 1*

		Time (months) to second sample										
Round 1	**Second sample**	**<6**	**6–11.9**	**12–17.9**	**18–23.9**	**24–29.9**	**30–35.9**	**36–41.9**	**42–47.9**	**48+**	**No second sample**	**Total**
HC2+	HC2+					1	35	40	12	13		101
	HC2–					1	63	85	41	38		228
	No. tested					2	98	125	53	51	222	551
	Persistence (%)					50.0	35.7	32.0	22.6	25.5		30.7
HC2+/LBA+	HC2+/LBA+						24	30	7	8		69
	HC2 other						28	33	23	24		108
	No typed						52	63	30	32	131	308
	Persistence (%)						46.2	47.6	23.3	25.0		39.0
HPV16+	HPV16+						4	8	1	1		14
	Other						11	11	3	7		32
	No. tested						15	19	4	8	28	74
	Persistence (%)						26.7	42.1	25.0	12.5		30.4
HPV16+/18+[a]	HPV16+/18+						5	8	1	2		16
	Other						16	16	7	10		49
	No typed						21	24	8	12	47	112
	Persistence (%)						23.8	33.3	12.5	16.7		24.6
HPV5types+[b]	HPV 5 types+						13	11	3	3		30
	Other						24	26	12	15		77
	No typed						37	37	15	18	69	176
	Persistence (%)						35.1	29.7	20.0	16.7		28.0

a HPV16+/18+ = HPV16+ and/or HPV18+.
b HPV5types+ = HPV16+ and/or HPV18+ and/or HPV31+ and/or HPV33+ and/or HPV45+.

TABLE 26 *HPV testing and typing results in round 1 and round 2*

Round 1	Round 2	Time (months) to round 2: 30–35.9	36–41.9	42–47.9	No second sample	Total
HC2+	HC2+	202	221	84		507
	HC2–	519	537	228		1284
	No. tested	721	758	312	2022	3813
	Persistence (%)	28.0	29.2	26.9		28.3
HC2+/LBA+	HC2+/LBA+	121	129	54		304
	HC2 other	551	422	193		1166
	No typed	672	551	247	1114	2584
	Persistence (%)	18.0	23.4	21.9		20.7
HPV16+	HPV16+	29	29	9		67
	Other	198	146	63		407
	No. tested	227	175	72	331	805
	Persistence (%)	12.8	16.6	12.5		14.1
HPV16+/18+[a]	HPV16+/18+	34	29	10		73
	Other	273	200	84		557
	No typed	307	229	94	447	1077
	Persistence (%)	11.1	12.7	10.6		11.6
HPV5types+[b]	HPV 5 types+	62	52	22		136
	Other	395	282	126		803
	No typed	457	334	148	651	1590
	Persistence (%)	13.6	15.6	14.9		14.5

a HPV16+/18+ = HPV16+ and/or HPV18+.
b HPV5types+ = HPV16+ and/or HPV18+ and/or HPV31+ and/or HPV33+ and/or HPV45+.

TABLE 27 *Cytological abnormality in round 2 by HPV testing and typing results in round 1 and round 2 – women not treated in round 1*

Round 1	Round 2	Abnormal cytology *n*	%	Negative cytology *n*	%	OR	(95% CI)	*p*-value
HC2+	HC2+	155	33.8	304	66.2	10.22	(7.05 to 14.80)	< 0.001
	HC2-	51	4.8	1022	95.3			
HC2+/LBA+	HC2+/LBA+	98	35.6	177	64.4	4.35	(3.09 to 6.11)	< 0.001
	HC2 other	94	11.3	738	88.7			
HPV16+	HPV16+	26	42.6	35	57.4	4.34	(2.24 to 8.39)	< 0.001
	Other	32	14.6	187	85.4			
HPV16+/18+[a]	HPV16+/18*	28	42.4	38	57.6	4.73	(2.59 to 8.63)	< 0.001
	Other	46	13.5	295	86.5			
HPV5types+[b]	HPV 5 types+	45	36.6	78	63.4	3.145	(2.190 to 5.43)	< 0.001
	Other	73	14.3	436	85.7			

OR, odds ratio.
a HPV16+/18+ = HPV16+ and/or HPV18+.
b HPV5types+ = HPV16+ and/or HPV18+ and/or HPV31+ and/or HPV33+ and/or HPV45+.

TABLE 28 *Cytological abnormality in round 2 by HPV testing and typing results in round 1 and round 2, and randomisation – women with negative cytology and not treated in round 1*

		Concealed arm					Revealed arm				
		Abnormal cytology		Negative cytology		Total	Abnormal cytology		Negative cytology		Total
Round 1	Second sample	*n*	%	*n*	%	*n*	*n*	%	*n*	%	*n*
HC2+	HC2+	30	35.7	54	64.3	84	63	28.5	158	71.5	221
	HC2–	3	1.6	181	98.4	184	22	3.8	550	96.2	572
HC2+/LBA+	HC2+/LBA+	23	39.0	36	61.0	59	40	31.2	88	68.8	128
	HC2 other	6	6.5	86	93.5	92	30	8.4	328	91.6	358
HPV16+	HPV16+	4	36.4	7	63.6	11	14	50.0	14	50.0	28
	Other	2	7.4	25	92.6	27	14	14.6	82	85.4	96
HPV16+/18+[a]	HPV16+/18*	5	41.7	7	58.3	12	14	46.7	16	53.3	30
	Other	5	11.4	39	88.6	44	21	13.7	132	86.3	153
HPV5types+[b]	HPV 5 types+	10	40.0	15	60.0	25	21	34.4	40	65.6	61
	Other	9	13.2	59	86.8	68	24	11.2	191	88.8	215

a HPV16+/18+ = HPV16+ and/or HPV18+.
b HPV5types+ = HPV16+ and/or HPV18+ and/or HPV31+ and/or HPV33+ and/or HPV45+.

from the English pilot of LBC implementation[41] and inflated to the 2006–7 financial year.[59] The mean duration of screening consultations was adopted from the English pilots (13:45 minutes, 95% CI 12:25 to 15:05 minutes) and weighted according to the likelihood that a GP or a practice nurse would be the sample taker (on four-fifths of occasions the sample taker was a nurse).[41] Staff time was costed accordingly (see *Table 29*).

Laboratory transport in primary care
General practices are normally served by hospital laboratory transport systems. We assumed that the arrangements for conveying cervical sample vials would remain unaltered and the costs would be unaffected.

Cytology laboratory costs
In determining mean costs for examinations of LBC samples, three distinct cost components were identified: laboratory equipment, consumables and staffing needed for processing the ThinPrep vials containing the cellular material; staining of the processed slides, ready for examination; and reading and reporting the slides.

Our modelling of laboratory configurations for processing LBC samples showed that the most advantageous scenario financially, from the perspective of the English NHSCSP, assumed that each of the 28 subregions within the nine QARCs had at least one centralised processing laboratory with satellite laboratories where the slides were reported. Five-yearly contracts for leasing Thinprep T3000 and T2000 processors would be placed by the QARCs on behalf of the laboratory networks, giving a total cost for England including VAT of £14,807,000.[43] As the national workload of cervical slides in 2004–5 was 4,022,269, the total processing cost per slide would be £3.68. Consequently, an LBC equipment cost per slide of £3.15 (excl. VAT), inclusive of consumables and labour, was adopted for the ARTISTIC base-case cost analyses. For a sensitivity analysis, the cost per slide was varied between £3.00 and £4.20.

Staining of LBC slides for women in the ARTISTIC trial was undertaken in each of the two cytology laboratories. The costs of staining activities were obtained from the study of LBC pilot sites[41] and were uplifted to 2006 prices, giving a staining cost per slide of 25 pence.

Examination and reporting of LBC slides for ARTISTIC women was undertaken in the two laboratories. Mean times (minutes) were obtained from the timing surveys for the initial (primary) screening of all prepared slides, rapid review of negative slides, checking of abnormal slides and secondary reading of abnormal slides by cytopathologists.[44] As there was very little difference in the mean times recorded in the second and third surveys, the means for the different activities recorded during the final survey in the Manchester laboratory were used for the calculations of the cytoscreener and biomedical scientist labour costs (see *Table 30*).

When attributing salary costs to the different grades of laboratory staff (*Table 31*) the mid-scale point for the corresponding band in the newly introduced Agenda for Change salary structure was applied. NHS employer's costs were also included (that is, the employer's national insurance contribution plus 14% of salary for employer's contribution to superannuation). Cytoscreeners are recommended not to screen for more than 2 hours continuously.[60] In the cost analyses 16.7% was added to the corresponding staff costs. However, the unit costs for laboratory activities do not include overhead charges because they were the same for both arms.

TABLE 29 *Primary care cost items*

Cost items	Sources of resource use and cost data	Cost (£)
Invitation letter	Pilot estimate inflated from 2002 to 2006 costs[41]	3.43
Cost/min of GP time	Unit Costs of Health and Social Care – 2006[39]	2.20
Cost/min of practice nurse time	Unit Costs of Health and Social Care – 2006[39]	0.43
Weighted cost of consultation	Pilot (weights) and Unit Costs of Health and Social Care – 2006[39]	10.78
Total cost of consultation for sample taking		14.21

TABLE 30 Durations of time for reading and reporting LBC slides

Examination stage	Source	Duration in minutes (including reporting time) (SD)
Primary reading	Timing survey of cytoscreeners and BMSs[44]	5:40 (1:52)
Rapid review	[a]NHSCSP Recommendations[60]	1:30
	Timing survey of cytoscreeners and BMSs[44]	2:05 (0:27)
Checking	Timing survey of cytoscreeners and BMSs[44]	5:40 (1:52)
Secondary reading	Timing survey of cytopathologists[44]	6:23 (2:00)

BMS, biomedical scientist.
a Used in the base case cost analyses.

For the cost analyses, two types of costs for LBC samples were calculated (see *Table 32*): the costs associated with a negative or an inadequate sample (with the prepared slide requiring only primary screening and rapid review), and the costs associated with an abnormal sample (where the prepared slide would require primary screening, checking and secondary screening by a cytopathologist).

Virology laboratory costs for HPV testing

When deriving unit costs for the HC2 technology used for HPV testing, the estimates were based on a general assumption that HPV testing had been introduced throughout the English NHSCSP. Alternative scenarios for adopting the technology were considered: primary screening jointly with LBC and HPV testing (as in the revealed arm of the trial); HPV testing as a triage for women with borderline or mild LBC results; and HPV testing as the primary screening with LBC used to triage women with +ve HPV results. Each of the scenarios was associated with a specific set of costs. However, in accordance with the cytology costs, laboratory overhead costs were not included.

The HC2 assaying technique for HPV DNA testing, developed by QIAGEN, is performed using either a manual or an automated system of equipment. A single manual system, as used for ARTISTIC, processes 88 samples in a 4-hour period; the maximum capacity for an automated system is 352 samples per 4-hour run. Systems may be purchased or leased. Most consumable products are standard laboratory items; the main exceptions are reagents and, when the samples being tested are in an LBC medium, the kits needed for converting the fluid in the LBC vials. However, if HPV testing were adopted as the sole method for primary screening, a different type of cervical sampler would be used by sample takers that did not require conversion before DNA analysis. Laboratory staff costs for the manual and automated systems were derived, based on the mid-point of the biomedical scientist pay rate band.[40] Durations of time spent by technical staff in operating the two types of systems were assessed from observational fieldwork for the manual system in the ARTISTIC virology laboratory and projections for the automated system.

TABLE 31 Cost per minute for cytology laboratory staff

Laboratory staff grade	Source	Cost/minute (£)
Cytoscreener	Agenda for Change[40]	0.22
Biomedical scientist	Agenda for Change[40]	0.26
Pathologist	Unit Costs of Health and Social Care – 2006 (no allowance for qualifications[a])[39]	0.98
Pathologist	Unit Costs of Health and Social Care – 2006 (including qualifications allowance[a])[39]	1.22

a The equivalent annual cost of medical training and postgraduate education.

TABLE 32 *Summary of laboratory costs for negative and abnormal LBC samples*

Laboratory component	Cost (£) of negative/inadequate sample	Cost (£) of abnormal sample
LBC equipment costs (including staff costs)	3.15	3.15
Staining of slides	0.25	0.25
Reading and reporting slides	1.72	9.00
Adjustment for breaks	0.29	0.23
Total cost	5.41	12.73

Contract prices for purchasing or leasing HC2 systems were provided by QIAGEN according to a range of assumptions over the annual capacity required to process HPV samples for the English NHSCSP. However, as the prices were provided in confidence, the unit costs in *Table 33* also include consumables and staff costs. Again, VAT is omitted. The table presents costs for two scenarios: HPV DNA testing of LBC samples (the cost of the LBC vial is not included), and HPV testing on cervical samples collected solely for that purpose (that is, if HPV testing was adopted as a 'stand-alone' test using a QIAGEN sampler kit). In the revealed arm, HPV tests were repeated for some women without the cytology being examined. A cost per event of £17.91 was derived, which took account of the primary care consultation, the LBC cervical sampler and the virology test.

Colposcopy-related costs

The work activity survey of colposcopy clinics participating in the ARTISTIC trial revealed variations in clinical policies with respect to treating women at their first attendance ('see and treat') and retaining women on review by performing follow-up colposcopies and/or cervical samples. So, rather than relying on national reference costs, the finance departments for seven hospital trusts responsible for the ARTISTIC clinics were asked to provide their unit costs for these colposcopy-related events, including histology examinations of biopsied samples. Six trusts responded, although at differing levels of comprehensiveness, partly as the result of NHS reference cost purposes; there has not been a national requirement to fully identify costs for procedures performed on an outpatient basis. However, two trusts did assist in a detailed manner. Central Manchester & Manchester Children's (CM&MC) Hospitals NHS Trust undertook a cost accounting exercise by firstly formulating care pathways for women referred for colposcopy. Average trust unit costs were derived based on 2006–7 financial and activity data at St Mary's Hospital for a new colposcopy clinic attendance and a follow-up attendance. These prices took account of the types of biopsies performed, histological examinations made and cervical samples taken, and included labour costs and overheads. Salford Royal NHS Foundation Trust provided instead specific costs for the different colposcopy-related activities drawn from the trust's reference cost submission for 2005–6 (*Table 34*).

The average annual costs for new and follow-up colposcopies (£300.51 and £150.26 respectively) were adopted for the main cost analyses, while the detailed unit costs for specific resource events (e.g. biopsies and histological examinations) recorded for women individually were used in a sensitivity analysis. This was proposed because the colposcopy clinic for St Mary's Hospital serves an academic department of obstetrics and gynaecology, and so the clinic's pattern of colposcopic activities

TABLE 33 *Unit costs for HPV tests performed on LBC and HPV cervical samples*

Test volume per annum	HPV on LBC sample		HPV sample only	
	Manual systems	Automated systems	Manual system	Automated systems
240,000	£10.57	£10.38	£10.06	£9.87
500,000	£10.36	£10.11	£9.83	£9.58
4,000,000	£7.00	£6.61	£6.25	£5.87

TABLE 34 Unit costs for colposcopy-related activities provided by two NHS trusts

Clinical activity	Trust's unit cost (£)[a]	
	CM&MC (St Mary's Hospital)	Salford Royal
Colposcopy (OPCOP1)		253.78
New referral (average unit cost)	300.51	
Follow-up attendance (average unit cost)	150.26	
Biopsy of cervix uteri (OPBCU1)		
Punch biopsy	[98]	181.68
Ring (loop) biopsy	[293]	181.68
Other specified or unspecified		181.68
Cervical LBC test performed in clinic	[49]	87.18
Histology: reporting on		
Punch biopsy	[58]	47
Large loop excision	[85]	49
Loop biopsy or diathermy	[91]	49
Cone biopsy	[79]	49
Other biopsy		56.53
Simple hysterectomy	[119]	
Radical hysterectomy	[191]	
Upper genital tract major procedure (hysterectomy)		
Hysterectomy	4920	
Inpatient elective		4197.95
Inpatient non-elective		5746.66

CM&MC, Central Manchester & Manchester Children's Hospitals NHS Trust; Salford, Salford Royal NHS Foundation Trust. OPCOP1 and OPBCU1 are NHS reference cost codes for Colposcopy and Biopsy of Cervix Uteri respectively.
a The costs inside square brackets were incorporated into the average unit costs for new referrals and follow-up attendances according to the numbers of colposcopy-related activities during 2006–7.

and associated costs may not have been fully representative of the colposcopic management of ARTISTIC women in general. Also, during the trial, most women who chose to undergo colposcopy after repeated HPV +ve test results were examined at the St Mary's clinic. LBC samples were usually taken in the clinics by using the SurePath technique and that was reflected in the colposcopy costs.

Resource use

Duration of follow-up

The cost analyses were based on resource-generating events recorded for individual trialists between the date of their round 1 LBC sample in the trial until 1 May 2007. Within that period, events were recorded during round 2 for 12,615 women in the revealed arm (68.6%) and 4150 women in the concealed arm (67.8%). *Table 35* shows that the mean duration for all the 24,510 women was 4.8 years, and there was almost no difference between the two arms in terms of mean, minimum and maximum numbers of years. Overall, about 4000 women were followed up for 5.5 years or longer.

Screening tests in primary care

Table 36 shows the numbers of adequate LBC samples and HPV tests per woman that were analysed throughout the duration of the trial until 1 May 2007 (that is, during the first and second rounds). The cervical samples were taken in GP surgeries and community clinics.

TABLE 35 Duration of women's participation in the trial

Trial arm	Mean (years)	*n*	SD	Median (years)	Minimum (years)	Maximum (years)	Range (years)
Concealed	4.83	6124	0.57	4.87	2.85	5.83	2.98
Revealed	4.82	18,386	0.58	4.87	2.87	5.83	2.96
Total	4.82	24,510	0.58	4.87	2.85	5.83	2.98

p test: analysis of variance: F = 0.002; *p* = 0.966.

TABLE 36 Numbers of HPV tests and LBC tests per woman from adequate cervical samples taken in primary care by randomisation in rounds 1 and 2

Adequate LBC tests per woman in round 1	Concealed	Revealed – HPV tests per woman in round 1							
		1	2	3	4	5	6	7	Total
1	5401	**15,119**[b]	792	47	0	0	0	0	15,958
2	124	179	**325**[b]	64	4	0	0	0	572
3	240	152	246	**315**[b]	24	0	0	0	737
4	256	95	173	227	**268**[b]	8	0	0	771
5	87	33	63	66	66	**59**[b]	3	0	290
6	15	6	11	9	10	8	**5**[b]	0	49
7	1	1	2	0	4	1	0	**1**[b]	9
Total	6124	15,585	1612	728	376	76	8	1	18,386

Adequate LBC tests per woman in round 2	Concealed	Revealed – HPV tests per woman in round 2						
		0	1	2	3	4	5	Total
0	[1974][a]	[5771][a]	90	7	0	0	0	5868
1	3650	809	**9784**[b]	406	16	2	0	11,017
2	350	64	352	**530**[b]	43	0	0	989
3	104	13	62	103	**178**[b]	13	1	370
4	31	2	10	28	24	**52**[b]	2	118
5	13	0	3	1	3	10	**3**[b]	20
6	2	0	1	0	0	2	1	4
Total	6124	6659	10,302	1075	264	79	7	18,386

a The numbers inside square brackets represent women who were not screened in round 2.
b Numbers of HPV tests where cytology was not examined appear in the cells identified in bold.

In the revealed arm, women who were cytology –ve but HPV +ve in round 1 were invited to return after 12 months for an HPV test only, and again at 24 months in some cases. As a result, in *Table 36*, 942 revealed women in round 1 and 580 revealed women in round 2 had HPV tests without cytological examination of the cervical sample (the numbers of 'stand-alone' HPV tests appear above the cells identified in bold). Occasionally a cervical sample was taken from a woman using the conventional Papanicolaou method, but for convenience, these smears have been categorised as LBC. In addition, a small proportion of LBC samples were classified as 'inadequate' for cytological examination. Because of a technicality, these events were not recorded in the trial database. So, in the baseline analyses we accounted for an inadequate rate of 2.5%, which was the LBC inadequate rate recorded in the Central Manchester Laboratory in 2007, by adding 2.5% of the cost of an inadequate sample to the cost of each adequate smear. During the study, very few vials with insufficient cellular medium for HPV testing were transferred to the Virology Department. These vials were immediately rejected and did not incur processing costs. As a consequence, when deriving the cost for HPV testing, no allowance was made for inadequate specimens.

