Appendix accompanying the article:

Cost-effectiveness of HPV test of cure following treatment for Cervical Intraepithelial Neoplasia in England: Results from the NHS Sentinel Sites Study:

Model structure and assumptions for natural history, screening compliance and management

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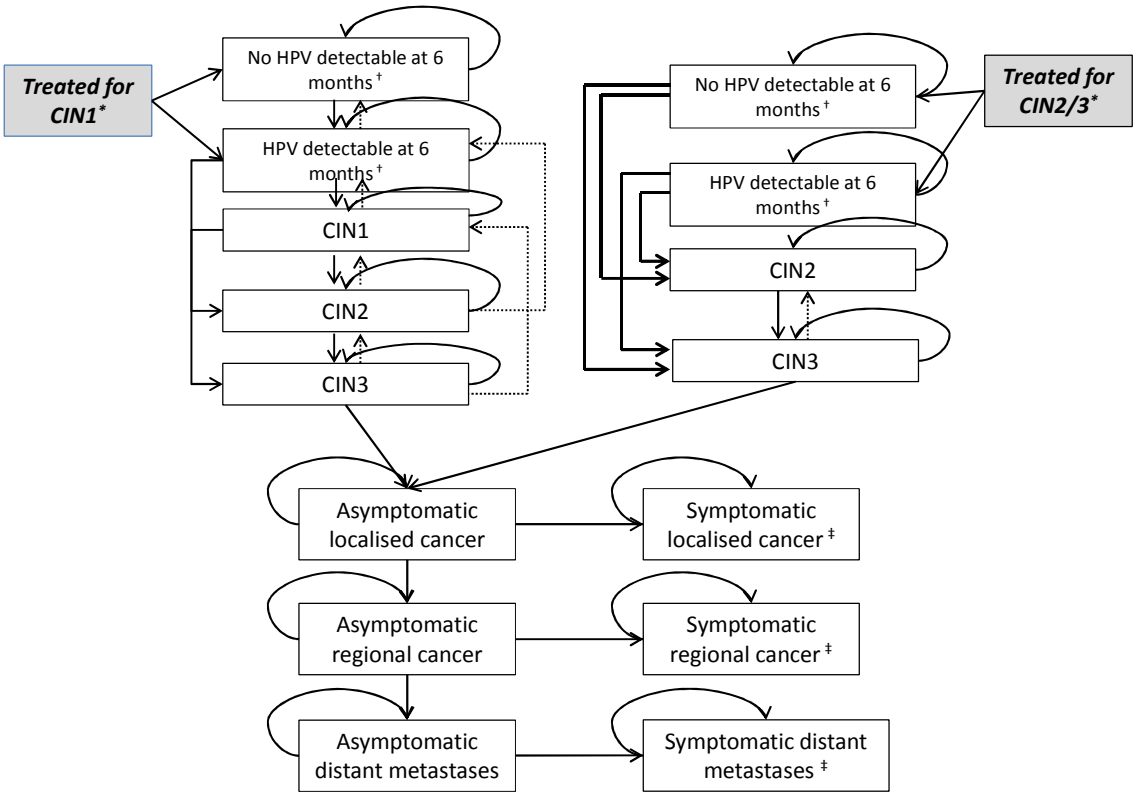
1. Natural history model of disease recurrence

The structure of the natural history model is depicted in Figure A1. The natural history model simulates the development of recurrent cervical intraepithelial neoplasia (CIN) and invasive cervical cancer in cohorts of women treated for CIN. The natural history model component for CIN and cervical cancer development in women previously treated for CIN was adapted from the post-treatment recurrence component of a previously published population-based model which included components for CIN natural history, cervical screening, post-treatment recurrence and invasive cancer survival.[1] After incorporating screening, management and compliance appropriate to the setting, this larger model has been previously calibrated to the age-specific prevalence of oncogenic HPV in cytologically-normal women, observed rates of histologically confirmed high-grade lesions, and cervical cancer age-specific incidence and mortality rates.[2-4] The age-standardised annual progression rate from CIN3 to asymptomatic localised cancer was calibrated to be 1.3%, consistent with the available data.[5]

Women successfully treated for CIN were assumed to be histologically negative after treatment (although treatment failure at 3.7% was also included in the model). The model assumed 16% of successfully treated women remained infected with HPV (see Table A1). This proportion was obtained from a systematic review of the relevant literature[2 3] and was assumed to be the same in women treated for low-grade and high-grade CIN. Women treated for CIN1 were assumed to be at a post-treatment risk for new infections and to follow a natural history for HPV and CIN consistent with the general at-risk female population. Women treated for histologically-confirmed CIN2/3 were assumed to be at an increased risk for recurrent CIN2+, with the risk in this group dependent on post-treatment HPV status. The rate of disease recurrence was obtained via systematic review of recurrence rates and of the relative risk of recurrence in HPV-positive versus HPV-negative women after treatment.[2 3]

The parameters used by the model in the simulation of the natural history of CIN after treatment for CIN1, for disease recurrence after treatment for CIN2/3, and for the natural history of invasive cervical cancer, are summarised in Table A1.

Figure A1. Schematic of the model of recurrent CIN and invasive cervical cancer*



***CIN**: Cervical intraepithelial neoplasia; **HPV**: Human papillomavirus*

* In each cycle, an age-specific rate of having benign hysterectomy and death from causes other than cervical cancer are also applied.

† The probability of recurrent disease is dependent on whether HPV infection is potentially detectable at 6 months post-treatment, irrespective of whether or not the post-treatment strategy under evaluation actually includes HPV testing at 6 months.

‡ In each cycle, patients diagnosed with invasive cervical cancer experience an additional stage-specific rate of cervical cancer mortality and an age-specific rate of death from causes other than cervical cancer. Patients who survive 5 years are considered cancer survivors.