Colposcopy-related resource use

The ARTISTIC Trial's colposcopy database was analysed to identify the frequency of the women's colposcopy clinic attendances and the clinical procedures performed. A total of 1567 women underwent colposcopy in round 1 and 358 women in round 2; almost 80% were in the Revealed arm in each round. *Tables 37* and *38* indicate that there was no statistical difference between the two arms in terms of the age distribution of the women undergoing colposcopy, the mean age overall being 33 years.

As reported in the Methods section, the key cost-generating events for women referred for colposcopy are: colposcopic examinations, biopsies taken, treatments performed, histological examinations and cervical samples. Hysterectomies may also be performed.

Colposcopies

Two-thirds of all women undergoing colposcopy in round 1 had one or more follow-up clinic attendances (*Table 39*). The patterns of follow-up attendances were generally similar within each arm, so overall, 20.5% of all attendances were made by concealed women and 79.5% were made by revealed women.

In round 2, 51.4% of the women undergoing colposcopy in the concealed arm attended a clinic on two occasions compared with 38.7% in the revealed arm, a difference bordering on statistical significance. However, the time span for recording colposcopy attendances in the ARTISTIC dataset for round 2 was shorter than for round 1.

Biopsies performed

When undergoing colposcopy, 11.6% (37/320) of the concealed women and 20.1% (251/1247) of the revealed women in round 1 did not have a biopsy taken (chi-squared $p = 0.001$), a reflection of the volume of HPV +ve women who were simply examined colposcopically. However, for the women who were biopsied, the mean number of biopsies per person was 1.59 in the concealed arm and 1.54 in the revealed arm.

TABLE 37 *Mean age of ARTISTIC women who underwent colposcopy according to round and randomisation*

	Mean	No. (%) of women	SD
Round 1			
Concealed	34.01	320 (20.4)	10.06
Revealed	32.96	1247 (79.6)	10.10
Total	33.18	1567 (100.0)	10.10
Round 2			
Concealed	32.35	74 (20.7)	9.48
Revealed	33.17	284 (79.3)	10.29
Total	33.00	358 (100.0)	10.12

In round 1, $p = 0.099$; in round 2, $p = 0.539$.

TABLE 38 *Age distribution of colposcoped women according to round and randomisation*

		Age group (years)					
		< 25	25–34	35–44	45–54	> 54	Total
Round 1							
	Concealed *n* (%)	61 (19.1)	124 (38.8)	83 (25.9)	41 (12.8)	11 (3.4)	320 (100.0)
	Revealed *n* (%)	317 (25.4)	445 (35.7)	305 (24.4)	133 (10.7)	47 (3.8)	1247 (100.0)
Round 2							
	Concealed *n* (%)	18 (24.3)	28 (37.8)	18 (24.3)	9 (12.2)	1 (1.4)	74 (100.0)
	Revealed *n* (%)	73 (25.7)	101 (35.6)	60 (21.1)	39 (13.7)	11 (3.9)	284 (100.0)

Round 1, p test: chi-squared $p = 0.179$; round 2 p test: chi-squared $p = 0.804$.

Colposcopic treatments undertaken

In round 1, 60.3% (193/320) of the concealed women and 50.7% (632/1247) of the revealed women underwent treatment (chi-squared $p = 0.003$). In round 2, the comparative results were 35.1% (26/74) concealed and 24% (68/284) revealed ($p = 0.072$). There may have been under-recording of treatments in round 2, however, because of the restricted follow-up period, as *Table 40* indicates.

TABLE 39 *New and follow-up attendances at colposcopy clinics in rounds 1 and 2*

	Attendances at colposcopy clinics									
		Follow-up attendances								
Round 1	**1st (new)**	**1st**	**2nd**	**3rd**	**4th**	**5th**	**6th**	**7th**	**8th**	**Total attendances**
Concealed	320	221	128	39	16	7	2	1	0	734
% of total women		69.1%	40.0%	12.2%	5.0%	2.2%	0.6%	0.3%		20.5%
Revealed	1247	819	469	208	70	28	9	2	2	2854
% of total women		65.7%	37.6%	16.7%	5.6%	2.2%	0.7%	0.2%	0.2%	79.5%
Total women	1567									3588
p test, chi-squared		0.253	0.432	0.049	0.667	0.950	0.853	0.579	0.473	

	Attendances at colposcopy clinics						
		Follow-up attendances					
Round 2	**1st (new)**	**1st**	**2nd**	**3rd**	**4th**	**5th**	**Total attendances**
Concealed	74	38	6	1	1		120
% of total women		51.4%	8.1%	1.4%	1.4%		21.8%
Revealed	284	110	30	6	1		431
% of total women		38.7%	10.6%	2.1%	0.4%		78.2%
Total women	358						551
p test, chi-squared		0.050	0.532	0.674	0.304		

***TABLE 40** Colposcopy clinic attendances at which treatments were performed*

Round 1	Attendances at colposcopy clinic at which treatment was performed: 1st (new)	Follow-up attendances: 1st	2nd	3rd	4th	5th	6th	7th	Total women treated
Concealed	66 (34.2%)	108 (56%)	13 (6.7%)	5 (2.6%)	1 (0.5%)	0	0	0	193 (100%)
Revealed	225 (35.6%)	336 (53.2%)	42 (6.6%)	19 (3%)	7 (1.1%)	2 (3.2%)	0	1 (1.6%)	632 (100%)
Total	291	444	55	24	8	2	0	1	825
p test, chi-squared	0.289	0.016	0.547	0.960	0.577				

Round 2	Attendances at colposcopy clinic at which treatment was performed: 1st (new)	Follow-up attendances: 1st	2nd	3rd	Total women treated
Concealed	11 (42.3%)	14 (53.8%)	1 (3.8%)		26 (100%)
Revealed	19 (27.9%)	45 (66.2%)	4 (5.9%)		68 (100%)
Total	30	59	5		94
p test, chi-squared	0.024	0.526	0.970		

Follow-up smears

Many women also had cervical samples taken when attending the clinics. Altogether during round 1, 607 smears were recorded for the concealed arm, and 2448 for the revealed arm (mean per woman undergoing colposcopy 1.90 and 1.96 respectively). The rates for round 2 were noticeably lower [1.27 (94/74) and 1.09 (309/284) respectively].

Hysterectomies

Seven women with abnormal cervical cytology were referred for a hysterectomy. They were in round 1; three were in the concealed arm and four were in the revealed arm.

Trial costs

Cost comparisons between randomised arms were carried out for round 1 and for the ARTISTIC trial overall. The costed events conform with the trial protocol; that is, LBC screening alone for the concealed arm, and LBC screening and HPV testing for the revealed arm. The consolidated costs incorporated in the baseline cost analyses for the trial and the additional scenarios (2, 3a and 3b) are presented in *Table 41*. The table also identifies the numbers of resource use events in the concealed and revealed arms to which the costs were attributed. The time period covered by round 1 was the first 30 months after a woman's valid round 1 sample, and the cost results for the full trial covered all resource events in both rounds 1 and 2 until 1 May 2007.

The mean costs per woman for round 1 and the full trial are presented in *Table 42*. These costs incorporate all cytology-, virology- and colposcopy-related events. In round 1, the mean (SD) cost per concealed woman was £55.97 (£177.87), (95% CI, £51.52 to £60.42); the mean (SD) cost for the revealed arm was significantly greater at £72.40 (£174.63), (95% CI, £69.88 to £74.92) ($p < 0.001$). The difference between the mean (SD) costs over the two screening rounds was equally significant: £77.10 (£186.99), (95% CI, £72.42 to £81.78) for the concealed arm compared with £99.96 (£187.41), (95% CI, £97.25 to £102.67) for the revealed arm ($p < 0.001$).

Mean costs were calculated for age groups, banded in 5-year intervals, to observe differentials both across age ranges and between arms within age bands (*Table 43*).

TABLE 41 *Summary of consolidated costs for resource-use items and resource usage in round 1 and the full trial according to randomisation*

		Numbers of resource use events			
		Round 1		Full trial	
Resource item	Cost (£) 2006	Concealed (6124 women)	Revealed (18,386 women)	Concealed (6124 women)	Revealed (18,386 women)
Primary care					
Sample taking consultation (adequate samples only)	14.21	7925	24,204	12,788	38,905
Cytology laboratory					
Negative LBC sample	5.41	6513	19,842	11,030	33,511
Abnormal LBC sample	12.73	1412	4362	1758	5394
Adjustment for inadequate samples (2.5%)	0.48				
Virology laboratory					
HPV test on LBC sample	6.61	NA	23,067	NA	36,662
Repeat HPV test (LBC sample taking consultation plus test)	17.98		963		1237
Colposcopy clinic					
New attendance	300.51	320	1247	394	1531
Follow-up attendance	150.26	414	1607	460	1754
Inpatient treatment					
Hysterectomy	4920	3	4	3	4

TABLE 42 *Mean cost per woman in the ARTISTIC trial covering screening and colposcopy-related events for round 1 and for the full trial*

		ARTISTIC trial mean cost per woman	
Trial arm		Round 1	Full trial
Concealed ($n = 6124$)	Mean cost (£)	55.97	77.10
	95% CI	51.52 to 60.42	72.42 to 81.78
	SD	177.87	186.99
Revealed ($n = 18,386$)	Mean cost (£)	72.40	99.96
	95% CI	69.88 to 74.92	97.25 to 102.67
	SD	174.63	187.41
Total ($n = 24,510$)	Mean cost (£)	68.30	94.25
	95% CI	66.1 to 70.5	91.9 to 96.6
	SD	175.58	187.56
p-value		$p < 0.001$	$p < 0.001$

TABLE 43 *Mean cost (£) per woman according to age group for round 1 and for the full trial*

Age groups		ARTISTIC round 1 Concealed arm	ARTISTIC round 1 Revealed arm	ARTISTIC full trial Concealed arm	ARTISTIC full trial Revealed arm
20–24	Mean cost	81.41	129.27	106.73	165.28
	95% CI	67.48 to 95.34	119.07 to 139.47	91.67 to 121.79	154.2 to 176.36
	n	647	1952	647	1952
25–29	Mean cost	84.16	99.56	110.50	129.44
	95% CI	69.21 to 99.11	90.93 to 108.19	94.19 to 126.81	120.01 to 138.87
	n	645	1945	645	1945
30–34	Mean cost	64.72	80.14	86.09	109.20
	95% CI	50.3 to 79.14	73.75 to 86.53	71.24 to 100.94	102.21 to 116.19
	n	927	2759	927	2759
35–39	Mean cost	47.78	69.26	70.92	95.81
	95% CI	39.9 to 55.66	66.77 to 71.75	62.11 to 79.73	88.25 to 103.37
	n	965	2982	965	2982
40–44	Mean cost	58.43	65.04	76.72	91.19
	95% CI	43.11 to 73.75	57 to 73.08	61.11 to 92.33	82.82 to 99.56
	n	828	2551	828	2551
45–49	Mean cost	43.30	54.66	62.65	81.86
	95% CI	35.76 to 50.84	49.5 to 59.82	54.36 to 70.94	76.2 to 87.52
	n	685	2032	685	2032
50–54	Mean cost	44.62	46.56	66.01	70.89
	95% CI	26.69 to 62.55	42.15 to 50.97	47.64 to 84.38	66.08 to 75.7
	n	623	1755	623	1755
55–59	Mean cost	30.89	43.46	46.40	66.74
	95% CI	24.39 to 37.39	38.77 to 48.15	39.62 to 53.18	61.68 to 71.8
	n	500	1473	500	1473
60–64	Mean cost	27.69	37.19	42.26	58.51
	95% CI	20.88 to 34.5	33.06 to 41.32	34.99 to 49.53	53.68 to 63.34
	n	304	937	304	937
Total	Mean cost	55.97	72.40	77.10	99.96
	95% CI	51.52 to 60.42	69.88 to 74.92	72.42 to 81.78	97.25 to 102.67
	n	6124	18,386	6124	18,386

In the revealed arm, women aged 20–24 years had the highest mean cost both in round 1 and in the full trial, a finding attributable to higher rates of HPV infection among the youngest women. In the concealed arm, the slightly older age group, 25–29 years, had the highest mean costs in both scenarios. *Figure 16* demonstrates how, across the age spectrum, there was generally a systematic decline in mean costs from the youngest to the oldest age groups in the two arms. Observed deviations from this trend in the concealed arm were attributable to the high cost of a hysterectomy procedure.

Costs for alternative screening policies

Based on the trial data, alternative scenarios for sequences of LBC and HPV tests and protocols for managing women were analysed. For ease of reference, the protocols for managing women according to the scenarios are described in *Box 1*, and illustrated in flow charts in *Figures 17* and *18*.

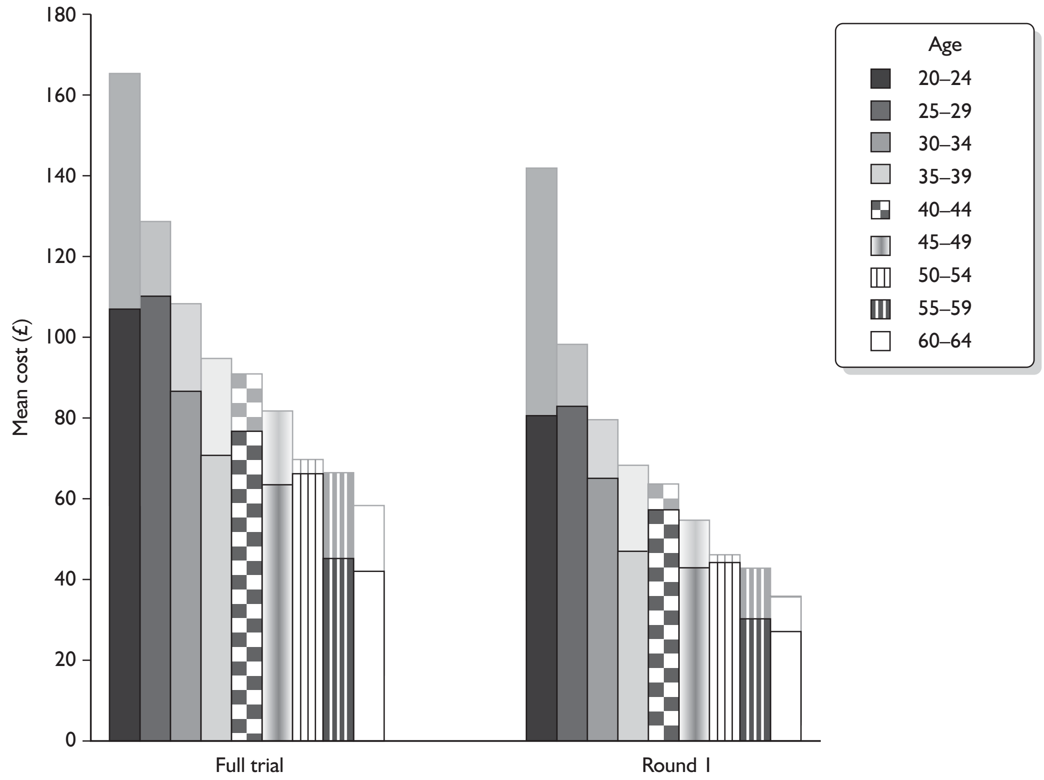

FIGURE 16 *Mean costs for age groups: concealed arm vs revealed arm (in washed shades).*

The trial protocol included a further permutation: revealed women with borderline or mild dyskaryosis in round 1 were to be recalled at 24 months even if their 12-month cytology and HPV results were negative (see *Figure 2*).

Before analysing the scenarios for alternative screening policies, the following adjustments were made to the cost inputs for the alternative screening scenarios, the resource use events having occurred within the first 30 months:

- For scenario 2, involving primary screening with LBC, and HPV testing to triage women with borderline or mild cytological changes. About 10% of all screened women would be affected. Hence the HPV test cost would be £10.11 based on a national workload of about 500,000 tests per year. As those women in the revealed arm with negative LBC reports would not be tested for HPV, they would have a £0 costs for colposcopy.
- For scenario 3, in which HPV testing is the method for primary screening, women who have a positive test are triaged with LBC. In the revealed arm of the trial, 15.6% of women had a positive HPV screening result. The triaged women with positive cytology would be managed according to the trial protocol.

There are two versions of scenario 3. In the first version (scenario 3a), the screening sample is taken with a cervical sampler designed by QIAGEN specifically for HPV testing. Women identified for triaging return to their GP surgery to have another sample taken with an LBC sampler. In the second version (scenario 3b), the screening sample is performed with an LBC cervical sampler, and so the sample's cytology can be analysed without triaged women reattending. The costs of the HPV stand alone screening in scenario 3a was £20.08 (£5.87 for the test itself – see *Table 33* – and £14.21 for the return visit by the triaged women for LBC sample taking). In scenario 3b, the costs for HPV testing were the same as in the trial, but the LBC laboratory costs would decrease overall as a result of the lower volume of samples identified for processing. Finally, we assumed that vials containing smear specimens identified for triage (either by LBC or HPV testing) would be transferred between laboratories using routine interlaboratory transport arrangements.

BOX 1 *Protocols for managing women following routine recall*

Scenario 1

The ARTISTIC trial protocol for Round 1, and for the full trial (*Figure 17*).

Scenario 2

Primary screening with LBC; women with borderline or mild dyskaryotic results to be triaged by HPV testing on the LBC smear sample;

- those with a positive HPV result to be referred for colposcopy
- those with a negative HPV result would return to routine recall.

All women with moderate or worse cytology to be referred for colposcopy.

All women with normal cytology would return to routine recall.

Scenario 3a

Primary screening with HPV testing using QIAGEN HPV cervical samplers; women with a positive result to be advised to be resampled in primary care with an LBC cervical sampler for cytological examination;

- those with an abnormal LBC report to be referred for colposcopy
- those with a normal LBC report to have a second HPV test at 12 months; if the result is positive, they would be referred for colposcopy; if the result is negative, they would return to routine recall.

All women with a negative HPV result would return to routine recall.

Scenario 3b

Primary screening with HPV testing using LBC cervical samplers; women with a positive result to have the cytology examined promptly;

- those with an abnormal LBC report to be referred for colposcopy
- those with a normal LBC report to have a second HPV test at 12 months; if the result is positive, they would be referred for colposcopy; if the result is negative they would return to routine recall.

All women with a negative HPV result would return to routine recall.

Cytological screening using LBC, followed promptly by an HPV test for women with borderline or mild dyskaryosis would be the most cost-saving strategy for a national screening programme. *Table 44* shows that the mean cost for the LBC screening policy (scenario 2) of £43.98 per woman was significantly cheaper than the current practice of screening with LBC, as undertaken in the concealed arm of the trial (that is, a mean cost of £55.97 per woman) ($p < 0.001$).

According to *Table 45*, for every age group, apart from the youngest of 20–24 years, a policy of LBC screening and HPV triage would be less costly than the current practice of LBC screening. It is worth noting, moreover, that the recently revised guidance on women's eligibility for screening no longer extends to women under 25 years of age.

Adjusted mean costs and adjusted cases of CIN2+ and CIN3+ detected

Observed cases of high-grade histology in round 1, on which the following analyses are based, were: revealed arm, CIN2+ 452, CIN3+ 233; concealed arm, CIN2+ 133, CIN3+ 82. The age distribution of women in the ARTISTIC trial arms differed from the age distribution of women covered by the NHSCSP for England.[42] The age groups for the trial had been powered to detect differences between arms, and these recruitment targets impacted on the absolute numbers of CIN3+ cases detected, and the mean cost per arm. To enable us to extrapolate our findings to the general screened population therefore we needed to make suitable adjustments.

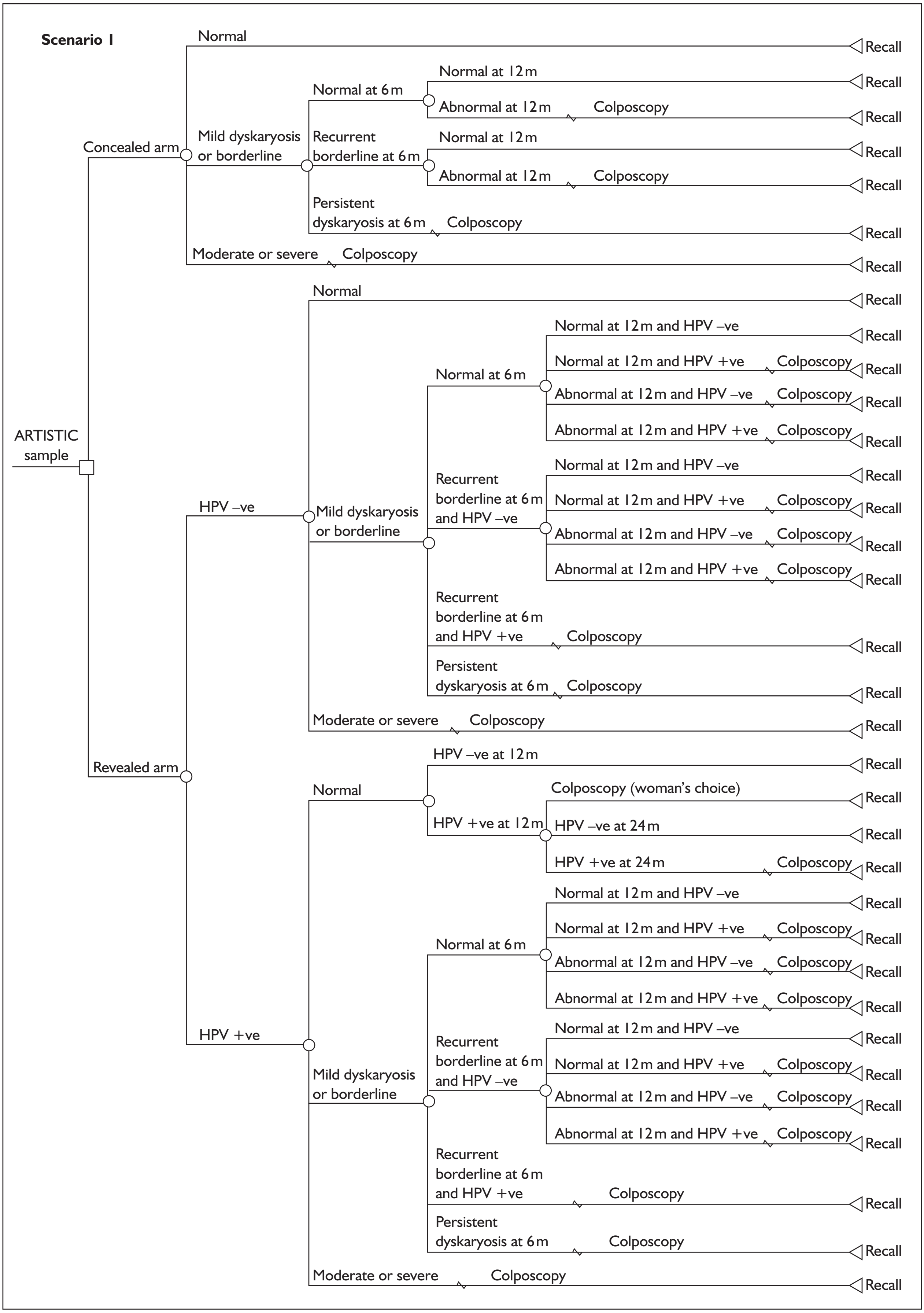

FIGURE 17 *Flow chart for the ARTISTIC trial protocol. m, months.*

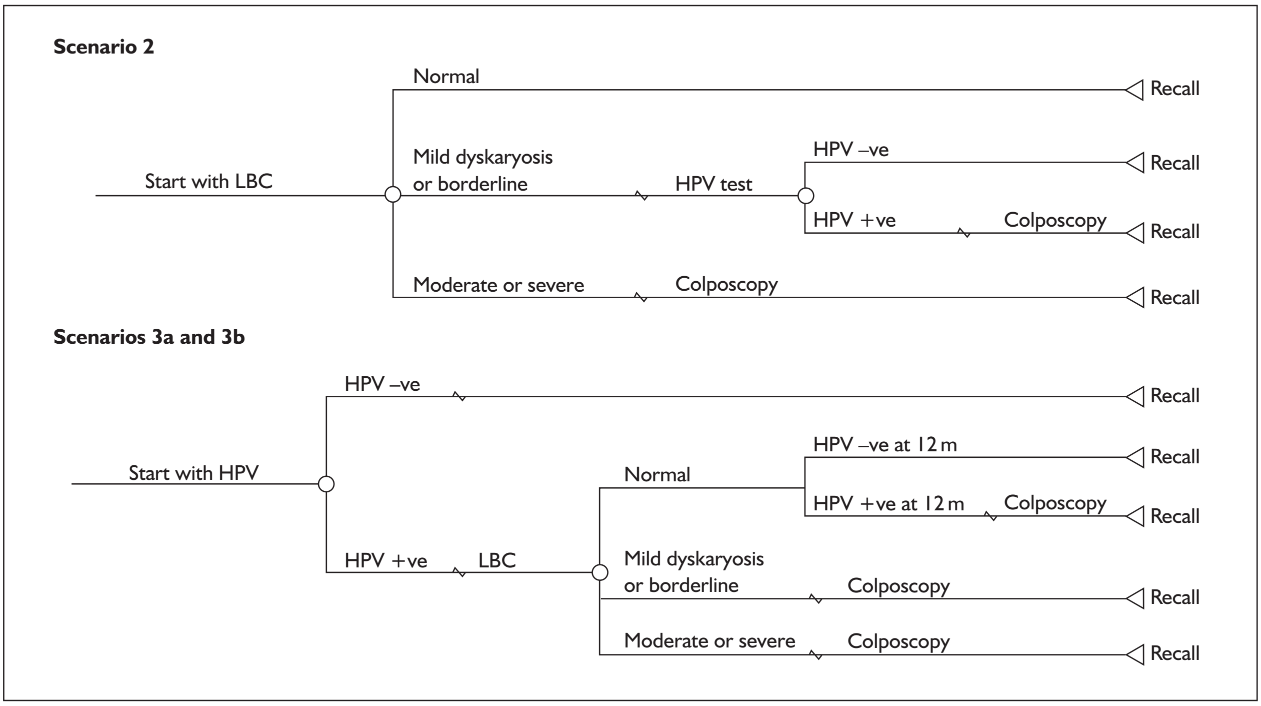

FIGURE 18 *Flow charts for the protocols for alternative screening policies. m, months.*

The published statistics for England for women on routine recall who were screened in 2006–7[42] were used for generating weightings for the 5-year age groups within the ARTISTIC trial arms, including the 20–24-year age group. (Refer to *Table 70* in Appendix 6 for the derived weights). The cost analyses were then repeated for the trial and for the alternative screening policies (*Table 46*).

The impact of the age adjustment was to reduce the mean cost per woman for the trial arms and the alternative screening policies. In particular, the adjusted mean cost of £38.76 for the LBC/HPV triage scenario was £5.22 cheaper than the unadjusted mean cost in *Table 44*. In addition to the adjustment to the age distribution, incidence rates were recalculated, so that direct comparisons between arms could be made with respect to detected cases of CIN2+ and CIN3+. In *Table 47* the adjusted rates are per 1000 screened women in England.

According to the adjusted rates, screening with LBC and HPV in the revealed arm resulted in a higher rate of moderate or worse cases (CIN2+) than screening with LBC alone.

Incremental costs, benefits and incremental cost-effectiveness ratios

There were 28 additional cases of CIN2+ in the revealed arm compared with the concealed arm after the adjustments to the arm sizes for round 1 were made (that is, once the adjustments were made, there were 349 CIN2+ cases for the revealed arm and 321 CIN2+ cases for the concealed arm). So the incremental cost of detecting an additional CIN2+ as a consequence of introducing HPV testing alongside LBC in the National Screening programme was calculated. The incremental cost-effectiveness ratio (ICER) was £8788 per additional CIN2+ case.

The histology results suggest that there is some benefit from adding an HPV test to LBC screening, because in the revealed arm there were 32 women who underwent colposcopy who were cytology –ve and HPV +ve and who had moderate to severe dyskaryosis. Their histology results included nine CIN3/carcinoma in situ, one CGIN1/2, and 22 CIN2. After adjustments (to reflect the actual English population age distribution) this was equivalent to an increase in the rate of detection of CIN3+ of 0.34 per 1000 women at an ICER of £38,771, and an increase in the rate of detection of CIN2+ of 1.25 per 1000 women and an ICER of £10,546.

Sensitivity analyses

To test the impact of key variables on the results of the analyses a range of one-way extreme scenario analyses were undertaken.

TABLE 44 *Mean cost per woman for alternative screening policies*

Trial arm and circumstances		Mean cost per woman for screening scenarios		
		Scenario 2 LBC with HPV for borderline or mild triage	Scenario 3a HPV sampler screening followed by LBC sample triage	Scenario 3b HPV screening and LBC triage on same sample
Concealed as observed in the trial ($n = 6124$)	Mean cost (£)	55.97	55.97	55.97
	95% CI	51.52 to 60.42	51.52 to 60.42	51.52 to 60.42
	SD	177.87	177.87	177.87
Revealed according to proposed policy ($n = 18,386$)	Mean cost (£)	43.98	53.75	54.87
	95% CI	42.01 to 45.95	51.63 to 55.87	52.72 to 56.95
	SD	136.18	146.88	143.63
p-value		< 0.001	0.333	0.627

HPV test cut-off levels

Although the trial adopted the threshold of ≥ 1 RLU/Co recommended by the manufacturer for determining whether an HPV test result was positive or negative, reanalysis of the results for round 1 using alternative cut-off points indicated that fewer women would be referred for colposcopy whereas undetected CIN3+ cases would have been few in number (*Table 18*). This sensitivity analysis explored the cost and outcome implications of selecting ≥ 2 RLU/Co as the threshold.

The age-adjusted CIN2+ and CIN3+ rates per 1000 screened women for the alternative screening policies (Scenarios 2, 3a/b in *Table 48*) were similar for both 1 and 2 RLU thresholds, although they were slightly lower than the rates for the revealed arm of the trial. More specifically, at 1 RLU cut-off point, Scenario 3 would not miss any CIN3+ in women above the age of 50 years, while Scenario 2 would not have missed any CIN3+ above the age of 44 years. The 2 RLU cut-off point offered similar benefits to older women. [Note that only nine CIN3+ lesions were detected among the 5613 women aged 50–64 years in round 1 of the trial and all had moderate or severe cytology and were HPV +ve (*Table 8*) – a rate of 1.6 per 1000 trial participants.]

As predicted, the scenarios' mean costs for the 2 RLU threshold were lower than for 1 RLU threshold. Scenario 2 remained the least costly screening policy, being £9.07 cheaper than Scenario 3b and much cheaper than either of the trial arms.

Colposcopy itemised costs

For the colposcopy-related sensitivity analysis, the average unit costs for new and follow-up clinic attendances were substituted by unit costs covering procedures performed during the attendances (biopsies, histology examinations or cervical samples), the costs having been supplied by a second hospital trust (refer to *Table 34*). Using this itemisation approach, the mean colposcopy cost for each woman who attended a clinic on one or more occasions was almost doubled: the itemised mean cost for these women being £965.39 (SD £602.24) compared with £491.22 (SD £351.73) when the average unit costs were applied. *Table 49* shows that when the two types of costs were applied to the trial arms, the itemised costs approach produced significantly greater means costs; £983.99 for the revealed arm and £893.11 for the concealed arm.

Best and worst case scenarios

The final sensitivity analysis compared hypothetical 'best' case and 'worst' case scenarios for combining resource costs. The assumptions for the scenarios are detailed in *Box 2*.

The age-adjusted mean costs per woman in the 'best' case scenarios (*Table 50*) were slightly lower than the baseline age-adjusted mean costs (see *Table 46*), the best case mean for the revealed arm in round 1 being £63.47 versus £65.04 at baseline, and £38.03 versus £38.76 for Scenario 2. The worst case scenarios (*Table 51*) generated means that were 36% to 59% more costly than those for the best case scenarios. Scenario 2 was the strategy with the greatest cost difference (£38.03 best case

TABLE 45 *Mean cost per woman according to age group for alternative screening policies*

Age groups		Screening policies: Concealed arm round 1	Revealed arm round 1	Scenario 2 LBC with HPV for borderline or mild triage	Scenario 3a HPV sampler screening with LBC triage	Scenario 3b HPV screening with LBC sampler and triage
20–24	Mean cost	81.41	129.27	85.35	110.80	107.70
	95% CI	67.48 to 95.34	119.07 to 139.47	77.03 to 93.67	101.8 to 119.8	98.9 to 116.5
	n	647	1952	1952	1952	1952
25–29	Mean cost	84.16	99.56	65.19	83.06	82.00
	95% CI	69.21 to 99.11	90.93 to 108.19	58.16 to 72.22	75.38 to 90.74	74.52 to 89.48
	n	645	1945	1945	1945	1945
30–34	Mean cost	64.72	80.14	49.66	63.19	63.83
	95% CI	50.3 to 79.14	73.75 to 86.53	44.58 to 54.74	57.56 to 68.82	58.35 to 69.31
	n	927	2759	2759	2759	2759
35–39	Mean cost	47.78	69.26	41.27	50.03	51.73
	95% CI	39.9 to 55.66	66.77 to 71.75	34.98 to 47.56	43.43 to 56.63	45.22 to 58.24
	n	965	2982	2982	2982	2982
40–44	Mean cost	58.43	65.04	36.58	41.39	43.60
	95% CI	43.11 to 73.75	57 to 73.08	30.97 to 42.19	35.56 to 47.22	37.85 to 49.35
	n	828	2551	2551	2551	2551
45–49	Mean cost	43.30	54.66	29.10	33.86	36.21
	95% CI	35.76 to 50.84	49.5 to 59.82	25.76 to 32.44	30.29 to 37.43	32.76 to 39.66
	n	685	2032	2032	2032	2032
50–54	Mean cost	44.62	46.56	26.30	29.43	32.05
	95% CI	26.69 to 62.55	42.15 to 50.97	23.53 to 29.07	26.42 to 32.44	29.14 to 34.96
	n	623	1755	1755	1755	1755
55–59	Mean cost	30.89	43.46	23.91	25.02	27.92
	95% CI	24.39 to 37.39	38.77 to 48.15	22.69 to 25.13	23.04 to 27.22	26.49 to 29.35
	n	500	1473	1473	1473	1473
60–64	Mean cost	27.69	37.19	22.81	25.66	28.40
	95% CI	20.88 to 34.5	33.06 to 41.32	20.89 to 24.73	23.19 to 28.13	25.81 to 30.45
	n	304	937	937	937	937
Total	Mean cost	55.97	72.40	43.98	53.75	54.87
	95% CI	51.52 to 60.42	69.88 to 74.92	42.01 to 45.95	51.63 to 55.87	52.79 to 56.95
	n	6124	18,386	18,386	18,386	18,386
	SD	177.87	174.63	136.18	146.88	143.63

The shaded cells indicate the least costly option for each age group.

TABLE 46 *Age-adjusted mean costs for ARTISTIC and alternative screening policies*

Trial arm and circumstances	Age-adjusted mean cost per woman (£)				
	ARTISTIC round 1	ARTISTIC full trial	Scenario 2 LBC with HPV for borderline or mild triage	Scenario 3a HPV sampler screening with LBC triage	Scenario 3b HPV screening with LBC sampler and triage
Concealed arm as observed in the trial	51.86	72.18	NA	NA	NA
Revealed arm according to trial or proposed policy	65.04	91.54	38.76	46.50	48.12
Increment	13.18	19.36	–13.10[a]	–5.36[a]	–3.74[a]

a The difference between the mean cost for the scenario and the mean cost for the concealed arm in round 1.

TABLE 47 *Age-adjusted rates per 1000 screened women in England of cases of CIN2+ and CIN3+ based on round 1 of the ARTISTIC trial*

Trial protocol	Age adjusted rates per 1000 screened women for round 1	
	Cases of CIN2+	Cases of CIN3+
Concealed arm	17.5	11.04
Revealed arm	19	9.81

TABLE 48 *Mean costs for scenarios in relation to the HPV test cut-off level and age adjusted rates of per 1000 screened women of CIN2+ and CIN3+*

		Scenario 1 round 1 of the trial	Scenario 2 LBC with HPV for borderline or mild triage	Scenario 3a HPV sampler screening followed by LBC sample triage	Scenario 3b HPV screening and LBC triage on same sample
Concealed					
	Mean £	62.85	NA	NA	NA
	95% CI	57.38 to 68.32			
Revealed					
1 RLU	Mean £	79.25	47.23	56.98	58.76
	95% CI	76.15 to 82.35	44.83 to 49.63	54.43 to 59.54	56.25 to 61.27
CIN2+	Rate[a]	19	17.75	17.71	17.71
CIN3+	Rate[a]	9.81	9.47	9.48	9.48
2 RLU	Mean £	77.57	46.83	53.72	55.90
	95% CI	74.49 to 80.64	44.45 to 49.22	51.23 to 56.20	53.46 to 58.34
CIN2+	Rate[a]	18.80	17.75	17.38	17.38
CIN3+	Rate[a]	9.79	9.49	9.46	9.46

a Rate per 1000 women.

TABLE 49 *Sensitivity analysis: mean colposcopy-related costs for women attending colposcopy clinics during the full trial*

	Type of colposcopy unit costs			
	Itemised costs for clinic activities		**Average unit costs for new and follow-up attendances**	
Full trial	**Concealed arm**	**Revealed arm**	**Concealed arm**	**Revealed arm**
Mean (SD) cost per woman	£893.11 (£561.33)	£983.99 (£611.12)	£513.40 (£455.69)	£485.51 (£319.49)
Number of women	394	1531	394	1531
p test	0.008		0.160	

Sources of costs: refer to *Table 34*.

versus £60.55 for the worst case), mainly because the worst-case assumptions concerning LBC screening of all women involved increased costs for analysing and reporting LBC samples and an inadequate sample rate of 4.5%. Nonetheless, the scenario remained the least costly strategy, being 16% cheaper (£11.52) than the worst case mean for the trial's concealed arm in round 1. The cost scenarios 3a and 3b were very similar irrespective of the assumptions.

Psychological and psychosexual effects of HPV testing

The numbers of subjects in the trial according to initial screening test results and the numbers of questionnaires sent together with response rates are shown in *Table 52*. The overall response rate was 69% with the highest response rate among cytology –ve/HPV –ve women in the revealed arm and lower rates among women in the concealed arm and among those who were HPV +ve. Numbers of responses were reduced for the Sexual Rating Scale (SRS) as this questionnaire was only completed by women with a current sexual partner. Women who tested cytology +ve/HPV +ve were significantly younger [median 28.5 years, interquartile range (IQR) 23.2–35.4 years] than the women who were cytology +ve/HPV –ve (median 39.3 years, IQR 31.7–46.9 years, Mann–Whitney $p < 0.0001$), cytology –ve/HPV +ve (median 32.7 years, IQR 25.4–42.0 years, $p < 0.0001$), and cytology –ve/HPV –ve (median 40.8 years, IQR 33.0–50.3 years, $p < 0.0001$).

Preliminary analyses compared the face-to-face sample ($n = 89$) with the mailed sample ($n = 2465$). Overall levels of caseness were 35.1% in the mailed sample and 28.1% in the face-to-face pilot sample.

After adjustment for age and initial screening outcome, lower GHQ caseness was observed in the face-to-face subjects compared with mailed subjects (adjusted odds ratio 0.73, 95% CI 0.45 to 1.17, $p = 0.19$) and lower GHQ scores (adjusted mean difference 21.12, 95% CI 22.27 to 0.035, $p = 0.057$) in face-to-face interviews compared with postal interviews. Similar reductions were observed for STAI-STATE (adjusted mean difference 24.3, 95% CI 26.9 to 21.7, $p = 0.0001$), STAI-TRAIT (23.3, 95% CI 1.2 to 22.7, $p = 0.007$), and Miller Behavioural Style Scale (20.86, 95% CI 21.7 to 0.07, $p = 0.033$), and an increase for SSQ (5.6, 95% CI 0.4 to 10.7, $p = 0.033$) was observed. As there was evidence of differences in outcome for the two modes of data collection, face-to-face interview data were excluded from the main analysis.

The reason for this difference is not clear, but when adjustment for potential confounders was made (age and cytology grade), the differences were not statistically significant. It may be that face-to-face interviews allowed a degree of reassurance.

Comparison between randomised arms of the trial

Table 53 gives the GHQ caseness rate broken down by initial screening test results and intervention group. There was no evidence of a higher level of caseness in the revealed arm compared with the concealed arm (odds ratio 1.00, 95% CI 0.82

BOX 2 *Sensitivity analysis: assumptions for the 'best' case and 'worst' case scenarios*

Best case scenario

- LBC equipment cost reduced to £3.00 per sample
- cost of HPV test reduced by 10% [£5.87, equivalent to testing an HPV cervical sample using an automated system at maximum capacity (*Table 33*)]
- inadequate rates of zero for LBC tests
- average unit costs for colposcopy clinic attendance (*Table 34*).