Table A1 - Parameters used by the model for the natural history of recurrent CIN and invasive cervical cancer

Parameter	Value*
Annual progression and regression rates in the women who were successfully treated for CIN1[† §]	
Incidence of new oncogenic HPV infections	
30-34 years	0.0732
35-39 years	0.0592
40-44 years	0.0553
45-49 years	0.0379
50-54 years	0.0378
55-59 years	0.0273
60-64 years	0.0192
65-69 years	0.0175
70-74 years	0.0175
Clearance of HPV infection	
30-39 years	0.5500
40-44 years	0.5000
45-49 years	0.4500
50-54 years	0.4000
55-59 years	0.3500
60-74 years	0.3000
HPV to CIN1	
30-44 years	0.0900
45-74 years	0.0700
HPV to CIN2	
30-34 years	0.0200
35-44 years	0.0100
45-74 years	0.0050
CIN1 to Uninfected	0.2300
CIN1 to HPV	0.0300
CIN1 to CIN2	
30-44 years	0.0300
45-74 years	0.0400
CIN1 to CIN3	
25-39 years	0.0300
40-74 years	0.3310
CIN2 to Uninfected	0.3150
CIN2 to HPV	0.0350
CIN2 to CIN1	0.1215
CIN2 to CIN3	
30-34 years	0.1500
35-44 years	0.1800
45-54 years	0.2000

Parameter	Value*
55-64 years	0.2200
65-74 years	0.2400
CIN3 to CIN1	
30-34 years	0.0700
35-59 years	0.0300
60-74 years	0.0100
CIN3 to CIN2	
30-39 years	0.0500
40-49 years	0.0200
50-59 years	0.0150
60-74 years	0.0100
CIN3 to asymptomatic localised cancer	
30-34 years	0.0100
35-39 years	0.0175
40-44 years	0.0225
45-49 years	0.0250
50-54 years	0.0300
55-64 years	0.0350
65-74 years	0.0400
Health status after successful treatment for CIN[ll]	
HPV detectable at 6 months	0.1580
No HPV detectable at 6 months	0.8420
Annual rate of recurrent disease after successful treatment for CIN2/3	
No HPV detectable to CIN2[ll]	0.0015
No HPV detectable to CIN3[ll]	0.0033
HPV to CIN2[ll]	0.0527
HPV to CIN3[ll]	0.1115
CIN2 to CIN3	*Same rate as for women successfully treated for CIN1*
CIN3 to CIN2	*Same rate as for women successfully treated for CIN1*
CIN3 to non-symptomatic localised cancer	*Same rate as for women successfully treated for CIN1*
Annual progression rate of non-symptomatic invasive cervical cancer	
Localised to regional spread	
30-49 years	0.0592
50-59 years	0.1316
60-69 years	0.2925
70-74 years	0.6500
Regional cancer to distant metastases	0.0450

Parameter	Value*
Annual symptomatic detection rate of invasive cervical cancer‡	
Localised cancer	0.1500
Regional cancer	0.3000
Distant cancer	0.9000

***CIN**: Cervical intraepithelial neoplasia; **HPV**: Infected with human papillomavirus but without cervical intraepithelial neoplasia;*

* Because the time step used in the model was 6 months, the parameters applied were the equivalent 6-monthly rate, which were converted from the values presented after taking into account competing risks in each transition.

† Parameters for transitions in women aged 30-74 years only are presented, as these were the only parameters applied in this study (determined by the age range of the simulated cohorts and the length of the simulation).

‡ Parameters from a previously calibrated and validated model. [1-4]

§ Parameter values are equivalent to those for the general at-risk female population.

‖ Parameters obtained from a systematic review of the international literature.[2 3]

In each cycle, an age-specific rate of death from causes other than cervical cancer was applied for women in all health states and an age-specific rate of benign hysterectomy was applied to women without detected cervical cancer cancer. The rate of death from causes other than cervical cancer was calculated using data for all-cause mortality[6] after subtracting the appropriate cervical cancer mortality rate.[7]. The age-specific hysterectomy rate was obtained from a prior study.[8]

2. Configuration of modelled cohort

In the primary analysis, we assumed an age and disease distribution among treated women consistent with that observed at the HPV Sentinel Sites[9] (data obtained via personal communication, Rachel Kelly, Institute of Cancer Research, London). Age was included in the model because many factors

were age-dependent, including screening recommendations and aspects of management, screening compliance, other cause mortality, probability of benign hysterectomy or unsatisfactory colposcopy, and natural history parameters. The grade of CIN for which women were initially treated was included in the model, because the original guidelines prescribed differential follow-up for women treated for CIN1 to that for women treated for CIN2/3.[10]

Women included in the HPV Sentinel Sites evaluation were aged 25-64 years and otherwise met eligibility criteria for cervical cancer screening. Some of the HPV Sentinel Sites used HPV triage in the management pathway leading to initial treatment, and some used NHS guidelines which were current at that time (that is, women were referred to colposcopy on the basis of cytology results only; HPV triage was not performed in the management of borderline or mild cytology results). Because the population seen at colposcopy and then subsequently treated may differ in terms of distributions of age and grade of disease when referral protocols differ, for sensitivity analysis we constructed alternative, theoretical, treated populations, with differing age and/or incoming CIN grade distributions. The source of data for each theoretical alternate population is summarised in Table A2; in addition to data from the Sentinel Sites, we also used information from a cohort of women treated for CIN in London, Manchester, and Aberdeen, described in Kitchener et al (2008).[11] Alternate Population 1 has an age distribution consistent with the Kitchener study cohort (in which 73% of the treated population were aged less than 35 years), whilst the CIN distribution remains consistent with that seen at the HPV Sentinel Sites. Alternate Population 2 has a distribution of CIN1 vs. CIN2/3 consistent with the Kitchener study cohort (in which 24% were treated for CIN1, and 76% for CIN2/3), but an age distribution consistent with the HPV Sentinel Sites. Alternate Population 3 is consistent with the Kitchener study cohort both in terms of age and grade of CIN distribution at baseline. The various parameter value combinations are shown Table A3 (values in bold are used in the primary analysis; values in square brackets refer to Alternative Populations 1-3 as described above).