Worst case scenario

- LBC equipment cost increased to £4.20 per sample assuming that laboratories have individual contracts for Thinprep processors or additional transport requirements
- additional time for rapid reviewing of LBC slides (35 seconds or 13 pence per slide), and qualification allowance for staff undertaking secondary reading [£0.24 per minute (*Tables* 30 and *31*)]
- costs of HPV tests applied to manual systems
- cervical sample inadequate rate of 4.5% (as for England in 2006/7)[42]
- itemised unit costs for colposcopy clinic activities.

TABLE 50 *Sensitivity analysis: age-adjusted mean costs for the 'best' case scenario applied to ARTISTIC round 1, the full trial and to alternative screening policies*

	Age-adjusted mean cost per woman (£) ('best' case scenario)				
Trial arm	**ARTISTIC round 1**	**ARTISTIC full trial**	**Scenario 2 LBC with HPV for borderline or mild triage**	**Scenario 3a HPV sampler screening with LBC triage**	**Scenario 3b HPV screening with LBC sampler and triage**
Concealed	51.06	70.88	NA	NA	NA
Revealed	63.47	89.01	38.03	45.76	47.22
Increment	12.41	18.13	–13.03[a]	–5.30[a]	–3.84[a]

a The difference between the mean cost for the scenario and mean cost for the concealed arm in round 1.

TABLE 51 *Sensitivity analysis: age-adjusted mean costs for the `worst' case scenario applied to ARTISTIC round 1, the full trial and to alternative screening policies*

	Age-adjusted mean cost per woman (£) ('worst' case scenario)				
Trial arm	**ARTISTIC round 1**	**ARTISTIC full trial**	**Scenario 2 LBC with HPV for borderline or mild triage**	**Scenario 3a HPV sampler screening with LBC triage**	**Scenario 3b HPV screening with LBC sampler and triage**
Concealed	72.07	96.51	NA	NA	NA
Revealed	97.60	129.49	60.55	69.25	71.68
Increment	25.53	32.98	–11.52[a]	–2.83[a]	–0.39[a]

a The difference between the mean cost for the scenario and mean cost for the concealed arm in round 1.

TABLE 52 *Sample and response rates by initial screening test results*

Initial screening test results		Revealed arm			Concealed arm		
HPV	Cytology	No. in trial	Questionnaires sent/returned	%	No. in trial	Questionnaires sent/returned	%
–ve	–ve	14,321	1341/987	75.5	4774	455/336	74.5
+ve	–ve	1667	624/417	66.2	550	175/105	62.9
–ve	mild/borderline	1165	422/295	70.2	391	142/92	64.8
+ve	mild/borderline	875	313/205	63.7	304	110/71	64.5
	Ineligible[a]	358	–	–	105	–	–
Total		18,386	2700/1904	70.7	6124	882/604	71.1

a Including Moderate (271), Severe (177), Possible invasion (3), Glandular neoplasia (12).
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to 1.23, $p = 0.98$). Among women with negative cytology and HPV+ve, 42% had GHQ caseness in the revealed arm compared with 35% in the concealed arm, but in a logistic regression model adjusted for age and initial screening outcome, this was not statistically significant ($p = 0.21$). Similarly, for women who were mild dyskaryosis/borderline and HPV +ve, the caseness rates were 42% and 47% in the revealed and concealed arms respectively ($p = 0.44$).

Table 54 gives the mean scores for the individual measures broken down by initial screening test results and intervention group and summarises the regression analyses. When an overall comparison was made between the two arms in weighted analyses, there was no evidence of a significant difference between the revealed and the concealed arm in any scores except the SRS, in which there was some evidence of reduced sexual satisfaction in the revealed arm compared with the concealed (adjusted mean difference -2.40, 95% CI -4.70 to -0.09, $p = 0.042$).

When planned subgroup comparisons were made according to initial screening outcome, the adjusted mean difference in GHQ scores between the revealed arm and the concealed arm was 0.74 (95% CI -0.63 to 1.91, $p = 0.22$) for women with negative cytology. Among women who were mild or borderline, the corresponding difference in GHQ scores was -1.19 (95% CI –2.98 to 0.40, $p = 0.12$).

TABLE 53 *GHQ caseness (GHQ ≥ 4) by initial screening test results*

Initial screening test results		Revealed arm			Concealed arm					
HPV	Cytology	Freq.	%	*n*	Freq.	%	*n*	Odds ratio[a]	(95% CI)	*p*-value
–ve	–ve	286	29.4	972	106	32.0	331			
+ve	–ve	170	41.8	407	36	35.0	103	1.33	(0.85 to 2.09)	0.213
–ve	mild/ borderline	115	39.4	292	36	39.6	91			
+ve	mild/ borderline	84	41.8	201	32	47.1	68	0.80	(0.46 to 1.40)	0.437
Total[b]		222.9	37.6	593	717	38.3	1872	1.00	(0.82 to 1.23)	0.982

a Revealed vs concealed arms adjusted for age-band.
b Estimates weight by sample fraction from main study.
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TABLE 54 *Questionnaire scores by initial screening test results and intervention arm*

Measure	Initial screening results		Revealed arm			Concealed arm			Age adjusted		
	HPV	Cytology	Mean	(SD)	*n*	Mean	(SD)	*n*	Mean diff.[a]	(95% CI)	*p*-value
GHQ	–ve	negative	3.31	(5.18)	972	3.22	(4.80)	331			
	+ve	negative	4.77	(6.21)	407	4.02	(5.77)	103	0.74	(–0.63 to 1.91)[c]	0.22
	–ve	mild/borderline	4.22	(5.63)	292	4.29	(5.83)	91			
	+ve	mild/borderline	4.57	(5.44)	201	5.75	(6.50)	68	– 1.19	(–2.98 to 0.40)[c]	0.121
	total[b]		4.26	(5.73)	1872	4.18	(5.71)	593	–0.01	(–0.65 to 0.60)[c]	0.968
STAI STATE	–ve	negative	35.85	(11.92)	971	36.00	(11.49)	331			
	+ve	negative	38.87	(13.33)	410	37.10	(12.58)	103	1.73	(– 1.27 to 4.53)[c]	0.202
	–ve	mild/borderline	37.99	(12.43)	290	40.66	(13.57)	91			
	+ve	mild/borderline	39.77	(12.05)	204	39.97	(12.35)	69	–0.25	(–3.79 to 3.03)[c]	0.885
	total[b]		38.10	(12.64)	1875	38.27	(12.61)	594	–0.31	(– 1.62 to 0.92)[c]	0.618
STAI TRAIT	–ve	negative	38.84	(11.34)	971	39.00	(11.13)	331			
	+ve	negative	40.54	(11.83)	413	39.39	(10.80)	105	1.07	(– 1.30 to 3.41)[c]	0.386
	–ve	mild/borderline	39.95	(11.08)	289	41.57	(12.43)	91			
	+ve	mild/borderline	41.28	(10.89)	204	40.88	(11.54)	69	0.36	(–2.80 to 3.53)[c]	0.819
	total[b]		40.12	(11.40)	1877	40.13	(11.49)	596	–0.10	(– 1.27 to 1.13)[c]	0.858
SRS	–ve	negative	51.28	(20.89)	803	50.81	(22.50)	271			
	+ve	negative	55.32	(22.95)	311	61.10	(23.74)	76	– 7.28	(– 12.74 to – 1.52)[c]	0.007
	–ve	mild/borderline	48.73	(23.34)	255	50.53	(21.26)	82			
	+ve	mild/borderline	62.67	(23.00)	151	62.46	(22.97)	54	0.15	(–6.60 to 7.12)[c]	0.965
	total[b]		53.32	(23.02)	1520	54.90	(23.00)	483	– 2.40	(–4.91 to 0.16)[c]	0.042

a Revealed vs concealed arms adjusted for age-band.
b Estimates weight by sample fraction from main study.
c Non-parametric bootstrap confidence interval.
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TABLE 55 *Observational comparison of HPV(+ve) with HPV(–ve) women in the revealed arm*

Initial cytology result		Odds ratio*	Mean difference[a]	(95% CI)	*p*-value
Negative	GHQ caseness	1.70		(1.33 to 2.17)	< 0.0001
Mild/borderline	(GHQ≥4)	1.07		(0.74 to 1.56)	0.724
Negative	GHQ score		1.43	(0.75 to 2.10) [b]	< 0.0001
	STAI-STATE		2.90	(1.40 to 4.39) [b]	< 0.0001
	STAI-TRAIT		1.53	(0.16 to 2.92) [b]	0.023
	SRS		1.46	(– 1.34 to 4.27)	0.306
Mild dyskaryosis/borderline	GHQ score		0.28	(–0.76 to 1.24) [b]	0.581
	STAI-STATE		1.56	(–0.59 to 3.80) [b]	0.174
	STAI-TRAIT		0.98	(– 1.05 to 2.97) [b]	0.354
	SRS		8.66	(4.30 to 13.02)	< 0.0001

a HPV +ve vs HPV –ve adjusted for age-band.
b Non-parametric bootstrap.
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Receiving an HPV +ve test was associated with a reduction in SRS among women whose cytology results were –ve (adjusted mean difference –7.28, 95% CI –12.60 to –1.96, $p = 0.007$).

Observational comparisons within the revealed arm of the ARTISTIC trial

Table 55 summarises the analysis comparing HPV –ve women with HPV +ve in the revealed arm. GHQ caseness was higher among women with HPV +ve/cytology –ve (41%) compared with HPV –ve/cytology –ve (29%). After adjustment for age in a logistic model, the odds ratio comparing the groups was 1.70 (95% CI 1.33 to 2.17, $p < 0.0001$). Correspondingly, women with HPV +ve/cytology –ve had higher GHQ mean scores than HPV –ve/cytology –ve women (adjusted mean difference 1.43, 95% CI 0.75 to 2.1, $p < 0.0001$). A similar difference was noted for the STAI-STATE score with an increase of 2.90 (95% CI 1.40 to 4.39, $p < 0.0001$) and STAI-TRAIT score with an increase of 1.53 (95% CI 0.16 to 2.92, $p = 0.023$).

Within the revealed arm, women with HPV +ve/cytology –ve had a similar level of sexual satisfaction compared with those who were HPV –ve/cytology –ve (adjusted mean difference 1.46, 95% CI –1.34 to 4.27, $p = 0.31$). It should be noted that in the concealed arm there were significant differences in sexual satisfaction between women with –ve cytology who were HPV +ve and HPV –ve with an adjusted mean difference of 9.40 (95% CI 4.14 to 14.66, $p < 0.0001$). In the revealed arm, women with mild dyskaryosis/borderline cytology/HPV +ve expressed a higher level of sexual satisfaction than those who were HPV –ve with a mean difference after adjustment for age of 8.66 years (95% CI 4.30 to 13.02, $p < 0.0001$). A trend in the same direction was noted in the concealed arm (adjusted mean difference 5.63, 95% CI –1.73 to 13.00, $p = 0.13$).

Chapter 4
Discussion

The primary aim of the ARTISTIC trial was to test the hypothesis that HPV testing would achieve greater sensitivity in primary cervical screening than cytology. Because of the NHSCSP standard, it was not considered ethical to deny women a cytology screen by undertaking a trial of cytology versus HPV testing. Cytology was therefore compared with cytology plus HPV testing by concealing HPV test results in the standard (concealed) arm rather than not performing it. The trial data can however be used to estimate the performance of cytology or HPV as sole initial tests each triaged by the other in terms of effectiveness and cost. ThinPrep and HC2 were selected in 2001 as an approved combination which could be reliably tested from the same liquid sample so that the LBC and HPV tests would not affect each other.

The ARTISTIC trial has been a pioneering experience in terms of cervical screening in the UK. It was at the leading edge in using both LBC and HPV testing in the primary screening process. The embedding of the trial in the NHSCSP has the crucial advantage of applicability of the findings across the UK, although national guidelines and pre-existing arrangements did impose certain restrictions. When the trial began in 2001 the normal screening interval in Manchester and many other regions was still 5 years at all ages and LBC was not generally available. We decided to use LBC in anticipation of the 2003 NICE recommendation that LBC should be introduced nationally because we wished to ensure that the ARTISTIC cytology data would still be relevant to the NHSCSP at the end of the study. We included women aged 20–24 both because they were still being invited for routine screening in 2001 and because many HPV infections are acquired in this age-range. Our HPV and cytology data, including those on younger women, have already been used by the Health Protection Agency to model the costs and benefits of HPV vaccination within the NHSCSP.

There were several initial challenges involved in this trial. First, there was a need to engage a large sector of primary care, particularly the practice nurses who take the large majority of cervical cytology samples. Because of the novelty of HPV testing in primary screening there was a need to obtain individual signed consent from 25,000 women which was obtained separately, for both participating and for using residual material for further research. This process was greatly facilitated by the payment of £10 per recruited woman provided by additional service support funding from the Department of Health. The large spread of practices and FPCs resulted in a broad socioeconomic range with the trial cohort being representative of Greater Manchester. The fact that the trial was embedded in the NHSCSP makes the results generalisable across the country with respect to disease prevalence and adherence to recall for round 2 screening.

The second challenge was to train the practices in LBC and to educate screeners about HPV testing and its implications. A considerable effort was required but the reward was a virtually problem-free process thereafter. The practices involved in ARTISTIC deserve considerable credit for the contribution that their effort and commitment have made to the advancement of cervical screening.

The third challenge was to achieve the highest possible follow-up in round 2. A recall rate of 60% may not seem impressive, but the normal 3-year recall rate for Greater Manchester was less than 60%. Women are continuing to return for round 2, but data had to be frozen at some point to report the outcomes of the trial in a timely fashion. A novel aspect of follow-up in ARTISTIC was the recall of cytology –ve/HPV +ve women in the revealed arm. These women needed to understand that the reassurance of a cytology –ve result should not dissuade them from attending for HPV follow-up. In the event we had achieved a 65% rate of HPV follow-up, at the time the data were frozen, but this did not occur on schedule in many cases.

The most significant difference between the study population and women routinely screened in the English National Programme was that we recruited women aged 20–24, who have been excluded from the National Programme since 2005. For the economic analyses comparing costs for different screening scenarios the study population has therefore been standardised for age against the routinely screened population from the Annual

Report of the National Programme for England. The age distribution of women entering the trial aged 25–64 years is similar to those screened in the National Programme (*Table 56*).

Main findings

Rates of cytological abnormality

The rate of high-grade abnormal cytology in round 1 was similar to that expected when the protocol was developed, but higher than expected for borderline abnormalities. We believe that this reflects the higher sensitivity of LBC than conventional cytology, further increased by some overcalling following the introduction of LBC, but it does not bias the randomised comparisons.

The rate of high-grade cytological abnormality in round 2 was dramatically lower than in round 1. Three factors could have influenced this. The most important may be that the sensitivity of LBC was greater than previous conventional cytology. A recently reported trial from the Netherlands claimed superior sensitivity by LBC.[61] The second was the shorter screening interval (3 years) compared with previous routine screening (5 years), giving less time for incident disease to develop. The third is that the trial cohort was 3–4 years older by round 2. Rates of HPV prevalence and cytological abnormality decline sharply with age, particularly in younger women, and this age difference between round 1 and round 2 was further increased in the overall results by the lower proportion of young women who attended for round 2. The reduction in moderate or worse cytology from round 1 to round 2 was still more than fourfold (adjusted odds ratio 0.21, 95% CI 0.10 to 0.43) in a regression analysis adjusting for age and previous smear history. We therefore conclude that a substantial burden of prevalent disease that was missed at the previous smear test by conventional cytology was detected by LBC. If this is correct, large reductions will soon be seen in national abnormality rates as increasing numbers of women who have already been screened once by LBC return for their next routine test. This would have important implications for all cost–benefit analyses related to cervical screening, including the predicted costs and benefits of HPV vaccination.

Clinical outcomes

The combination of cytology and HPV testing in the revealed arm did result in a small but statistically significant reduction in the detection of CIN2+ in round 2; this was the pre-specified primary outcome. This result was found when the broader definition of round 2 was introduced in order to reduce excluded cases which were simply due to delay in women attending for round 2 screening. However, when the results of the two screening rounds were summed there was no significant difference between the concealed and revealed arms.[62]

An outcome of the trial specified in the protocol was a reduction in the prevalence of high-grade disease detected in round 2 in the revealed arm among women who were cytology –ve and HPV +ve in round 1. The comparison of the randomised arms should have greater statistical power in this subgroup than overall because clinical follow-up and management did not differ between the arms for other women. As expected, the rate in round 2 in this subgroup was lower in the revealed than in the concealed arm for both CIN2+ (*Table 14*: 1.9% revealed, 4.0% concealed; $p = 0.06$) and CIN3+ (0.8% revealed, 1.8% concealed; $p > 0.1$). Both observed rates were therefore halved, but the trial failed to achieve statistical significance for the reduction in CIN3+ because of the unexpectedly low prevalence of high-grade pathology in round 2 both overall and in this subgroup. The complementary observation is the unexpectedly low prevalence of high-grade histology detected in round 1 among cytologically –ve/HPV +ve women when they were recalled for repeat HPV testing [*Table 14*: 32 CIN2+ (1.9%) and 10 CIN3+ (0.6%) in round 1 among 1675 cytologically –ve/HPV +ve women in the revealed arm]. The rates of high-grade disease summed over rounds 1 and

TABLE 56 *Relative proportions of women screened according to age group in the NHSCSP and in ARTISTIC rounds 1 and 2*

Age group (years)	NHSCSP	ARTISTIC round 1	ARTISTIC round 2
25–29	14.6	11.8	8.9
30–39	31	34.7	32.6
40–49	28.5	27.9	29.9
50–64	25.8	25.6	28.6

TABLE 57 *CIN3+ detected in randomised screening trials*

Trials	Numbers randomised		Round 1				Round 2				Combined			
			Standard		+HPV		Standard		+HPV		Standard		+HPV	
	Standard	+HPV	freq	(/1000)	freq	(/1000)	freq	(/1000)	freq	(/1000)	freq	(/1000)	freq	(/1000)
POBASCAM	8580	8575	40	(4.7)	68	(7.9)	54	(6.3)	24	(2.8)	94	(11.0)	92	(10.7)
SWEDESCREEN	6270	6257	55	(8.8)	72	(11.5)	30	(4.8)	16	(2.6)	85	(13.6)	88	(14.1)
ARTISTIC	6124	18,386	80	(13.1)	233	(12.7)	16	(2.4)	25	(1.4)	99	(15.5)	258	(14.1)

2 are therefore similar (*Table 14*: overall CIN2+ rate 3.8% revealed, 4.0% concealed). Whether a CIN3 was diagnosed in round 1 or round 2 is sometimes ambiguous. Several CIN3+ cases on the revealed arm had a cytologically –ve/HPV +ve sample in round 1 followed by a series of repeat samples, with CIN3 finally diagnosed more than 30 months after round 1. Our definition of the round 2 sample classified these as round 2 diagnoses, but this is questionable. If they had been referred for colposcopy earlier such cases would have been classified as round 1 diagnoses, increasing the difference between the arms in round 2 but not the overall difference over both rounds. The analyses of CIN2 and CIN3+ shown in *Table 14* are repeated in *Table 15* with the alternative definitions of round 1 and round 2 samples and diagnoses listed in the footnotes to *Table 15*, which were chosen to include CIN3+ cases excluded under the original definitions. The rates are higher, but the differences between the concealed and revealed arms are similar to those shown in *Table 14*.

Our results therefore support the previous hypothesis that the detection of CIN3+ in cytologically –ve women by HPV testing in round 1 would lead to a similar reduction in detection in round 2, although we expected higher detection rates and hence more precise estimates. Other non-randomised studies had suggested that this would be the case, and two recently published major randomised trials from Sweden (Swedescreen)[14] and the Netherlands (POBASCAM)[15] have shown similar results. The Finnish trial will report in 2009.

In a National Programme the effectiveness of cervical screening depends on the cumulative effect of successive rounds, so the results of screening trials must be considered over both round 1 and the next round. In the Swedescreen and POBASCAM trials there was a higher detection of CIN2+ and CIN3+ in the HPV intervention arms during round 1 and reduced incidence of CIN3+ in round 2 of screening. ARTISTIC showed no difference over both rounds, and both the Swedescreen and POBASCAM trials also showed no difference between the arms when the prevalence (round 1) and incidence (round 2) rounds were combined. This is shown in *Table 57*. The denominators for the ARTISTIC rates in the second round shown in *Table 57* include all randomised women. The round 2 rates per 1000 for CIN3+ shown in *Table 15*, with fewer exclusions and adjustment for incomplete follow-up, are 4.4 (concealed) and 2.4 (revealed), almost identical to those in Swedescreen.

It is important to note that these trials did not employ LBC but comparing the relative sensitivity of LBC and conventional cytology is difficult, not least because of different age ranges which will affect the actual rates of disease detection. Both ARTISTIC and the Swedescreen trial detected a higher rate of CIN3+ in round 1 than at the next round on both arms. The POBASCAM study actually detected a slightly lower CIN3+ rate in round 1 than at the next round, for reasons that are not clear. Screened women in POBASCAM were aged 29 years or older according to the national protocol. There is a great deal of prevalent CIN in previously unscreened women aged 29 which should be detected at first screen, unless missed by conventional cytology. The sensitivity of HPV testing is uniformly high, but the sensitivity of conventional cytology has varied widely.[12] It is difficult to escape the conclusion that LBC was more sensitive in ARTISTIC than earlier conventional cytology, and that the differences between the trials shown in *Table 57* reflect differences in the sensitivity of cytology. This conclusion differs from other published work comparing LBC and cytology which concluded that they were equivalent. This includes an Italian randomised controlled trial of LBC versus conventional cytology[63] and a systematic review,[58] which included mainly studies of high prevalence cohorts referred for colposcopy and the principal primary screening study included was the Italian study referred to above. We believe that the intensive training adopted in the NHSCSP with the introduction of LBC, plus the relatively high mild abnormality rates with referral to colposcopy accounted for the difference.

Cohort data from round 1 and round 2

The ARTISTIC trial cohort represents the largest population of women in the UK to have undergone routine cervical screening with both LBC and HPV testing. The study population spanned the 20–64 age range of screened women when the trial opened, although the lower age threshold for routine cervical screening in England has since been increased from 20 to 25 years. Our age-specific HPV +ve rates in different grades of cytological abnormality were similar to those in the HART study in which over 10,000 women were screened with conventional cytology and HC2 testing, but our overall HPV prevalence was slightly higher at each age. HPV prevalence in the HART study declined from 14.5% in women aged 30–34 years to 3.8% in women aged 55–59 years;[64] the corresponding rates in our cohort were 18.5% at 30–34 years and 6% at 55–59 years. Our higher rates may be partly the result of regional differences in the UK (2004). The HART study was conducted in five centres across Britain, and the highest HPV prevalence was found in the Manchester area, where 16% of 30–34 year olds were +ve for HPV (P Sasieni, Cancer Research UK, personal communication). There may also have been a continuing increase in HPV prevalence in this population.

A study conducted in the same area as ARTISTIC between 1988 and 1993 reported HPV prevalence based on MY0911 consensus primer PCR of 18% in women aged 20–24 years declining to 3% in women aged 50–54 years.[32] Differences in HPV detection sensitivity may account for part of the disparity. The cross-reaction with low-risk types obtained with HC2 will result in a proportion of apparent high-risk false positives, particularly in older women. However, most of this increase over time is likely to be real, reflecting a continuing increase in HPV infection that began in the 1960s and caused a rapid increase in cervical cancer mortality among young British women until the NHSCSP was launched.[4] It is worthwhile noting that if HC2 were used with a cut-off of 2 pg/Co (instead of 1, as used in ARTISTIC) on the new screened age range of 25–64, the overall HR HPV +ve rate would fall from 15.6% in ARTISTIC, to 10.5%. If HPV tests are to show maximum clinical utility there needs to be an appropriate balance of sensitivity and specificity which will best be demonstrated in large prospective longitudinal studies like ARTISTIC.

Several conclusions relevant to the potential role for HPV testing in primary routine screening are suggested by the relationships between age, HPV detection and severity of cytology in round 1 to the ARTISTIC trial (*Table 7*). However, very different relationships are seen in round 2 (*Table 11*).

Round 1 results

In women with detectable HPV the prevalence of moderate dyskaryosis is 20-fold to 30-fold higher than in HPV –ve women at all ages, and severe dyskaryosis is increased more than 100-fold. The prevalence of mild dyskaryosis in HPV +ve women is about 10-fold higher than in HPV –ve women below age 50 years and more than five-fold higher above age 50 years. Although a great majority (87%) of women aged under 30 years with mild dyskaryosis are HPV +ve, this proportion falls to 58% (233/398) at age 30–49 years and to only 28% (18/65) at age 50–64 years, confirming a useful role for HPV triage. The prevalence of borderline abnormalities in HPV +ve women is about twice as high as in HPV –ve women at each age, and although there may be some overcalling by LBC, our results indicate that many borderline abnormalities are not caused by HPV. The prevalence of moderate or severe dyskaryosis in HPV +ve women was about 12% throughout the premenopausal years, suggesting that the natural history of HPV infection may be much the same in premenopausal women irrespective of age, although CIN3 is rarer in HPV-infected women aged 50 years or over. In women aged 30 years or over, our round 1 data suggest that the main effect of replacing cytology by HPV testing in primary screening would be the replacement of HPV –ve abnormal smears, most of which would be borderline, by a similar number of HPV +ve/cytology –ve smears among women referred for follow-up. For those aged 20–29 years, however, the number who were HR HPV +ve was about 50% greater than the number with abnormal cytology, suggesting the need for a secondary test before colposcopy.

The use of patient choice indicated a preference for colposcopy to determine whether there was an underlying lesion or not. Of those who chose a repeat test, a higher proportion did not attend suggesting that in the event of early recall because of an HPV +ve result, colposcopy should be recommended for persistent HPV +ve results. This is supported in a recent paper by the Swedescreen Trial Group.[65] Had colposcopy been used for all women who had been cytology –ve/HPV +ve at baseline and HPV +ve at 12 months, a few more CIN3+ would have been detected but many more colposcopies would have been needed. Another strategy worthy of evaluation would be to use HPV16/18 restricted typing to prioritise immediate referral to colposcopy, and employ early recall, e.g. at 12 months for non-16/18 HPV +ve women.

Round 2 results

The marked reduction in high-grade cytology can be seen by comparing the overall results by age in round 1 (*Table 7*) and round 2 (*Table 11*) for HPV detection and cytological abnormality. In women who were aged 30–49 in round 1, the prevalence of moderate or severe cytology among HPV +ve women was 11.6% (197/1697) in round 1 and only 2.4% (13/551) in round 2, and in those aged 50–64 in round 1 the rate was 4.6% (17/367) in round 1 and zero (0/135) in round 2. The respective proportions of abnormal smears that were moderate or severe in women aged 25–29, 30–49 and 50–64 in round 1 were 20.4%, 13.6% and 7.4%, and 12.7%, 4.5% and 1.9% in round 2. This low prevalence of high-grade disease in older women in round 2 suggests that accumulated disease missed by previous conventional cytology was reliably detected by LBC.

HPV genotyping

The ARTISTIC trial has also provided the largest collection of HPV-typed primary screening cervical samples from the UK. Although from a limited geographic area, the setting in primary care makes this a representative population of women, across the cervical screening age range. The HPV type may be clinically important as the proportion of HC2 +ve women who were infected with HPV16 increased with cytological abnormality, from 14% in those with negative cytology to 55% in those with severe dyskaryosis. The HPV type might be used to determine whether to refer for colposcopy immediately, repeat the test, or defer any investigation until the next routine screen 3 years later. With the prospect of type 16/18-specific HPV prophylactic vaccines becoming implemented, data on these types in the screened population is of considerable importance in terms of what proportion of current abnormalities may still occur, notwithstanding a degree of cross-protection reported for HPV31, 33 and 45.[66] The high proportion of women with abnormal cytology who are HR-HPV +ve but HPV16/18 –ve is clinically significant; they account for 32% (18% of moderate or worse, 14% of borderline or mild) of all CIN2+ lesions.

The five most prevalent types (16, 18, 31, 51 and 52) together account for 60% of the 3512 HR-HPV infections detected (*Table 22*); HPV16 and HPV18 account for 32%. The overall prevalence of HR-HPV infection decreased sharply with age, from 27% below age 30 to 10% at 30–39, 4.2% at 40–49 and 2.5% at 50–64. The prevalence in Manchester between 1988 and 1993 was about 40% lower at each age (16% at age 20–29, less than 3% above age 40).[33] Although this change in prevalence may be explained by differences in assay sensitivity, more likely, it may reflect a genuine increased prevalence in this population as suggested by the increased UK diagnoses of genital warts between 1972 and 2005.[67] The difference in prevalence between young and older women is less marked in most other countries.[68] Most HR-HPV types show a similar age distribution, with relatively minor differences in the type distribution above and below age 30. HPV33 showed the most marked difference, being detected in 9.3% of women with HR-HPV below age 30 and only 4.5% at older ages (*Table 21*: $p < 0.001$).

HPV persistence

The data on persistence provides not only estimates of HC2 +ve persistence, but also type-specific persistence. It is clear that HC2 +ve persistence between rounds 1 and 2 conferred a very significant increased risk of abnormal cytology (odds ratio 10.22; 95% CI 7.05 to 14.8).

Many would feel that retesting cytology –ve/HPV +ve women at 12 months would be reasonable, but our data suggest that 40–50% would still test HC2 +ve with type-specific rates being very similar. Rates of persistence are somewhat lower at 24 months, particularly type-specific rates.

LBA –ve/HC2 +ve samples

The failure of the LBA to confirm that 31.5% of the HC2 +ve samples contain HC2 HR-HPV types is a cause of concern, especially if this assay were to be used as a front-line screening test. This is partly the result of the demonstrated cross-reaction with other putative HR types as well as low-risk types. The fact that 20.5% failed to yield any detectable HPV type is, however, problematic. Analysis of a small subset of these samples by GP5+/6+ PCR revealed that a proportion did contain HPV although the type was undetermined. The use of the improved, commercially available Linear Array assay[69] to confirm these HC2 +ve samples should improve the confirmatory rate. There would, however, still remain a substantial number of samples that do not appear to contain a demonstrable HPV genotype. Approximately half of these samples give an HC2 RLU value of between 1 and 2, providing further evidence that it may be advisable to raise the HC2 cut-off level as has been previously suggested.[70] Only 5% of CIN2+ were HC2 +ve/LBA –ve at a cut-off of 1 RLU/Co and a cut-off of 2 RLU/Co would have resulted in a failure to detect four out of 28 CIN2+ in this category.

HPV types in ARTISTIC

Differences in the relative frequencies of different HPV types are seen both between and within continents. The gross international differences between HPV subtypes[68] indicate that infections often involve viruses that have evolved in the region over many centuries, but there is now substantial intercontinental mixing through increased migration. Among HR-HPV +ve women with negative cytology the relative frequencies for several of the common HPV types were similar to those in other European countries reported by Clifford *et al.*,[72] although the proportion in our study was substantially greater for HPV52 and for the combined total of types 39, 51, 59 and 68. In a recent study of urine samples from American women aged 18 to 25 years, the distribution between the 13 HR-HPVs detected by HC2 was also similar to that seen in Manchester, with HPV16 being twice as prevalent as any other type, followed by types 51, 52, 39, 59 and 18.[73] A strikingly different distribution was recently reported amongst 1921 American women aged 14–59 years, with HPV types 52, 59 and 51 being more common than HPV16.[74] Whereas the prototype Roche Line Blot Assay was used in both studies the variation in type distribution observed may reflect the different sample types used, self-sampling cervicovaginal samples being used in the US study.

The proportion of women with HPV16 who had borderline or mild cytology was increased by the presence of other HR-HPVs (*Table 23*: 28.3% for single infections, 45.3% for multiple infections), but the proportion with moderate or worse cytology was not (26.2% for single infections, 25.3% for multiple infections).

The observation that in the cohort women who had a single HPV-type infection, HPV16, HPV31 and HPV33 were more prevalent among those with high-grade compared with negative cytology is consistent with data from the POBASCAM trial showing that among HR-HPV +ve women, those with either HPV16 or HPV33 were more likely to have CIN2+.[75]

Impact of vaccination

The data in *Table 23* provide a basis for modelling the overall effect of vaccination on cervical cytology. The simplest assumption is that elimination of HPV16 and HPV18 would give women with either or both of these viruses but no other HR-HPV the cytological profile of those with no HR-HPV, with 5% remaining HC2 +ve and the remainder becoming HC2 –ve, while those also infected with other HR-HPVs would move to the category of HR-HPV without HPV16 or HPV18. On this basis the number with moderate or worse cytology would be reduced by 45% in a population with this age distribution, but the number with borderline or mild cytology would fall by only 7%, giving an overall reduction of 12% in the number with abnormal cytology, and reducing the number with any HR-HPV by 27%.

The impact of vaccination on cytological abnormality rates will be considerably less in women aged over 30, as a far lower proportion of low-grade cytological abnormalities are HPV +ve in older women. HPV16 and/or HPV18 were detected in 260 of 930 (28%) women aged under 30 with low-grade (borderline or mild) cytology, and in only 111 of 1720 (6.5%) at age 30–64 years. In the absence of broader cross-protection the large majority of low-grade and many high-grade abnormalities would still occur in vaccinated women. This is consistent with the data emerging from clinical trials of prophylactic vaccine, which show very much greater efficacy in preventing CIN2+ than for low-grade abnormalities. Final results of the PATRICIA Trial of Cervarix, the bivalent 16/18 vaccine being used in the UK HPV vaccination programme, showed that not only was there over 90% efficacy in preventing types 16 and 18 associated CIN2+, but there was very significant cross-protection against CIN2+ associated with types 31, 33 and 45.[66] These other types are associated with a far lower proportion of CIN2+ lesions than type 16. The extent to which the bivalent vaccines directed against types 16 and 18 would prevent abnormalities associated with non-vaccine types as part of a multiple infection is not yet clear. Only 57% of infections with HPV16 or HPV18 in low-grade cytology and 66% in high-grade cytology involved no other HR-HPV.

More detailed age-specific analysis of these data will help to validate models of the likely impact of vaccination on subsequent cervical screening before long-term follow-up of current trial cohorts. The planned follow-up of ARTISTIC women to the next routine screening round will also provide estimates of type-specific risk over 6 years in women with negative baseline cytology.

Economic analysis

Trial participation

In the trial research protocol, the economic evaluation was planned to synthesise the costs to the NHS with the clinical effects at the trial end point, with the results being reported as an incremental cost-effectiveness ratio in terms of the additional cost per high grade cytology detected, assuming that a difference in effects was found between screening with cytology alone or with HPV testing alongside cytology. However, as no significant difference was observed in the diagnostic outcomes for the concealed and revealed arms, the economic analyses concentrated on cost comparisons between the alternative screening strategies, but even this activity was constrained in certain respects.

Although the trial was planned to cover two screening rounds with an interval of 3 years between rounds, the end point for reporting the study was reached before all women rescreened in round 2 had been fully followed-up. Thus, some women in round 2 were not comprehensively costed because their management was incomplete. Another difficulty arose during round 2 when clinical staff in primary care used the conventional Papanicolaou method for taking a woman's sample instead of the ThinPrep LBC method. Samples taken by this conventional method could not be tested for HPV. Finally, and very infrequently, an LBC vial transferred to the virology laboratory contained an insufficient quantity of fluid for HC2 analysis. These events probably happened randomly across the arms but, nevertheless, in the revealed arm in round 2, 888 (7%) women did not have an HPV test performed.

Technologies impacting on unit costs

An element of uncertainty impacting on the trial's resources was the adoption of the LBC screening system supplied by ThinPrep in place of the conventional Papanicolaou method at a time when there was very little UK experience in using LBC. Cytopathologists and cytoscreeners in the participating laboratories and sample takers in primary care had to be suitably trained before the trial was launched. The studies of LBC pilot sites in Scotland[47] and England[41] were completed 2 or 3 years later and the 'roll out' of LBC in cytology laboratories within the NHS was still ongoing in 2007. The economic evaluation for ARTISTIC was, nevertheless, committed to producing cost results that could be generalised to the NHSCSP for England, assuming that programme was organised efficiently.

For the purposes of estimating cytology laboratory costs, the NHS Purchasing and Supplies Agency provided indicative contract prices for ThinPrep equipment (T2000 and T3000 processors) and consumables. Then, by undertaking optimisation modelling, alternative 'hub and spoke' laboratory configurations for installing and operating these processors within the nine regional QARCs were generated. The role of transportation of samples and slides between laboratories was taken into account.[46] The optimal price of £3.15 (excluding VAT) identified from the modelling for processing a ThinPrep slide was equivalent to 58% of the overall cost for a negative or inadequate slide. The remainder of the cost was mainly staff time for reading the slides and reporting the findings. If a current research evaluation of automated technologies for scanning slides (the MAVARIC trial) has a positive outcome, the financial implications from a widespread adoption of the technology could be significant in terms of reducing staffing costs for assessing slides deemed to be negative.

To inform the cost estimation of HPV testing, QIAGEN, an international company that donated the HC2 processing equipment for the purpose of the trial, supplied indicative contract prices for purchasing or leasing systems for installation in laboratories to handle annual volumes of HPV tests arising from the NHSCSP for England. When deriving the baseline cost per test of £6.61 inclusive of staffing, we assumed that LBC cervical samplers had been used to take the women's samples and that automated systems would process 4 million tests annually. If, however, HPV testing with HC2 was introduced as a triage for borderline or mild dyskaryosis, the annual volume of tests would be substantially reduced (to around 240,000), and economies of scale would be reduced accordingly. So, the adjusted cost for the lower volume of tests was £10.38 for automated systems and £10.57 for manual systems, inclusive of staff time needed to convert the LBC samples before DNA analysis. In common with the LBC estimations, we assumed that the configuration of laboratories undertaking HPV testing was optimal within the regional QARCs, especially if 4 million HC2 tests were performed annually. If HPV testing was introduced only for triaging women, opportunities for rationalising the distribution of the QIAGEN processes might not be available, and so the cost per test could be adversely affected. Similarly, introducing LBC triage into a programme of HPV primary testing would probably affect adversely LBC unit costs, unless rationalisation of regional cytology laboratory services took place.

Resource use of the women

The 3 : 1 randomisation between arms was consistently reflected in the patterns of primary care and laboratory resource use by the trial participants. The concealed and revealed women were followed up for similar lengths of time (mean duration per arm of 4.8 years) and over the full trial the average number of LBC examinations was 2.1 per arm. There was a statistically significant difference in the proportions of women attending colposcopy clinics ($p < 0.0001$ for both round 1 and the full trial), mainly because the protocol for the revealed arm recommended that women who remained HPV +ve after defined periods of time should be assessed by colposcopy. However, among all the women who underwent colposcopy, almost no difference was observed between the arms in the mean number of clinic attendances per woman – 2.29 attendances for both concealed and revealed women in round 1 and 2.17 and 2.15 attendances respectively in the full trial.

In England, the 2005–6 national average unit cost for a colposcopy was £215 and £187 for a biopsy of cervix uteri,[76] and no distinction was made between initial and repeat examinations and treatments that might be performed. So, we chose instead to rely on information provided by the finance department from the Hospital Trust responsible for the colposcopy clinic in St Mary's Hospital where the majority of cytology –ve/HPV +ve women underwent colposcopy. In a bottom-up costing exercise, based on documented 'care pathway' and annual activity levels, average unit costs were derived for a first visit (£300.51) and a follow-up visit (£150.26). As there was no apparent difference between the trial arms in the duration of the episodes of colposcopic care, these costs were attributed to the first and follow-up clinic attendances recorded in the trial's colposcopy database. Our approach differed from other UK studies, where researchers have attributed a cost to an episode of care for women with CIN (covering initial diagnosis at colposcopy, management and follow-up), and a proxy outpatient cost for a colposcopy with no CIN. Legood and colleagues, for example, valued these events (in 2001–2 prices) as £624 for colposcopy and treatment for CIN, and £122 for colposcopy outpatients (no CIN) in their modelling based on the NHS pilot studies.[77] But the care of patients in the colposcopy clinics at the pilot sites had not been audited during the evaluation, unlike in our trial's database.

Short-term cost savings

ARTISTIC was a pragmatic trial in which NHSCSP protocols were followed for managing women whose smears were cytologically abnormal following conventional Papanicolaou screening. As HPV testing had not been introduced in the NHSCSP, the trial management protocols for women in the revealed arm who were HPV +ve were based on internationally recognised practice. At the conclusion of round 1 and at trial end point, the revealed arm was significantly more costly per woman than the concealed arm, the age-adjusted mean costs (covering screening and colposcopy-related events) being £51.86 versus £65.04 for round 1, and £72.18 versus £91.54 for the full trial. Primary care trusts are responsible for commissioning cervical screening services.[78] So, by scaling up these mean costs according to the total numbers of women screened in a primary care trust, we can assess the likely impact the introduction of HPV alongside LBC screening might have. For instance, 26,800 women in the Manchester primary care trust were screened in 2006–7.[42] According to current screening practice using LBC, the budget for their management over 3 years would be approximately £1,390,000, whereas the addition of routine HPV testing could increase the budget to £1,743,000. In Stockport primary care trust, 19,200 women were screened; the 3-year budget for their care could range from £996,000 to £1,249,000 depending on the screening policy selected. During the next recall round for these women it is likely that the combined LBC/HPV screening policy would remain more costly, although the budget would be smaller, because of the reduction in the incidence of cervical abnormalities among women who responded.