Table A2. Data sources and assumptions used for age and disease characteristics of theoretical model populations of treated women

Population	Age distribution of population	Disease distribution at the time of treatment
Primary analysis population	HPV Sentinel Sites	HPV Sentinel Sites
Alternative Population 1*	Kitchener (BJOG 2008)	HPV Sentinel sites
Alternative Population 2*	HPV Sentinel Sites	Kitchener (BJOG 2008)
Alternative Population 3*	Kitchener (BJOG 2008)	Kitchener (BJOG 2008)

*Populations used for sensitivity analysis.

Table A3. Characteristics of the modelled treated cohort: Distribution of age and grade of CIN at the time of initial treatment

Starting age (years)	Proportion by CIN grade within each age group (%) [value sets used in sensitivity analysis]			Proportion of population in age group (%) [value sets used in sensitivity analysis]
	CIN1	CIN2	CIN3+	
30 (midpoint representing a cohort 25 – 34 years)	**7** [8, 20, 21]	**33** [32,37,37]	**60** [60, 43, 42]	**63** [73, 63, 73]
42 (midpoint representing a cohort 35 – 49 years)	**13** [12, 29, 30]	**31** [31,35,34]	**56** [57, 36, 36]	**35** [25,35, 25]
57 (midpoint representing a cohort 50 – 64 years)	**40** [41, 41, 40]	**21** [21,29,30]	**39** [38, 30, 30]	**2** [2, 2, 2]
% of total treated	**10** [9.7, 23.6, 23.6]	**32** [31.8, 36.1, 36.1]	**58** [58.6, 40.3, 40.3]	**100**

Baseline values used for the primary analysis are shown in **bold** and values in square brackets refer to Alternative Populations 1-3. Some values adjusted so that totals add to 100% for each population.

3. Compliance assumptions

3.1 Assumed compliance with colposcopy attendance and follow-up after treatment

In the primary analysis, compliance rates for attending colposcopy were based on 2007-2008 statistics from the Cervical Screening Programme in England.[12] Compliance rates for follow-up after treatment were based on a study of women treated for CIN.[11] Table A4 summarises the assumed compliance with follow-up and the range used in sensitivity analysis.

We also considered a scenario where there was perfect compliance with all management recommendations (best case scenario). Women who did not attend for a follow-up visit were assumed to have the same probability of attending for a routine smear as the general population, unless they were symptomatic and thus re-attended earlier.

Table A4 - Compliance with follow-up after treatment

Parameter	Base case value	Range for sensitivity analysis
Compliance with colposcopy recommendation*	84% [12]	84% – 100%†
Compliance at 6 month follow-up visit	100%	-
Compliance at 12 month visit (among those who attended at 6 months)	85% [11]	85 - 100%†
Compliance at 24 month visit (among those who attended at 12 months)	83% [11]	83 - 100%†
Compliance with (re-)treatment	100%	-

* Based on observed "did not attend" (DNA) rates for follow-up colposcopies.[12]

† The high end of this range (100%) is an assumption, set to encompass the possibility of perfect compliance with colposcopy recommendations.

3.2. Assumed compliance for women discharged back to routine screening

We assumed that women who had been treated and then returned to routine screening would have similar compliance with routine screening recommendations as women in the general population. We

used registry data from Oxfordshire to estimate the cumulative re-screened proportion at various times after a negative smear for women who appeared on the register.[13] From this, and age-specific coverage data,[12] we derived an age- and interval-specific probability of a woman attending for routine screening, as previously described.[4] This allowed us to include the impact of some early and late re-screening. Because the data were derived from a region and at a time where three-yearly screening was recommended for all ages, we only applied these re-screening probabilities to women with a recommended screening interval of three years (ages 25-49 years). For women with a recommended screening interval of five years (ages 50-64 years), we assumed there would be no early or late re-screening, but that all women would re-attend every 5 years.

4. Management pathways

The model of post-treatment follow-up was constructed to incorporate management pathways for three alternative strategies (cytological only follow-up, Sentinel Site Protocol and the Extended HPV Follow-up Protocol). The model also included pathways to simulate management after colposcopy referral in previously treated women, as well as pathways of screening and colposcopy management for women who are returned to routine screening.

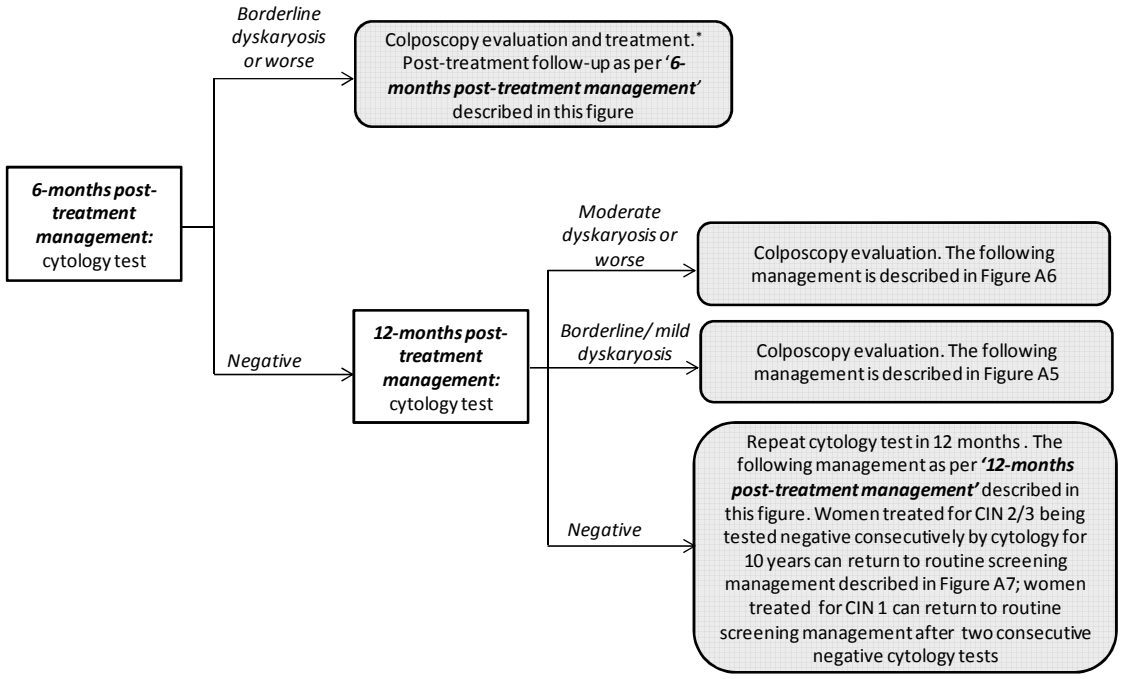
4.1 Management according to cytological only follow-up

The post-treatment management pathway is depicted in Figure A2. This was constructed according to the recommendations in Sections 9.2, 9.3 and 9.4 of the Colposcopy and Programme Management guidelines of the NHS Cancer Screening Programmes (2004).[10] Expert opinion was obtained for management details that were not directly specified in this guideline (Prof. Henry Kitchener, University of Manchester, personal communication).

In the model, women treated for CIN were followed-up with a cytology test at 6 months after treatment. At this follow-up visit, women with a borderline dyskaryosis or worse cytology result underwent colposcopy examination and were re-treated, and women with a negative cytology result were followed-up with annual cytology starting from 12 months post-treatment until testing negative

on either two consecutive annual follow-up visits (if treated for low-grade CIN), or ten consecutive visits (if treated for high-grade CIN), before returning to screening at the routine interval. Women with borderline dyskaryosis or worse cytology at any of the follow-up visits were referred to colposcopy and managed according to both colposcopy and cytology findings (further details of colposcopy management for women under post-treatment follow-up are given in Section 5.4).

Figure A2. Management according to cytological only follow-up



CIN 1: *Histologically-confirmed cervical intraepithelial neoplasia;* ***CIN2/3:*** *Histologically-confirmed cervical intraepithelial neoplasia;*

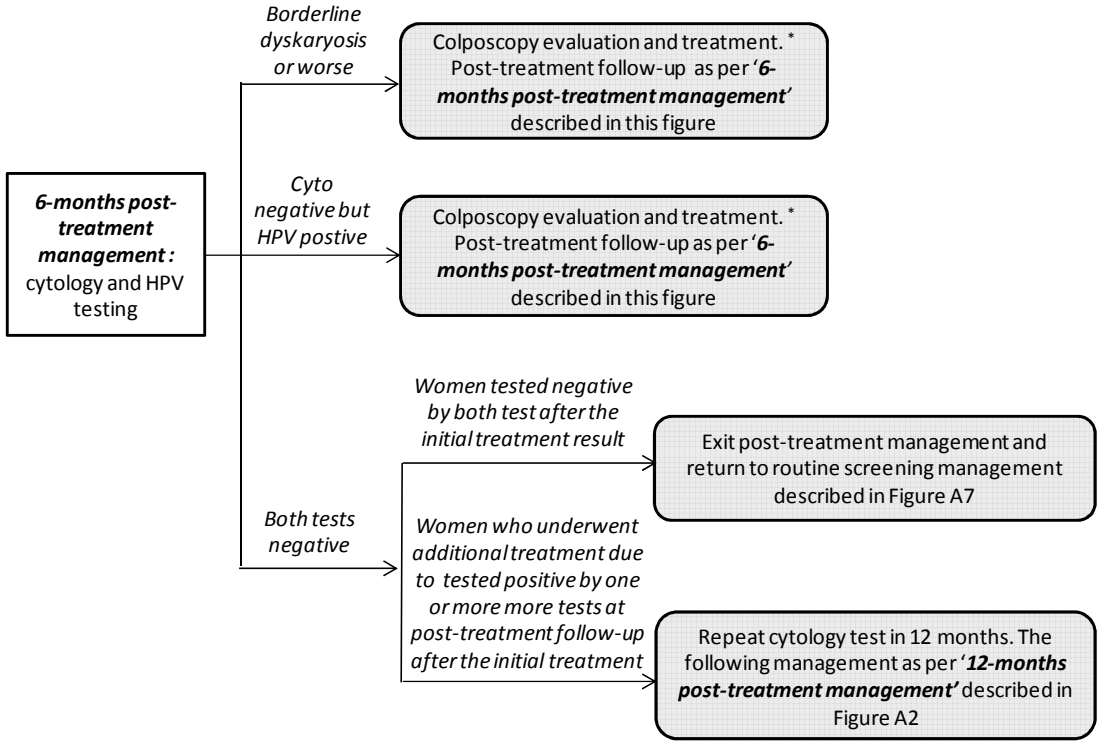
*Assumes all women with a cytological abnormality at 6 months will undergo colposcopy and receive re-treatment.

4.2. Management according to the Sentinel Site Protocol

The post-treatment management pathway constructed to simulate the Sentinel Site Protocol is depicted in Figure A3. This was constructed according to management specified at the Sentinel Sites,[9] and expert opinion was sought to informed details of the management that were not specified in the study protocol (Prof. Henry Kitchener, University of Manchester, personal communication). Under this protocol, women treated for CIN were followed-up with both cytology and HPV testing at 6 months after treatment. Women with borderline dyskaryosis or worse cytology or who were HPV positive underwent colposcopy and were re-treated; women testing negative with both tests were returned to routine screening (see Section 5.6). Re-treated women were followed-up with another

cytology and HPV test at 6-months and if negative by both tests, they received annual cytology testing thereafter.