The alternative screening policies (scenarios) that we considered incorporated greatly simplified protocols for managing women with abnormal results. The protocols were updated in response to recently available research evidence including the ARTISTIC trial's results. So, for instance, the proposed protocol for LBC screening followed by HPV triage for borderline or mild dyskaryosis results advised that women who were HPV +ve be referred directly for colposcopy, unlike in the revealed arm of the trial, where the borderline/mild women were resampled and tested for LBC and HPV at 6 months, with further triaging according to their results at 12 months and 24 months. In the other scenario where HPV testing is followed by LBC triage for women who are HPV-positive, women with negative cytology would be retested at 12 months, and if they were still HPV-positive, they would be referred for colposcopy. In the trial HPV testing was further repeated at 24 months for those women who preferred to avoid colposcopy after testing positive at 12 months.

The age-adjusted mean costs for the two triage screening scenarios using LBC cervical samplers, based on resource-use events incurred in round 1, were more favourable than current practice (£38.76 and £48.12 compared with £51.86), even though increasing numbers of women would be referred for colposcopy, particularly in the HPV primary-screening scenario. But if either of these policies was adopted, there is a risk that a marked expansion in the caseloads of colposcopic referrals could impact adversely on the administrative workloads of pathology laboratories where the women's cervical samples are analysed or tested. Many laboratories in England have assumed responsibility for referring women directly to colposcopy clinics, rather than expecting them to visit their GP surgery for a referral letter, and all laboratories have failsafe procedures to ensure that women who require referral are adequately informed and appropriately managed.[78]

Although the economic evaluation overall has not demonstrated cost advantages in adding HPV testing to the current cervical screening programme, the exploration of alternative screening policies has been more positive. However, in achieving cost savings, sacrifices would be made in terms of undetected cases of CIN – 1.5 cases of CIN2+ per 1000 screened women, according to the trial estimates for the revealed arm. The report from the study of the English pilot LBC sites, in which HPV testing was used as a triage, likewise explored alternative screening strategies. For the detailed modelling, clinical and cost data from the pilot sites were combined with other data taken from the literature to derive cost-effectiveness ratios for life-years gained.[41,77] Throughout the conduct of the ARTISTIC trial, we anticipated that we would undertake modelling beyond the trial end point, but relying specifically on clinical outcome data for the randomised arms generated across two rounds of the trial. However, as the outcome results for round 1 were so similar between the arms, and rates for the arms of detected cases of CIN3+ in round 2 were equally small, the trial evidence base would have had to be supplemented by evidence from the literature for modelling purposes. As this task was not undertaken, caution must be exercised when comparing the ARTISTIC economic results with those from the English pilot study.

The UK cervical screening programmes are responsive to new developments that have been robustly evaluated, specifically in the field of screening technologies and public health. The introduction in 2008 of the HPV vaccination programme for girls aged 12–13 years, followed in 2009 by a 2-year catch-up programme for girls up to 18 years, will have a moderating impact on resources allocated for cervical screening from 2015 onwards. In responding to these challenges, the NHSCSP may recommend the adoption of different screening regimes involving LBC and HPV testing (using differing cut-off thresholds) for women who have, or have not, been vaccinated in target age groups. Planning the changes will take time and national policy-makers will be reliant on robust research evidence for testing hypothesised strategies. The ARTISTIC trial carefully documented the clinical experience and outcomes of 24,510 screened women, recording their resource-use events in the primary care sector and in laboratories and colposcopy clinics in the acute hospital sector. This information, together with the detailed costings derived for these events and the accompanying cost-effectiveness analyses, should be treated as an archive that can be used repeatedly by policy-makers in the future.

Psychological analysis

This is the first study in which psychological and psychosexual outcomes have been reported in women receiving HPV results with the control of a randomised arm where the same HPV status was known but not revealed. This ensured a robust means of assessing the true impact of HPV testing when added to routine screening. The overall result was no significant difference in the GHQ caseness rates between the randomised arms of the trial. The reason for the high caseness rate is unclear although in a recently published randomised trial of management choice conducted in women with borderline/mild dyskaryosis from the same geographic area, the baseline GHQ caseness rates were 53% overall compared with 44% in the HPV-concealed arm of this trial.[27] Qualitative research in HPV testing has reported negative feelings, which could impact on psychological and psychosexual function, but the effect may not be sufficiently strong to impact on GHQ caseness.[79]

From the randomised comparisons, there was only weak evidence of increased psychological morbidity associated with an HPV result. The observational comparison of HPV +ve and HPV –ve within the revealed arm may be subject to bias as the psychological and behavioural characteristics of women who were HPV +ve appear to differ from those of women who were HPV –ve. This has been seen in terms of the differing levels of sexual satisfaction as measured by the SRS in the concealed arm. If one examines the GHQ score from the concealed arm, women who were HPV +ve tended to have higher GHQ scores than women who were HPV –ve (adjusted mean difference 0.78, 95% CI –0.43 to 1.99, $p = 0.21$). Although not significant, and perhaps imprecise as the result of a relatively small sample size, this suggests that the causal effect of revealing an HPV +ve result may not be as great as that implied by the observational comparisons.

With regard to GHQ mean scores, these are also higher (4.0 versus 3.2) in HPV +ve women compared with HPV –ve women in the concealed arm, suggesting an unclear relationship between HPV positivity and psychological functioning, perhaps through multiple partners and associated social factors. This may partly explain why in the controlled comparison, a revealed HPV +ve result was not associated with a significantly worse GHQ score or caseness rate. The data from this trial suggest that sexual functioning appears to be better in the HPV +ve women than HPV –ve women in the HPV-concealed arm, whether the women were cytologically –ve or abnormal.

This may be a function of current sexual activity and other social factors. Furthermore, telling women with negative cytology that they are HPV +ve appears to impact negatively on their sexual satisfaction, at least in the short term, compared with the HPV +ve women whose result is concealed. This effect is not seen in women with abnormal cytology. Women who are HPV +ve with or without negative cytology are likely to be currently more sexually active, perhaps with higher levels of sexual satisfaction than their HPV –ve counterparts.

It is clear from qualitative research that for individual women and their partners, reporting HPV +ve results has some adverse effects, but the results of this study clearly indicate that overall, women receiving cytology results do not experience a significant increase in psychological distress from HPV testing. The concealed HPV data indicate that HPV +ve women have higher GHQ scores than HPV –ve women, the reason for which is unclear. In addition, HPV +ve women appear to experience better sexual functioning overall than their HPV –ve counterparts.

Implications for screening

It might have been expected that HPV testing could have added significantly to the sensitivity of screening but this turned out not to be the case. This is probably partly because of the quality of training in cervical cytology in Manchester (and elsewhere in the UK), partly because of the rigour of national guidelines in terms of repeating low-grade abnormalities and, it appears, partly because of improvement in the sensitivity by using LBC. An important consideration is whether the performance of cytology and management of cytological abnormalities was enhanced in this trial. This is unlikely because the cytology was not separated from the rest of the laboratory's cervical screening workload and the management of abnormalities was according to standard national guidance. The rate of high-grade abnormality was exactly what was expected. However, the borderline rate was higher and there was an increased rate of colposcopy which would identify more disease. It is clear that cytology plus HPV testing is no more effective than cytology alone and it is more costly. The principal question for screening in the future is whether to continue with cytology, and triage by HPV for low-grade abnormalities (as being currently used in the NHSCSP 'Sentinel Site' project) or whether to test initially with HPV and triage +ve results with cytology. Women who are HPV +ve/borderline cytology are referred to colposcopy and those women who are borderline/HPV –ve can be returned to routine recall.

The cost analyses for alternative screening policies are based on actual ARTISTIC events which have been age-standardised to the screened population in England. These indicate that there is a cost-saving for cytology triaged by HPV compared with HPV triaged by cytology (age-standardised figures £38.76 versus £48.12). Both of these, however, are cheaper than current management with LBC, which requires many repeat tests. Although the ARTISTIC trial did not compare these approaches directly, the strategy of HPV initially would be more sensitive as demonstrated in many other studies. Cost savings in HPV would be achieved relative to LBC, by using an HC2 cut-off of 2 RLU to achieve greater specificity, and there is the potential to increase screening intervals. This will require further research using data from other studies as well as from ARTISTIC, which is continuing to follow up women to a third round at 6 years. One aspect of HPV screening as an initial stand-alone test is that there would be a small amount of undetected CIN (as would be the case for cytology) including some CIN3; however, it is believed widely that such lesions would not become cancers because virtually all cervical cancers, including adenocarcinomas, are HPV +ve. There appears to be a higher level of protection associated with an HPV –ve result 3 years earlier compared with cytology –ve, particularly as an additional

10 CIN3+ and 32 CIN2+ had been previously identified and treated in the HPV +ve group in round 1. By contrast the HPV +ve group remains at twice the risk of the whole population in round 2, although it accounts for only 8% of the screened women.

The unit costs of cytology and HPV testing appear rather similar. Furthermore, from the ARTISTIC data it appears that HPV triaged by cytology and vice versa would perform similarly. The cost-effectiveness therefore depends, to some extent, on the rates of referral for further investigation.

The cytology abnormality rates are 7–8% in England, with around 200,000 women receiving new colposcopy appointments per year. Among women over 25 years the HPV rates would be around 12.7%, lower than the 15.6% in the whole ARTISTIC cohort because of the high rates in the 20–24-year age group. Using a cut-off of 2 RLU would reduce the HPV +ve rate for women 25 years or older closer to 10%. From ARTISTIC data around 40% of HPV +ve women had abnormal cytology and at least one-quarter of the remainder with negative cytology could be expected to have persistent HPV requiring further investigation. This could result in around 50–60% of HPV +ve women being offered colposcopy, a figure not dissimilar to expected cytology triage referrals. An alternative to colposcopy for women with negative cytology and persistent HPV positivity would simply be to repeat cytology at 12 months and only refer if cytology is abnormal. This would reduce colposcopy referrals for this group of HPV +ve women, but the ARTISTIC experience was that at least 30% of these women failed to attend early recall.

The use of an HPV test which is designed to detect nucleic acid from a sexually transmitted virus is potentially difficult for a small proportion of women, although the evidence from ARTISTIC is that HPV testing did not increase psychological morbidity. Similarly experience from around the world does not suggest that HPV testing generates more distress than does abnormal cytology. Data from the Netherlands suggest that adding HPV testing to cervical screening did not affect participation rates,[80] but it is important to provide clear, consistent messages about HPV testing.

The introduction of HPV prophylactic vaccination would increase the rationale for HPV testing in primary cervical screening for both vaccinated and unvaccinated women. The rationale of vaccination is to prevent infection by oncogenic HPV and by so doing prevent precancerous lesions and cancers attributable to HPV types in the vaccine, currently types 16 and 18. It seems entirely possible that vaccines will be developed to achieve a broader degree of protection across more HPV oncotypes. A larger proportion of vaccinated women will therefore remain HPV –ve than is currently the case. It therefore seems logical to consider in the future, testing first for HPV and then, if negative, rescreening after agreed intervals and reserving cytology for HPV +ve women. This would have major implications for cytology activity as it would be cut to no more than 20% of current levels. This would present challenges in quality assurance in terms of maintaining positive predictive values as well as managing change, e.g. in terms of retraining to perform HPV testing.

Notwithstanding the epidemiological case in favour of primary HPV screening there is no doubt that LBC performed extremely well in ARTISTIC. ARTISTIC used exclusively ThinPrep. Around 50% of the LBC in England now use the SurePath system, which may or may not be as sensitive as ThinPrep and may or may not interact with HC2 as ThinPrep did. Whether or not the performance of LBC will be as good across England as it was in ARTISTIC will need to be checked by studying the data from cytology laboratories which converted to LBC around the same time as ARTISTIC and have gone through two rounds. It will be possible to compare the outcomes of women who have undergone two rounds of LBC, 3 years apart, with both SurePath and ThinPrep, in women who were previously cytologically negative and to compare these with the outcomes of similar women in ARTISTIC.

Our data provide some support for the case that a negative HPV test will provide longer protection, i.e that HPV has a longer negative predictive value than cytology. This is because as well as detecting prevalent lesions, HPV status confers levels of risk. A more robust comparison of the longer protection of HPV compared with cytology will be performed on the 6-year follow-up study.

The 6-year follow-up for the ARTISTIC cohort will also provide robust type-specific risk at 6 years for women with negative baseline cytology and valuable data for modelling the impact of vaccination on cytological abnormality. Finally, because blinding will be maintained, a comparison of cytology versus cytology plus HPV testing will be possible over two 3-year rounds of screening.

Primary screening with HPV testing in combination with cytology triage has been recommended only in women aged over 30 years[32,81] as HPV is so common in younger women. This conclusion seems questionable in the light of our round 1 results, as high-grade dyskaryosis is as common among HPV +ve women aged under 30 years as in those aged 30–49 years, and much more common than in women aged over 50 years. Our round 2 results however, suggest that the cost–benefit ratio of primary HPV testing at all ages, and particularly in older women, will appear to be worse when prevalent high-grade disease has already been detected and treated after two rounds of screening by LBC. The practical implications for the appropriate screening interval at different ages and the role of HPV testing will be clearer when data from round 3 are available and the pattern of cytological abnormality and HPV prevalence in the context of routine 3-yearly LBC can be observed in this cohort as well as in the national data.

The real challenge for primary HPV testing, however, would be the positive women who are cytologically negative. Further testing would be required because we do not yet have a specific test to identify those with CIN2+ with a reasonable positive predictive value. The advent of convenient restricted 16/18 typing kits and other biomarkers raises the possibility of referring test +ve women for immediate colposcopy and retesting the remaining HPV +ve women at 12 months. Importantly, however, retesting risks losing women. In our study, 35% did not return at 12 months. Patient choice indicated a majority preference for colposcopy and of those who chose repeat testing, again the majority did not return. Of those 265 who chose colposcopy at 12 months, 32 CIN2+ were diagnosed with positive predictive value of 12%. Although this is the most sensitive approach over a single round it is economically more expensive, and more complicated in terms of protocol given the lower specificity in younger women.

The findings of the ARTISTIC trial suggest the following in terms of future screening policy:

1. With the whole country now converted to LBC, there is no benefit in combining cytology and HPV testing as a primary screen.
2. HPV testing to triage low-grade cytological abnormalities for referral to colposcopy, was less costly than repeat cytology. This provides evidence to support national roll-out following a national cervical screening programme pilot study followed by limited implementation in Sentinel Sites which will report late 2009.
3. In the 5- to 10-year term however, the very high negative predictive value of HPV testing, which should allow longer screening intervals, combined with the availability of automated platforms for high throughput could make HPV testing an attractive replacement for LBC as the primary screen. This would require strategies to achieve the necessary specificity for colposcopy referral. By 2017 the HPV vaccinated generation in England (2012 in Scotland, Wales and Northern Ireland) will reach the screening age. This would not only mean fewer HPV +ve women, but our data also show that HPV testing would have the advantage of avoiding the detection of HPV –ve low grade cytology. This not only outnumbers HPV +ve low-grade cytology but also yields almost 20 times less CIN3+.
4. HPV primary screening would greatly reduce the volume of cytology with major implications for the number of cytology laboratories and the potential for cytoscreeners to retrain in HPV testing.
5. In the longer term, as the proportion of screened women who have been vaccinated increases, there will be a greater than 50% decrease in CIN2+ with significant implications not only for cytology practice but also colposcopy.

It should be noted that in terms of improved detection, strategies to increase the number of younger women who currently do not attend for screening are required. This could have a greater impact than any possible incremental increase in CIN2+ detection based on primary HPV testing.

The combination of HPV and cytology, one triaging the other, is challenging because of the need within the NHSCSP to achieve, by 2009, a primary screening result within 14 days of the cervical sample being taken. Because of the potential for mass testing, and the need to minimise costs, the processing of HPV will need to be undertaken in centralised laboratories to achieve economy of scale. For HPV triage this will mean a ‘hub and spoke’ arrangement whereby samples from women with low-grade abnormalities are sent to a central laboratory for HPV testing. This is being piloted in Sentinel Sites currently and with three runs/week HPV testing results can be available within 2 or 3 days of the sample being sent, which should allow composite results to be available within 14 days.

Research recommendations

1. Establish the sensitivity and longer-term negative predictive value of both HPV testing and cytology. This will emerge from the 6-year follow-up in this study.
2. Find evidence of the impact of LBC over two screening rounds from other centres. This is work that could be undertaken using routinely available data from other laboratories that have completed two screening rounds using LBC. This should involve both Thinprep and SurePath systems.
3. Strategies are needed to refine the application of HPV testing as a primary screen to maintain its sensitivity but increase specificity for onward referral to colposcopy. This could involve HPV genotyping and other biomarkers.

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- Professor Richard Hobbs, Independent Chair, Department Primary Care and General Practice, University of Birmingham, UK
- Professor Heather Cubie, NHS Lothian R&D Director, ACCORD, Queen's Medical Research Institute and Consultant Clinical Scientist, Specialist Virology Centre, Royal Infirmary of Edinburgh, UK
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The study Data Monitoring and Ethics Committee comprised the following members:

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HC Kitchener, J Peto, S Moss, R Dowie, G Corbitt, M Desai, P Maguire and C Roberts were all involved in the design of the study protocol. H Kitchener, J Peto, M Almonte, R Dowie, B Stoykova, A Sargent, C Roberts and M Desai were responsible for drafting the report and all members of the TMG provided valuable comments and criticism. H Kitchener was responsible for the overall supervision of the trial. J Peto, M Almonte, C Roberts and C Gilham carried out the statistical analysis. M Almonte was responsible for data management. R Dowie and B Stoykova produced the economic analysis. A Sargent, A Bailey and A Turner performed the virological studies. I Fletcher and C Roberts analysed the psychological data. The trial was co-ordinated by P Wheeler from 2001 to 2005, and subsequently by C Thomson, who also helped to produce the manuscript. We are indebted to Juanita Steele for her painstaking work in finalising the report.

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Kitchener HC, Almonte M, Wheeler P, Desai M, Gilham C, Bailey A, *et al*. on behalf of the ARTISTIC Trial Study Group. HPV testing in routine cervical screening: cross sectional data from the ARTISTIC trial. *Br J Cancer* 2006;**95**(1):56–61. Epub 13 June 2006.

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Appendix 1

National Screening Committee's criteria for appraising the viability, effectiveness and appropriateness of a screening programme

The criteria, which are set out below, are based on the classic criteria first promulgated in a World Health Organisation report in 1966 but take into account both the more rigorous standards of evidence required to improve effectiveness and the greater concern about the adverse effects of health care; regrettably some people who undergo screening will suffer adverse effects without receiving benefit from the programme.

These criteria have been prepared taking into account international work on the appraisal of screening programmes, particularly in Canada and the United States. It is recognised that not all of the criteria and questions raised in the format will be applicable to every proposed programme, but the more that are answered will obviously assist the National Screening Committee to make better evidence-based decisions.

All of the following criteria should be met before screening for a condition is initiated:

The condition

The condition should be an important health problem.

The epidemiology and natural history of the condition, including development from latent to declared disease, should be adequately understood and there should be a detectable risk factor or disease marker and a latent period or early symptomatic stage.

All the cost-effective primary prevention interventions should have been implemented as far as practicable.

The test

There should be a simple, safe, precise and validated screening test.

The distribution of test values in the target population should be known and a suitable cut-off level should be defined and agreed.

The test should be acceptable to the population.

There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals.

The treatment

There should be an effective treatment or intervention for patients identified through early detection, with evidence of early treatment leading to better outcomes than late treatment.

There should be agreed evidence-based policies covering which individuals should be offered treatment and the appropriate treatment to be offered.

Clinical management of the condition and patient outcomes should be optimised by all health-care providers before participation in a screening programme.

The screening programme

There must be evidence from high-quality randomised controlled trials that the screening programme is effective in reducing mortality or morbidity.

Where screening is aimed solely at providing information to allow the person being screened to make an 'informed choice' (e.g. Down syndrome, cystic fibrosis carrier screening) there must be evidence from high-quality trials that the test accurately measures risk. The information that is provided about the test and its outcome must be of value and readily understood by the individual being screened.