Figure A3. Management according to the Sentinel Site Protocol



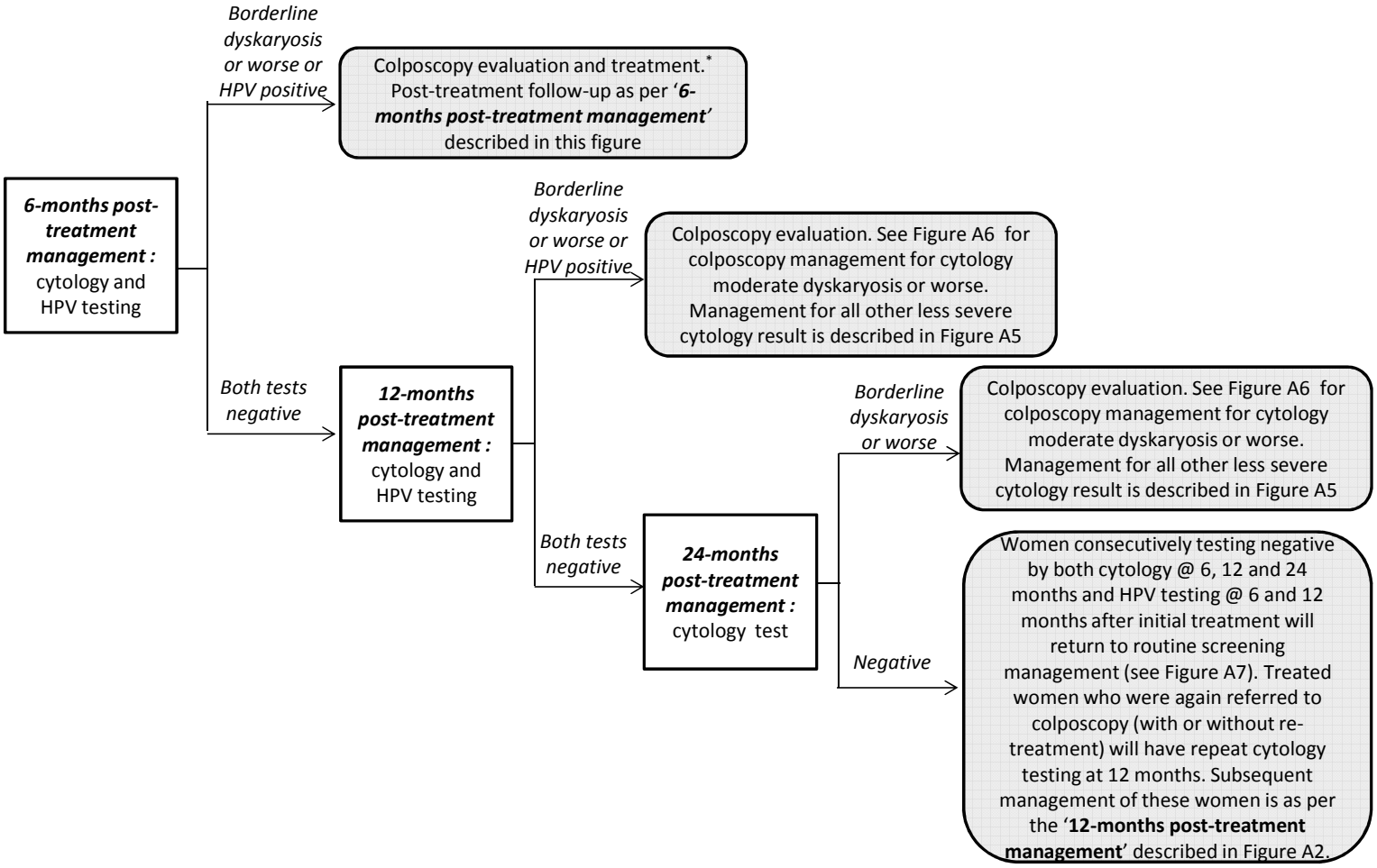
*Assumes all women with a cytology abnormality at 6 months will undergo colposcopy and receive re-treatment.

4.3 Management according to the Extended HPV Follow-up Protocol

The post-treatment management pathway constructed to simulate the Extended HPV Follow-up Protocol is depicted in Figure A4. This was constructed according the strategy evaluated by Kitchener et. al.[11] and expert opinion was sought to informed details of the management that were not specified in the study protocol (Prof. Henry Kitchener, University of Manchester, personal communication). Under this protocol, women treated for CIN were followed-up with both cytology and HPV testing at 6 months. Women with a borderline dyskaryosis or worse cytology or who were HPV positive underwent colposcopy and re-treatment; women testing negative were screened at 12 months with

both cytology and HPV testing and at 24 months with cytology alone. Women with a borderline dyskaryosis or worse cytology or who were HPV positive during the follow-up visits at 12 or 24 months post-treatment were referred to colposcopy and managed according to the colposcopy and cytology findings (see Section 5.4 for further details of colposcopy management). Women negative by cytology at 24 months post-treatment were returned to screening at the routine interval if they had been both cytology and HPV negative at 6 and 12 months after the initial treatment, but women who had previously had a one or both positive test results at either the 6 and 12 month visits continued annual cytology testing (described in Section 5.1).

Figure A4. Management according to the Extended HPV Follow-up Protocol



*Assumes all women with a cytology abnormality at 6 months will undergo colposcopy and receive re-treatment.

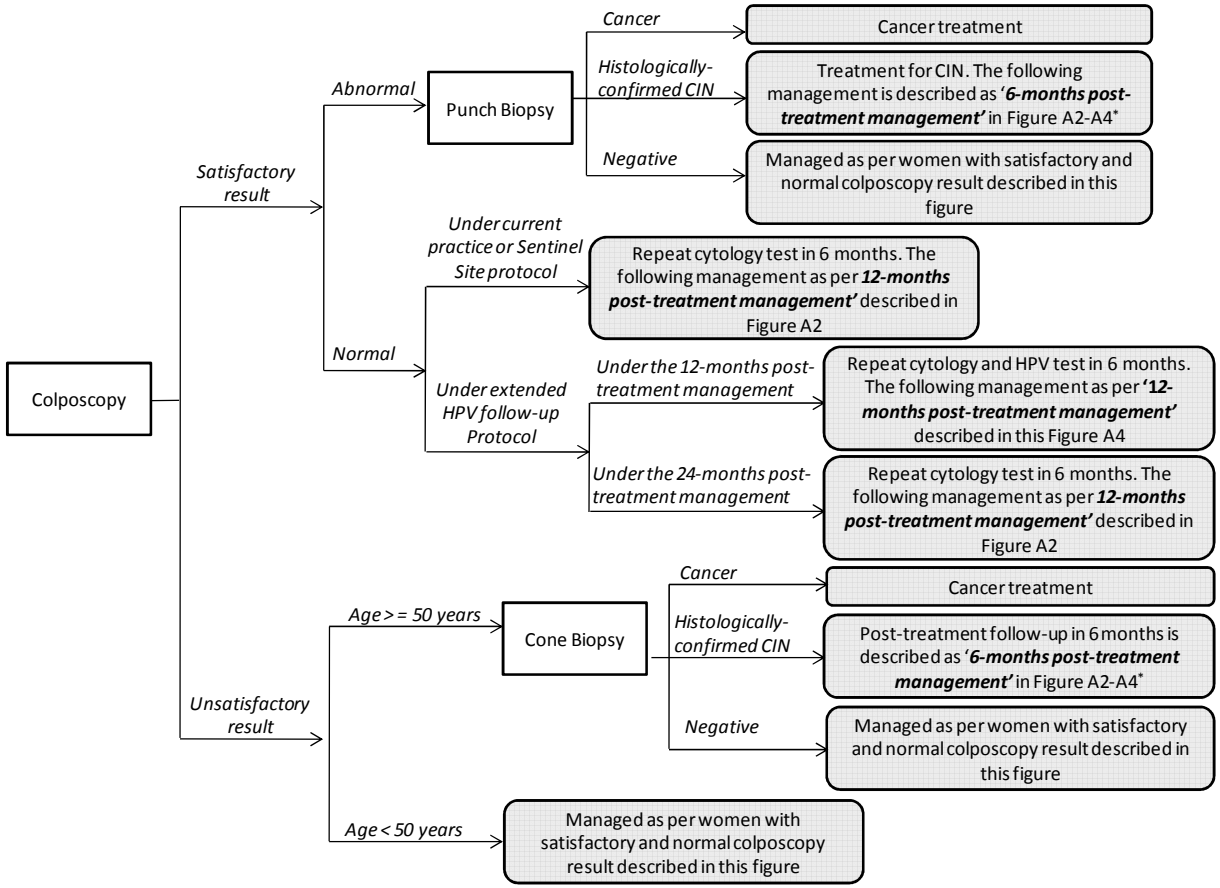
4.4 Post-colposcopy management for women undergoing post-treatment follow-up

The post-colposcopy management pathway for women referred with borderline/mild cytology when they are undergoing post-treatment follow-up is depicted in Figure A5. This pathway was constructed according to the recommendations in Section 9 of the 2004 NHS guidelines.[10] Expert opinion was sought for detailed aspects of management not directly specified in the guidelines (Prof. Henry Kitchener, University of Manchester, personal communication).

Women referred to colposcopy after a borderline or mild dyskaryosis cytology result, for whom colposcopy was satisfactory and normal, were followed-up at 6 months and then managed according to the applicable post-treatment management protocol. Women with a satisfactory but abnormal colposcopy result had a punch biopsy. Women diagnosed with invasive cervical cancer were referred to cancer treatment, women with histologically-confirmed CIN were treated and followed up at 6 months and were thereafter managed according to the applicable post-treatment management protocol, and women with negative histology were followed up at 6 months. Women with unsatisfactory colposcopy were followed up at 6 months (Figure A5).

The post-colposcopy management pathway for women referred with moderate/severe cytology when they are undergoing post-treatment follow-up is depicted in Figure A6. Women with a satisfactory but abnormal colposcopy received punch biopsy. Women with unsatisfactory colposcopy and women with satisfactory but normal colposcopy result were assumed to receive cone biopsy.

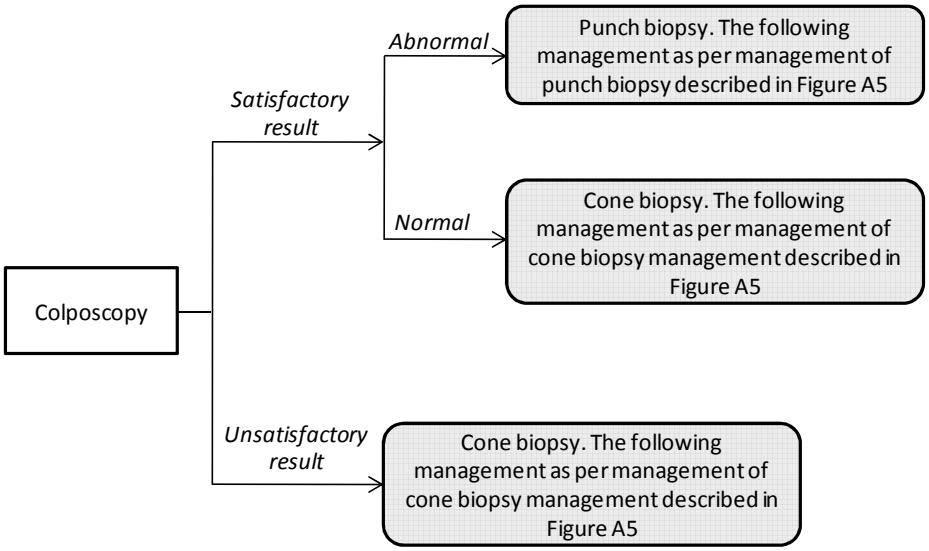
Figure A5. Post-colposcopy management for women post-treatment, who are referred to colposcopy after a borderline or mild cytology result



CIN: *Histologically-confirmed cervical intraepithelial neoplasia*

*Depending on which management protocol is being modelled; see Figure A2 for cytological only follow-up; A3 for the HPV Sentinel Sites protocol; A4 for the Extended HPV Follow-up Protocol)