There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/intervention) is clinically, socially and ethically acceptable to health professionals and the public.

The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment).

The opportunity cost of the screening programme (including testing, diagnosis, treatment, administration, training and quality assurance) should be economically balanced in relation to expenditure on medical care as a whole (i.e. value for money).

There must be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards.

Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be made available before the screening programme commences.

All other options for managing the condition should have been considered (e.g. improving treatment, providing other services), to ensure that no more cost-effective intervention could be introduced or current interventions increased within the resources available.

Evidence based information, explaining the consequences of testing, investigation, and treatment, should be made available to potential participants to assist them in making an informed choice.

Public pressure for widening the eligibility criteria for reducing the screening interval, and for increasing the sensitivity of the testing process, should be anticipated. Decisions about these parameters should be scientifically justifiable to the public.

References

1. Department of Health. *Screening of pregnant women for hepatitis B and immunisation of babies at risk*. London: Department of Health; 1998. (Health Service Circular: HSC 1998/127).

2. Wilson JMG, Jungner G. *Principles and practice of screening for disease*. Public Health Paper Number 34. Geneva: WHO; 1968.

3. Cochrane AL, Holland WW. Validation of screening procedures. *Br Med Bull*. 1971;**27**:3.

4. Sackett DL, Holland WW. Controversy in the detection of disease. *Lancet* 1975;**2**:357–9.

5. Wald NJ (editor). *Antenatal and neonatal screening*. Oxford: Oxford University Press; 1984.

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7. Gray JAM. *Dimensions and definitions of screening*. Milton Keynes: NHS Executive Anglia and Oxford, Research and Development Directorate; 1996.

Appendix 2

Results letter

«First_Name» «Last_Name»

«Address1»

«Address2»

«Address3»

«Post_Code»

Dear «First_Name»

Trial Number – «Trial_Number»	**Date of Birth** – «Date_of_Birth»

Thank you for continuing to take part in the *ARTISTIC* study. You will recall that you were randomised to the «Randomisation» group which means that you are notified of your HPV result.

You recently had a smear and HPV test:

Smear result –

HPV Result –

We would like to repeat the test in **July 2004**. This date will vary from other results letters you may have received and is due to the fact that you are participating in the study. All women in the trial are offered an LBC test three years after they agreed to enter the trial.

Human papillomavirus is a very common infection of the cervix. Most women have the virus at some time in their life, but most clear it without knowing they had it as it produces no symptoms. I enclose a leaflet about HPV for more information.

We will send you a reminder letter nearer the time.

You will also receive this result of your routine smear from the Health Authority. It is important that you realise that although you will receive two separate letters, they both apply to the same test.

Please telephone **0161 000 0000** if you have any queries or would like further information.

Yours sincerely

Professor H C Kitchener

Cc «GP_name»

«GPAddress1»

«GPAddress2»

«GPAddress3»,«GPPost_Code»

Appendix 3

HPV information leaflet

What is the Human Papillomavirus? (HPV)

Human Papillomavirus, HPV, is often called the wart virus. Most people have come across wart viruses in the form of warts and verrucas. However, there are now about 100 different types of Human Papillomavirus, and although they belong to the same family, they all behave differently. For example, the type that causes verrucas shows no interest in any other part of the body. There are other types of Human Papillomavirus, which cause visible genital warts but this virus is not associated with cervical cancer. Research has shown that certain types of HPV may be linked to abnormal changes in cervical cells, which can lead to cancer of the cervix (neck of the womb). Doctors are now interested in the role Human Papillomavirus testing may have in the early detection of this disease.

How do you get HPV?

Although there may be occasional exceptions, it is thought that Human Papillomavirus is sexually transmitted. It is estimated that approximately 70% of all women have this infection at some time in their life. However, because it can lie dormant for years, and because it produces no symptoms, no-one can be sure how long it may have been present in the cervix. Not all women with Human Papillomavirus will have abnormal cells in the cervix.

Is there a treatment for HPV?

At present there is no recommended treatment for Human Papillomavirus infection In the majority of cases the body's immune system will clear the infection as it would a common cold. In cases where the infection is persistent and not cleared naturally, more frequent monitoring for abnormal changes to the cervix may be required.

The future

Research is being undertaken in the Greater Manchester area to find out how best to manage this infection and whether HPV testing could improve the current cervical screening programme. There is also a great deal of work being done to produce a suitable vaccine.

FURTHER INFORMATION

Academic Unit Obstetrics & Gynaecology
1st Floor St Mary's Hospital
Whitworth Park
Manchester M13 0JH
Tel: 0161 000 0000

The University of Manchester
MANCHESTER
1824

HTA

A.R.T.I.S.T.I.C

A Randomised Trial In Screening To Improve Cytology

Human Papillomavirus

(HPV)

An Information Leaflet for Women

NHS CERVICAL SCREENING PROGRAMME

Appendix 4
Consent form

ARTISTIC

A Randomised Trial In Screening To Improve Cytology

THE UNIVERSITY of MANCHESTER

Principal Investigator: Professor Henry C Kitchener, Professor of Gynaecological Oncology
Trial Co-Ordinator: Paula Wheeler Telephone: 0161 000 0000 Fax: 0161 000 0000

Trial Number ☐☐☐☐☐

Consent Form

Tick Box

1. I confirm that I have read and understand the Information Leaflet dated 28/04/03 (version 7) for the above study and have had the opportunity to ask questions.
2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving reason, without my medical care or legal rights being affected.
3. I understand that relevant sections of any of my medical notes maybe looked at by responsible individuals from the Health Technology Assessment or from regulatory authorities. I give permission for these individuals to have access to my records. ☐
4. I agree to take part in the above study and to be randomised into one of two groups. ☐

Name and date of birth of patient	Date	Signature

Address and Post Code

Contact Telephone Number	NHS Number

Name of person taking sample	Date	Signature

Clinic / Surgery Details

5. In addition, I AGREE to my HPV sample being retained for future research. This will be stored anonymously. I understand that if I do not agree my sample will be destroyed at the end of the research study. ☐

Name and date of birth of patient	Date	Signature

Appendix 5

Patient trial information leaflet

You are being asked to take part in a study that is designed to look at ways of improving the smear test. Although the present NHS Screening Programme is very effective against preventing cervical cancers, research has shown that by doing an additional test on the sample it would be even more successful. This new test would look for infection in the cervix caused by the **H**uman **p**apilloma**v**irus or (HPV). Up to 70% of women have this infection in their cervix at some time in their life but in most cases this clears itself up. However it has been shown that if this virus infection persists, it can be associated with abnormal changes later on. Human papillomavirus testing may identify abnormal cells not detected by the smear test, or it may indicate the need for another smear sooner than the normal 3-5 year interval for smears. A study is needed to see whether HPV testing would improve screening. The trial is to be carried out in Greater Manchester and we need to recruit 28,000 women over 2 years. Smears in this trial will be taken in the normal way then transported in a special liquid. Liquid Based Cytology is simply a different technique of processing slides to be examined at the laboratory.

What will I have to do if I take part?

You make your appointment for a smear test at your GP's surgery or Family Planning Clinic. You will be asked to sign a **consent form** to say that you understand the trial, wish to participate and allow us to use the information collected. Each woman who agrees to take part will be allocated their own unique study number. The smear and HPV test will then be taken.

In order to see how effective the HPV test is we need to compare a group of women in whom the HPV result is known with a group of women in whom the HPV result is not known. One quarter of the women who take part will not be told of their HPV result. However you will still receive a letter from the Health Authority and the trial office regarding your smear result. All abnormal smears will be treated in the same way as they are now.

All information given will be treated confidentially

Do I have to take part?

Taking part is voluntary. If you decide not to participate you will still have your smear taken in exactly the same way. If you do enter the trial but wish to withdraw at any time then you are entirely free to do so. This will not affect your treatment.

What happens if I am allocated to the group where the HPV result is revealed?

You will be told both your HPV and smear test result. If your smear is abnormal, you will be managed under the current guidelines, the same as if you were not participating in the study. If the smear is normal, but the HPV result is positive we will repeat the HPV test 12 months later (in many cases the infection clears up itself). If it is still abnormal, you could choose between a repeat HPV test or a colposcopy (examination of the cervix). If the HPV test is still positive after 24 months we would wish to do a colposcopy.

What happens if I am allocated to the group where the HPV test is not being revealed?

Your management will be exactly how it is under the current system. You will be notified of your smear result and informed of any follow up where required.

Are there any benefits in participating in this study?

By taking part in this trial you will be assisting in providing evidence as to whether or not HPV testing picks up more abnormalities than the smear test alone. The implementation of testing for HPV might mean that in the future those women with normal smears and negative HPV results would need only attend for a smear say every 10 years. Before any changes to the programme can be made studies such as this one need to be carried out.

Most women are anxious at the time of having a smear test. This usually resolves when the smear is reported as normal. We are looking to see if the new HPV test effects levels of anxiety and to do this some women will be asked to complete a questionnaire. **This will be posted to you approximately 2 weeks after your result letter. Once completed you should return it in the accompanying pre-paid envelope. Your compliance in this is entirely voluntary. It will not effect your participation in the trial if you decide not to complete the questionnaire. All information will be treated confidentially.**

What do I do now?

Go along for your smear appointment as normal, taking your consent form with you. You can then inform the doctor or nurse that you wish to participate. They can also answer any questions that you may have.

For further information about the trial please contact:

Paula Wheeler Trial Co-Ordinator

0161 000 0000

Trial nurses on: 0161 000 0000

The University of Manchester

MANCHESTER 1824

HTA

A.R.T.I.S.T.I.C

A Randomised **T**rial **I**n **S**creening **T**o **I**mprove **C**ytology

Patient

Information

Leaflet

We are inviting you to take part in a new study of cervical smear testing. Please read this leaflet for details.

CERVICAL SCREENING PROGRAMME NHS

Appendix 6
Supplementary tables

TABLE 58 *Age, CIN2 and CIN3+[a] by cytological grade and HPV test in round 1 in the revealed arm*

Age in round 1	HPV –ve									HPV +ve								
	–ve			Borderline/Mild			Moderate+			–ve			Borderline/Mild			Moderate+		
	n	CIN2	CIN3+	*n*	CIN2	CIN3+	*n*	CIN2	CIN3+	*n*	CIN2	CIN3+	*n*	CIN2	CIN3+	*n*	CIN2	CIN3+
20–24	1053	–	–	101	4	–	5	1	1	390	7	5	303	27	28	81	26	32
25–29	1272	–	–	116	2	2	7	1	–	290	8	–	190	18	17	71	25	32
30–39	4464	–	–	380	7	–	9	2	3	507	5	4	251	27	19	114	29	56
40–49	3867	–	–	317	2	1	11	1	–	270	–	1	96	9	4	40	10	22
50–64	3711	–	–	205	3	–	8	–	–	218	2	–	27	1	–	12	3	6
All ages	14,367	–	–	1119	18	3	40	5	4	1675	22	10	867	82	68	318	93	148

a Including four invasive carcinomas and one adenocarcinoma.

TABLE 59 *Age, CIN2 and CIN3+[a] by cytological grade and HPV test in round 1 in the concealed arm*

Age in Round 1	HPV –ve									HPV +ve								
	–ve			Borderline/Mild			Moderate+			–ve			Borderline/Mild			Moderate+		
	n	CIN2	CIN3+	*n*	CIN2	CIN3+	*n*	CIN2	CIN3+	*n*	CIN2	CIN3+	*n*	CIN2	CIN3+	*n*	CIN2	CIN3+
20–24	358	–	–	31	1	1	–	–	–	128	–		99	6	6	26	8	11
25–29	436	–	–	38	1	–	–	–	–	87	–		59	10	6	25	5	18
30–39	1468	–	–	130	1	–	1	–	–	172	–		88	11	5	30	2	21
40–49	1268	–	–	114	1	1	5	1	–	75	–		41	2	1	13	3	7
50–64	1257	–	–	65	–	–	–	–	–	89	–		16	1	–	5	–	3
All ages	4787	–	–	378	4	2	6	1	–	551	–		303	30	18	99	18	60

a Including two invasive carcinomas and one adenocarcinoma.

DOI: 10.3310/hta13510

TABLE 60 *CIN2 and CIN3+[a] by cytological grade and HPV test in round 2 and age in round 1*

Age in round 1	HPV –ve									HPV +ve								
	–ve			Borderline/Mild			Moderate+			–ve			Borderline/Mild			Moderate+		
	n	CIN2	CIN3+	*n*	CIN2	CIN3+	*n*	CIN2	CIN3+	*n*	CIN2	CIN3+	*n*	CIN2	CIN3+	*n*	CIN2	CIN3+
20–24	649	–	–	23	–	–	–	–	–	192	–	–	82	7	4	11	5	3
25–29	852	–	–	37	2	–	–	–	–	127	–	–	52	8	3	13	1	6
30–39	3519	–	–	120	1	1	1	–	–	263	–	–	84	5	3	10	1	5
40–49	3435	–	–	83	1	–	1	–	–	156	–	–	35	2	2	3	–	1
50–64	3394	–	–	36	–	–	1	–	–	120	–	–	15	1	1	–	–	–
All ages	11,849	–	–	299	4	1	3	–	–	858	–	–	268	23	13	37	7	15

a Including one invasive carcinoma.

Age in round 1	HPV missing								
	Negative			Borderline/Mild			Moderate+		
	n	CIN2	CIN3+	*n*	CIN2	CIN3+	*n*	CIN2	CIN3+
20–24	179	–	–	23	2	–	3	2	–
25–29	172	–	–	19	1	–	2	1	–
30–39	399	–	–	31	–	–	2	–	–
40–49	263	–	–	17	2	–	–	–	–
50–64	207	–	–	6	–	1	2	–	1
All ages	1220	–	–	96	5	1	9	3	1

TABLE 61 *Cytology and histology in round 1 by different cut-off points*

RLU	< 1		1–1.99		2–3.99		4–9.99		10+		All women	
	n	%	*n*	%	*n*	%	*n*	%	*n*	%	*n*	%
Cytology in round 1												
–ve	19,154	89.6	526	2.5	328	1.5	354	1.7	1018	4.8	21,380	100
Borderline/mild	1497	56.1	83	3.1	49	1.8	89	3.3	949	35.6	2667	100
Moderate/worse	46	9.9	4	0.9	7	1.5	15	3.2	391	84.5	463	100
All women	20,697	84.4	613	2.5	384	1.6	458	1.9	2358	9.6	24,510	100
Histology by cytology in round 1												
–ve												
CIN2	–		4	18.2	–		3	13.6	15	68.2	22	100
CIN3+	–		1	10.0	2	20.0	–		7	70.0	10	100
Borderline/mild												
CIN2	22	16.4	4	3.0	3	2.2	6	4.5	99	73.9	134	100
CIN3+	5	5.5	2	2.2	1	1.1	3	3.3	80	87.9	91	100
Moderate/worse												
CIN2	6	5.2	2	1.7	2	1.7	4	3.4	102	87.9	116	100
CIN3+	4	1.9	1	0.5	4	1.9	8	3.8	195	92.0	212	100
CIN2+ in round 1	37	6.3	14	2.4	12	2.1	24	4.1	498	85.1	585	100

TABLE 62 *Cytology and histology in round 1 by different ranges of relative light units (RLU/co)*

RLU/Co	**<1**	**1+**	***1–1.99***	**2+**	***2–3.99***	**4+**	***4–9.99***	**10+**
Cytology in round 1								
Negative	19,154	2226	*526*	1700	*328*	1372	*354*	1018
Borderline/mild	1497	1170	*83*	1087	*49*	1038	*89*	949
Moderate/worse	46	417	*4*	413	*7*	406	*15*	391
All women	20,697	3813	*613*	3200	*384*	2816	*458*	2358
Histology by cytology in round 1								
Negative								
CIN2	–	22	*4*	18	–	18	*3*	15
CIN3+	–	10	*1*	9	*2*	7	–	7
Borderline/mild								
CIN2	22	112	*4*	108	*3*	105	*6*	99
CIN3+	5	86	*2*	84	*1*	83	*3*	80
Moderate/worse								
CIN2	6	110	*2*	108	*2*	106	*4*	102
CIN3+	4	208	*1*	207	*4*	203	*8*	195
CIN2+ in round 1	37	548	*14*	534	*12*	522	*24*	498

Columns in italic show the values lying within the range between the cut-offs of 1+, 2+, 4+ and 10+.

TABLE 63 *Prevalence of HPV16, HPV18 and other high-risk HPV types by age, cytology and histology in round 1*

	HC2 negatives	HPV 16	HPV 18 (not HPV 16)	Other HC2 positives[a]	Total
Age (years)					
20–24	1548 (60.1%)	315 (12.2%)	80 (3.1%)	632 (24.6%)	2575 (100%)
25–34	4867 (77.6%)	320 (5.1%)	127 (2.0%)	957 (15.3%)	6271 (100%)
25–34	6538 (89.2%)	112 (1.5%)	43 (0.6%)	638 (8.7%)	7331 (100%)
45–54	4707 (92.2%)	35 (0.7%)	15 (0.3%)	345 (6.8%)	5102 (100%)
55–64	3037 (94.0%)	21 (0.7%)	7 (0.2%)	166 (5.1%)	3231 (100%)
Cytology					
Negative	19,154 (89.6%)	318 (1.5%)	143 (0.7%)	1765 (8.2%)	21,380 (100%)
Borderline	1232 (68.9%)	125 (7.0%)	54 (3.0%)	378 (21.1%)	1789 (100%)
Mild	265 (30.2%)	152 (17.3%)	40 (4.6%)	421 (47.9%)	878 (100%)
Moderate	38 (14.0%)	107 (39.5%)	18 (6.6%)	108 (39.9%)	271 (100%)
Severe or worse	8 (4.2%)	101 (52.6%)	17 (8.8%)	66 (34.4%)	192 (100%)
Histology					
CIN1 or less	318 (40.8%)	104 (13.3%)	48 (6.2%)	310 (39.7%)	780 (100%)
CIN2	15 (7.1%)	85 (40.1%)	15 (7.1%)	97 (45.7%)	212 (100%)
CIN3/SCC	7 (2.7%)	157 (60.4%)	14 (5.4%)	82 (31.5%)	260 (100%)
CGIN/ADCC	3 (16.7%)	6 (33.3%)	6 (33.3%)	3 (16.7%)	18 (100%)
Abnormal cytology, no histology[b]	1200 (64.5%)	133 (7.1%)	46 (2.5%)	481 (25.9%)	1860 (100%)
Total	20,697 (84.4%)	803 (3.3%)	272 (1.1%)	2738 (11.2%)	24,510 (100%)

ADCC, adenocarcinoma; CGIN, cervical glandular intraepithelial neoplasia; SCC, squamous cell carcinoma.
a Not HPV16 or HPV18.
b Women with abnormal cytology in round 1 but no histology (abnormal cytology resolved or still being followed-up cytologically).

Comparison between the HC2 and AMPLICOR tests for high-risk HPV in cervical samples showing borderline cytological abnormalities

As shown in *Table 64*, an increased proportion of samples from women with borderline cytology were positive by AMPLICOR (38.7%) compared with HC2 (32.3%) ($p = < 0.001$). The overall agreement was 83.5% (Cohen's kappa value, 0.64). Where sample volumes were sufficient, genotyping by the prototype LBA showed that 77.4% (261/337) of the HC2 +ve samples contained an HR target type, with HPV16 and/or HPV18 detected in 29.4% (99/337) of the samples. By comparison, HR target types were detected in 70.1% (284/405) of the AMPLICOR positive samples, with HPV16 and/or HPV18 detected in 27.4% (111/405) of the samples. The clinical outcome during a 3-year follow-up period is shown in *Table 65*. The higher sensitivity of the AMPLICOR test which detected an additional 67 HPV +ve women was not translated into an increased CIN2+ detection rate with 43 (4.1%) cases being detected both in HC2 +ve and AMPLICOR +ve women. Hence, the increased sensitivity of the AMPLICOR for HPV detection does not appear to be of any clinical benefit but could result in significantly more women being triaged for colposcopy were it to be used in this setting.

TABLE 64 *HC2 vs AMPLICOR for women with borderline graded cytology*

	AMPLICOR (cut-off 0.2 ≥OD)		
HC2 (cut-off ≥1 RLU)	Positive	Negative	Total
Positive	288 (27.2%)	54 (5.1%)	342 (32.3%)
Negative	121 (11.4%)	595 (56.2%)	716 (67.7%)
Total	409 (38.7%)	649 (61.3%)	1058

McNemar's $\chi^2 = 25.65$; probability $> \chi_2 = < 0.001$.
Overall level of agreement, 83.5%; Cohen's kappa = 0.64; positive agreement = 62.2%.