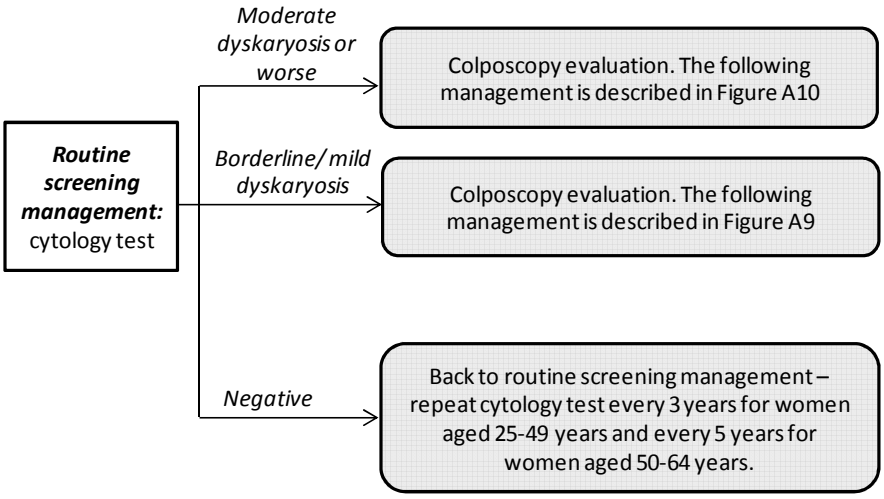
Figure A6. Post-colposcopy management for women post-treatment, who are referred to colposcopy with a moderate or severe dyskaryosis cytology result



4.5. Routine screening management

The model structure for management after routine screening is depicted in Figure A7. The model was constructed according to the recommendations of the 2004 NHS guideline.[10] Women were referred for colposcopy evaluation if the cytology result showed borderline dyskaryosis or worse. Women with a negative cytology result had a repeat cytology test in 3 years if they were aged 25-49 years or in 5 years if they were aged 50-64 years.

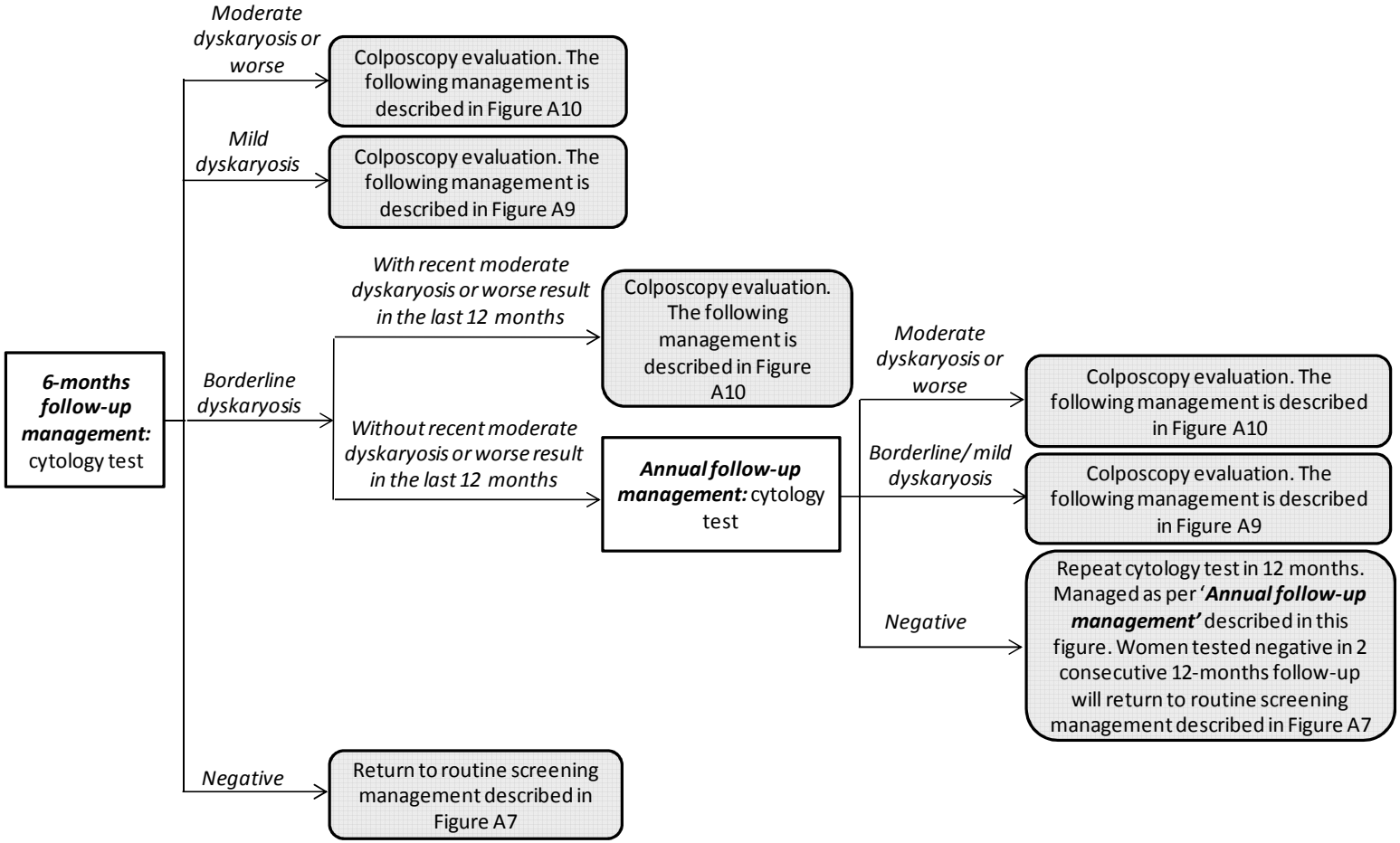
Figure A7. Management following routine screening



4.6 Follow-up management for women referred to colposcopy, found to harbour confirmed CIN 1 and not treated

The management pathways for women referred to colposcopy and then found to have a low grade abnormality that was not treated are depicted in Figure A8. The model was constructed according to the recommendations of the 2004 NHS guidelines.[10] Women were followed up with cytology at 6 months; women with a negative result were returned to routine screening, and women with mild dyskaryosis or worse were referred to colposcopy. If cytology was borderline dyskaryosis they were referred to colposcopy if they had a recent (12 month) history of moderate dyskaryosis or worse, or otherwise were followed up with cytology in 12 months. Women were followed up annually with cytology and were returned to screening at the routine interval after testing negative on two consecutive annual follow-up visits; women with borderline dyskaryosis or worse cytology were referred to colposcopy and managed according to both colposcopy and cytology findings (further details of colposcopy management are given in Section 5.7).