TABLE 65 *Clinical outcome in cases of discrepant and concordant results between HC2 and AMPLICOR*

	Cytological regression bord → neg (colposcopy not required)	**Colposcopy outcome**				**Unsatisfactory or did not return**	**Total no.**
		No CIN	**HPV/ CIN1**	**CIN2**	**CIN3+**		
Discrepant results							
HC2 neg/ AMP pos	101 (83.5%)	12 (9.9%)	5 (4.1%)	2 (1.7%)	0 (0%)	1 (0.8%)	121
HC2 pos/ AMP neg	36 (66.7%)	10 (18.5%)	4 (7.4%)	2 (3.7%)	0 (0%)	2 (3.7%)	54
Concordant results							
HC2 pos/ AMP pos	161 (55.9%)	40 (13.9%)	38 (13.2%)	16 (5.6%)	25 (8.7%)	8 (2.8%)	288
HC2 neg/ AMP neg	467 (78.5%)	70 (11.8%)	40 (6.7%)	7 (1.2%)	2 (0.3%)	9 (1.5%)	595
Total no.	765 (72.3%)	132 (12.5%)	87 (8.2%)	27 (2.6%)	27 (2.6%)	20 (1.9%)	1058

AMP pos, AMPLICOR positive; AMP neg, AMPLICOR negative; HC2 neg, HC2 negative; HC2 pos, HC2 positive.

Prospective analysis comparing HC2 and AMPLICOR in a group of ARTISTIC women during round 2

As shown in *Table 66*, a greater proportion of the 5020 women attending for routine screening were positive by AMPLICOR (17.1%) compared with HC2 (10.4%) ($p = < 0.001$). The overall agreement was 89.8% (Cohen's kappa value, 0.58). This discrepancy in positivity between AMPLICOR and HC2 is consistent across the age range.

Cytology results were available for 4272 women and the concordance between the two tests by different grade is shown in *Table 67*. The AMPLICOR test detected more HPV infection than HC2 in women with negative, borderline and mild cytology; however, both assays showed identical sensitivity for detecting HPV in women with moderate or severe grades of cytological abnormality. Follow-up samples will determine the significance of the extra HPV infections detected by AMPLICOR in women in the negative and low-grade cytology groups (particularly the extra 69 HPV16 and/or HPV18 women detected).

Although the AMPLICOR assay demonstrated greater sensitivity over the HC2 test it also appears to have lower specificity compared with HC2 as indicated by the reduced percentage of samples which could be typed as HR using either the prototype LBA or the LA commercial assay compared with those typed as HR in the HC2 +ve group. The overall performance of the LBA and the LA for the detection of HR target types is compared in *Figure 19*. The LA has increased sensitivity compared with the LBA for the detection of HC2/AMPLICOR target types with 73.9% (385/521) and 81.4% (424/521) of HC2 +ve samples containing a HR target type by the LBA and LA respectively. In comparison only 52.9% (455/860) and 53.0% (456/860) of AMPLICOR +ve samples contained a HR target type by the LBA and LA respectively.

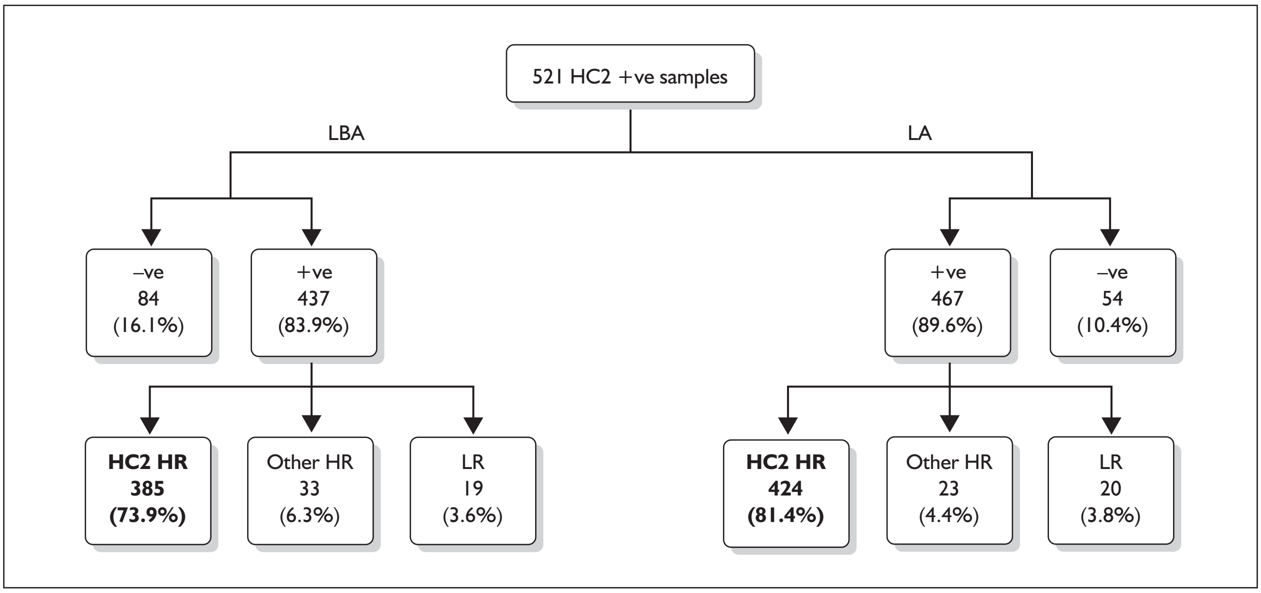
TABLE 66 *HC2 vs AMPLICOR for women attending routine screening*

	AMPLICOR (Cut-off 0.2 ≥ OD)		
HC2 (Cut-off ≥1RLU)	**Positive**	**Negative**	**Total**
Positive	435 (8.7%)	86 (1.7%)	521 (10.4%)
Negative	425 (8.5%)	4074 (81.2%)	4499 (89.6%)
Total	860 (17.1%)	4160 (82.9%)	5020

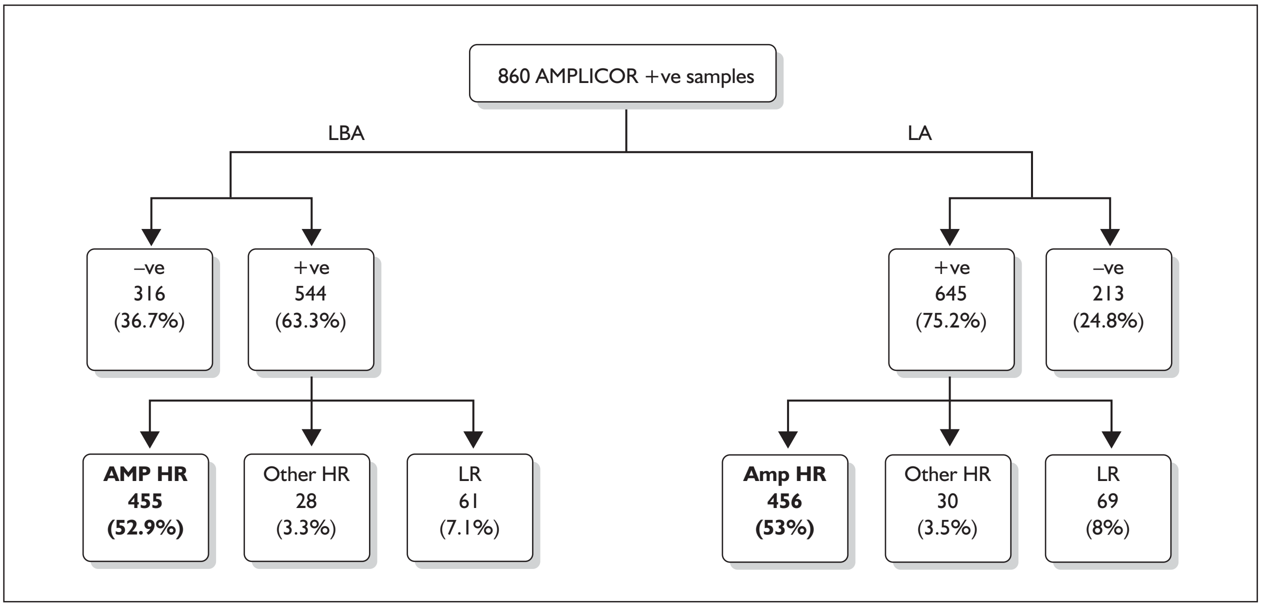
McNemar's $\chi^2 = 224.89$ $p \leq 0.001$.
Overall level of agreement = 89.8%; Cohen's kappa = 0.58; Positive agreement = 46%.

TABLE 67 *HC2 vs AMPLICOR for different cytology grades*

Cytology grade	HC2 pos/AMP pos	HC2 neg/AMP neg	HC2 pos/AMP neg	HC2 neg/AMP pos	Overall agreement
Negative ($n = 4024$)	251 (6.2%)	3376 (83.9%)	67 (1.7%)	330 (8.2%)	3627 (90.1%)
Borderline ($n = 155$)	60 (38.7%)	72 (46.5%)	4 (2.6%)	19 (12.3%)	132 (85.2%)
Mild ($n = 76$)	47 (61.8%)	14 (18.4%)	7 (9.2%)	8 (10.5%)	61 (80.3%)
Moderate ($n = 12$)	12 (100%)	0	0	0	12 (100%)
Severe ($n = 5$)	5 (100%)	0	0	0	5 (100%)



(A)



(B)

FIGURE 19 *Comparison between prototype LBA and the LA for positive HC2 samples (A) and AMPLICOR samples (B). HC2/AMPLICOR target high-risk (HR) types – 16, 18, 31, 33, 35, 39, 45, 51, 52, 56, 58, 59, 68; other HR types – 26, 53, 55, 66, 73, 82, 83, IS39; low-risk (LR) types – 6, 11, 40, 42, 54, 61, 62, 64, 67, 69, 70, 71, 72, 81, 84, CP6108. LA, Linear Array; LBA, line blot assay.*

TABLE 68 HPV typing results in round 1 and next adequate HPV sample

Round 1	Second sample	Time (months) to sample < 12.0	12.0–23.9	24.0–35.9	36.0–47.9	48.0 +	No second sample	Total
HPV16+	HPV16+	234	61	15	22	4		336
	Other	97	76	55	61	30		319
	No. tested	331	137	70	83	34	150	805
	Persistence (%)	70.7	44.5	21.4	26.5	11.8		51.3
HPV18+	HPV18+	70	15	5	6	2		98
	Other	46	44	21	24	9		144
	No. tested	116	59	26	30	11	77	319
	Persistence (%)	60.3	25.4	19.2	20.0	18.2		40.5
HPV31+	HPV31+	91	20	7	7	–		125
	Other	35	37	23	27	15		137
	No. tested	126	57	30	34	15	64	326
	Persistence (%)	72.2	35.1	23.3	20.6			47.7
HPV33+	HPV33+	45	13	–	–	2		60
	Other	42	18	10	10	8		88
	No. tested	87	31	10	10	10	35	183
	Persistence (%)	51.7	41.9	–	–	20.0		40.5
HPV35+	HPV35+	23	10	1	–	–		34
	Other	22	11	6	8	8		55
	No. tested	45	21	7	8	8	19	108
	Persistence (%)	51.1	47.6	14.3	–	–		38.2
HPV39+	HPV39+	50	15	–	3	1		69
	Other	50	36	23	16	12		137
	No. tested	100	51	23	19	13	60	266
	Persistence (%)	50.0	29.4	–	15.8	7.7		33.5
HPV45+	HPV45+	47	16	4	2	1		70
	Other	25	18	19	15	9		86
	No. tested	72	34	23	17	10	34	190
	Persistence (%)	65.3	47.1	17.4	11.8	10.0		44.9
HPV51+	HPV51+	54	18	2	2	–		76
	Other	63	43	16	17	12		151
	No. tested	117	61	18	19	12	78	305
	Persistence (%)	46.2	29.5	11.1	10.5	–		33.5
HPV52+	HPV52+	80	36	5	6	1		128
	Other	48	44	17	33	21		163
	No. tested	128	80	22	39	22	76	367
	Persistence (%)	62.5	45.0	22.7	15.4	4.6		44.0

TABLE 68 *HPV typing results in round 1 and next adequate HPV sample (continued)*

Round 1	Second sample	Time (months) to sample					No second sample	Total
		< 12.0	12.0–23.9	24.0–35.9	36.0–47.9	48.0 +		
HPV56+	HPV56+	23	8	3	1	–		35
	Other	40	32	9	14	11		106
	No. tested	63	40	12	15	11	41	182
	Persistence (%)	36.5	20.0	25.0	6.7	–		24.8
HPV58+	HPV58+	36	8	1	3	–		48
	Other	36	25	10	13	8		92
	No. tested	72	33	11	16	8	28	168
	Persistence (%)	50.0	24.2	9.1	18.8	–		34.3
HPV59+	HPV59+	26	15	1	4	–		46
	Other	36	27	10	14	10		97
	No. tested	62	42	11	18	10	56	199
	Persistence (%)	41.9	35.7	9.1	22.2	–		32.2
HPV68+	HPV68+	16	6	1	1	–		24
	Other	19	12	2	7	2		42
	No. tested	35	18	3	8	2	28	94
	Persistence (%)	45.7	33.3	33.3	12.5	–		36.4

TABLE 69 *Relative sensitivity and specificity for CIN2+ detection under different policies based on 220 CIN2 and 233 CIN3+ histologies detected in 18,386 women in the revealed arm in round 1 (see Figure 2)*

Screening policy	CIN2+				CIN3+	
	n (%) CIN2+ not detected	CIN2+ sensitivity	*n* (%) referred for colposcopy	CIN2+ specificity	*n* (%) CIN3+ not detected	CIN3+ sensitivity
Women aged 20–29 years (n = 3879)						
(236 CIN2+, 117 CIN3+)						
Cytology alone	20 (8.5%)	91.5%	874 (22.5%)	81.9%	5 (4.3%)	95.7%
Cytology with HPV triage of borderline lesions	27 (11.4%)	88.6%	696 (17.9%)	86.6%	6 (5.1%)	94.9%
HPV with cytology triage	31 (13.1%)	86.9%	645 (16.6%)	87.9%	8 (6.8%)	93.2%
HPV with cytology triage and repeat HPV if cytology –ve	11 (4.7%)	95.3%	1325 (34.2%)	69.8%	3 (2.6%)	97.4%
Cytology and HPV testing and repeat HPV if cytology –ve	0	100%	1554 (40.1%)	63.8%	0	100%
Women aged 30–39 years (n = 5725)						
(152 CIN2+, 82 CIN3+)						
Cytology alone	9 (5.9%)	94.1%	754 (13.2%)	89%	4 (4.9%)	95.1%
Cytology with HPV triage of borderline lesions	15 (9.9%)	90.1%	442 (7.7%)	94.5%	4 (4.9%)	95.1%
HPV with cytology triage	21 (13.8%)	86.2%	365 (6.4%)	95.8%	7 (8.5%)	91.5%
HPV with cytology triage and repeat HPV if cytology –ve	12 (7.9%)	92.1%	872 (15.2%)	86.9%	3 (3.7%)	96.3%
Cytology and HPV testing and repeat HPV if cytology –ve	0	100%	1261 (22%)	80.1%	0	100%
Women aged 40–64 years (n = 8782)						
(65 CIN2+, 34 CIN3+)						
Cytology alone	3 (4.6%)	95.4%	716 (8.2%)	92.5%	1 (2.9%)	97.1%
Cytology with HPV triage of borderline lesions	8 (12.3%)	87.7%	283 (3.2%)	97.4%	2 (5.9%)	94.1%
HPV with cytology triage	10 (15.4%)	84.6%	175 (2%)	98.6%	2 (5.9%)	94.1%
HPV with cytology triage and repeat HPV if cytology –ve	7 (10.8%)	89.2%	663 (7.5%)	93.1%	1 (2.9%)	97.1%
Cytology and HPV testing and repeat HPV if cytology –ve	0	100%	1204 (13.7%)	86.9%	0	100%
All women (n = 18,386)						
(453 CIN2+, 233 CIN3+)						
Cytology alone	32 (7.1%)	92.9%	2344 (12.7%)	89.3%	10 (4.3%)	95.7%
Cytology with HPV triage of borderline lesions	50 (11%)	89%	1421 (7.7%)	94.3%	12 (5.2%)	94.8%
HPV with cytology triage	62 (13.7%)	86.3%	1185 (6.4%)	95.6%	17 (7.3%)	92.7%
HPV with cytology triage and repeat HPV if cytology –ve	30 (6.6%)	93.4%	2860 (15.6%)	86.4%	7 (3%)	97%
Cytology and HPV testing and repeat HPV if cytology –ve	0	100%	4019 (21.9%)	80.1%	0	100%

TABLE 70 *Weights derived for age adjustments to round 1 of the ARTISTIC trial arms for use in the cost analysis*

Women on routine recall in England 2006–7		
Age at 31 March 2007	**Total recalled**	**Derived weight**
Under 20	1033	0.033
20–24	228,464	
25–29	693,448	0.101
30–34	606,956	0.124
35–39	628,554	0.150
40–44	591,196	0.155
45–49	484,767	0.134
50–54	380,122	0.111
55–59	337,906	0.103
60–64	284,406	0.089
65–69	63,550	NA
70–74	15,092	NA
75 and over	8417	NA

NA, not applicable to the ARTISTIC trial population.
Source: ref. 42.

Appendix 7

STARD checklist for reporting of studies of diagnostic accuracy (version January 2003)

Section and Topic	Item no.		On page no.
TITLE/ABSTRACT/ KEYWORDS	1	Identify the article as a study of diagnostic accuracy (recommend MeSH heading 'sensitivity and specificity').	iii
INTRODUCTION	2	State the research questions or study aims, such as estimating diagnostic accuracy or comparing accuracy between tests or across participant groups.	3–5
METHODS			
Participants	3	The study population: The inclusion and exclusion criteria, setting and locations where data were collected.	7
	4	Participant recruitment: Was recruitment based on presenting symptoms, results from previous tests, or the fact that the participants had received the index tests or the reference standard?	7
	5	Participant sampling: Was the study population a consecutive series of participants defined by the selection criteria in item 3 and 4? If not, specify how participants were further selected.	7
	6	Data collection: Was data collection planned before the index test and reference standard were performed (prospective study) or after (retrospective study)?	7
Test methods	7	The reference standard and its rationale.	8, 9, 11
	8	Technical specifications of material and methods involved including how and when measurements were taken, and/or cite references for index tests and reference standard.	15–17
	9	Definition of and rationale for the units, cut-offs and/or categories of the results of the index tests and the reference standard.	17
	10	The number, training and expertise of the persons executing and reading the index tests and the reference standard.	39
	11	Whether or not the readers of the index tests and reference standard were blind (masked) to the results of the other test and describe any other clinical information available to the readers.	8
Statistical methods	12	Methods for calculating or comparing measures of diagnostic accuracy, and the statistical methods used to quantify uncertainty (e.g. 95% confidence intervals).	20, 24
	13	Methods for calculating test reproducibility, if done.	NA
RESULTS			
Participants	14	When study was performed, including beginning and end dates of recruitment.	28
	15	Clinical and demographic characteristics of the study population (at least information on age, gender, spectrum of presenting symptoms).	31 (*Table 5*)

continued

Section and Topic	Item no.		On page no.
	16	The number of participants satisfying the criteria for inclusion who did or did not undergo the index tests and/or the reference standard; describe why participants failed to undergo either test (a flow diagram is strongly recommended).	27 (*Figure 5*)
Test results	17	Time-interval between the index tests and the reference standard, and any treatment administered in between.	NA
	18	Distribution of severity of disease (define criteria) in those with the target condition; other diagnoses in participants without the target condition.	NA
	19	A cross-tabulation of the results of the index tests (including indeterminate and missing results) by the results of the reference standard; for continuous results, the distribution of the test results by the results of the reference standard.	32 (*Table 6*)
	20	Any adverse events from performing the index tests or the reference standard.	NA
Estimates	21	Estimates of diagnostic accuracy and measures of statistical uncertainty (e.g. 95% confidence intervals).	NA
	22	How indeterminate results, missing data and outliers of the index tests were handled.	27
	23	Estimates of variability of diagnostic accuracy between subgroups of participants, readers or centres, if done.	NA
	24	Estimates of test reproducibility, if done.	NA
DISCUSSION	25	Discuss the clinical applicability of the study findings.	91–3

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We look forward to hearing from you.

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