Figure A8. Follow-up management for women referred to colposcopy, found to have confirmed CIN1 and not treated

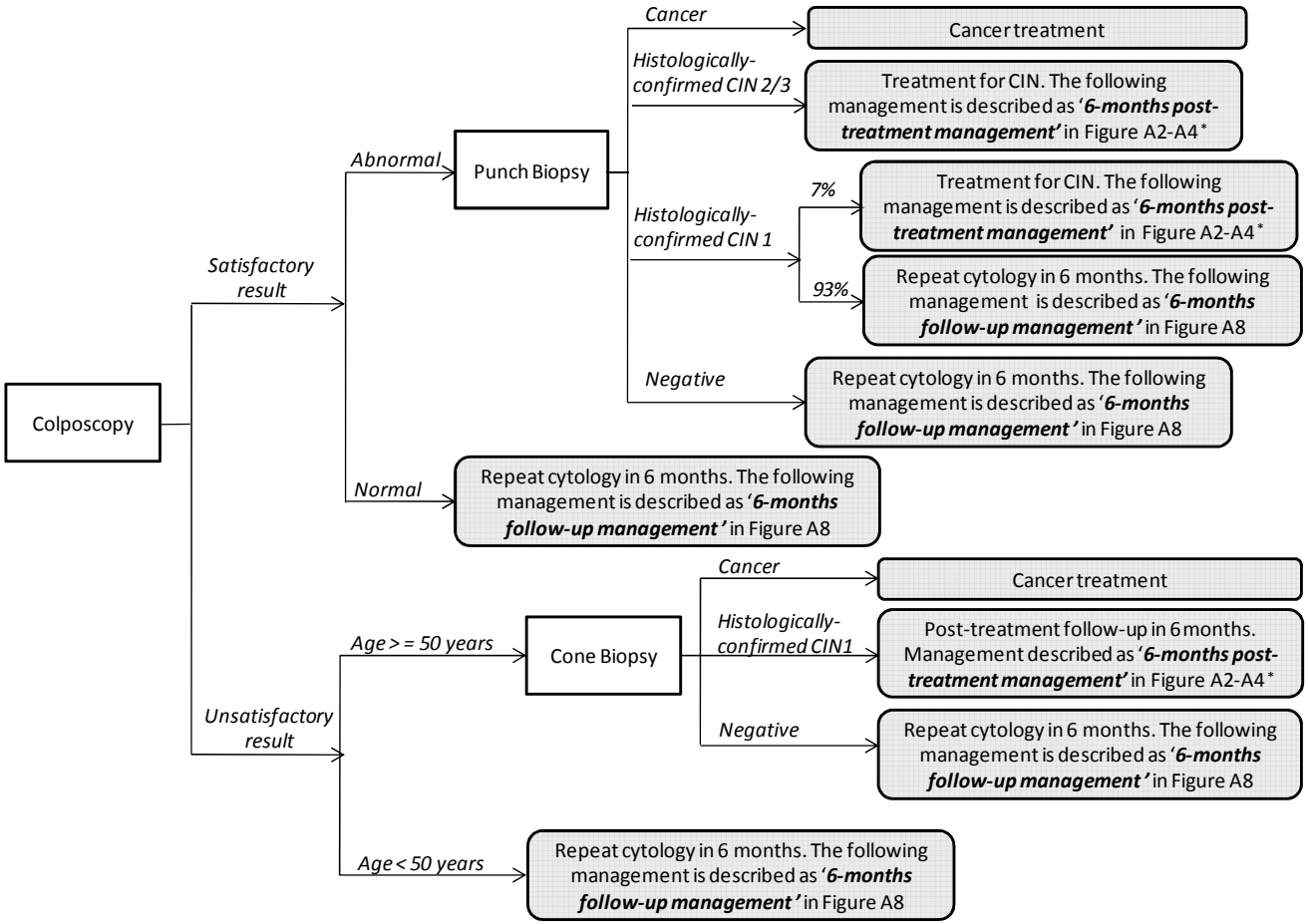


4.7 Routine post-colposcopy management

Routine post-colposcopy management is depicted in Figures A9 and A10. The structures were constructed according to the recommendations of the 2004 NHS guidelines.[10] Women referred with borderline or mild dyskaryosis who had satisfactory and normal colposcopy were followed at 6-months and were managed as shown in Figure A8. Women with satisfactory and abnormal colposcopy were further diagnosed with punch biopsy. Women diagnosed with invasive cervical cancer were referred to cancer treatment. Women with histologically-confirmed CIN2/3 were treated, as were 7% of women with histologically-confirmed CIN1 (consistent with observed data on women with confirmed CIN1 from the Sentinel Sites).[9] All women treated for CIN were followed at 6 months post-treatment, and managed according Figures A2, A3 and A4. The remaining women with histologically-confirmed CIN1 and all women with negative histology were referred to repeat cervical screening in 6 months and were managed as shown in Figure A8. Women with unsatisfactory colposcopy findings were managed as per women with satisfactory and normal colposcopy if they were aged less than 50 years; women aged 50 years or over were treated with cone biopsy. Among women who received cone biopsy treatment, women diagnosed with cancer were referred to cancer treatment; women diagnosed with histologically-confirmed CIN were referred to post-treatment follow-up in 6 months (described in Figures A2, A3 and A4); and women with negative histology were followed at 6 months follow-up as per women with satisfactory and normal colposcopy result.

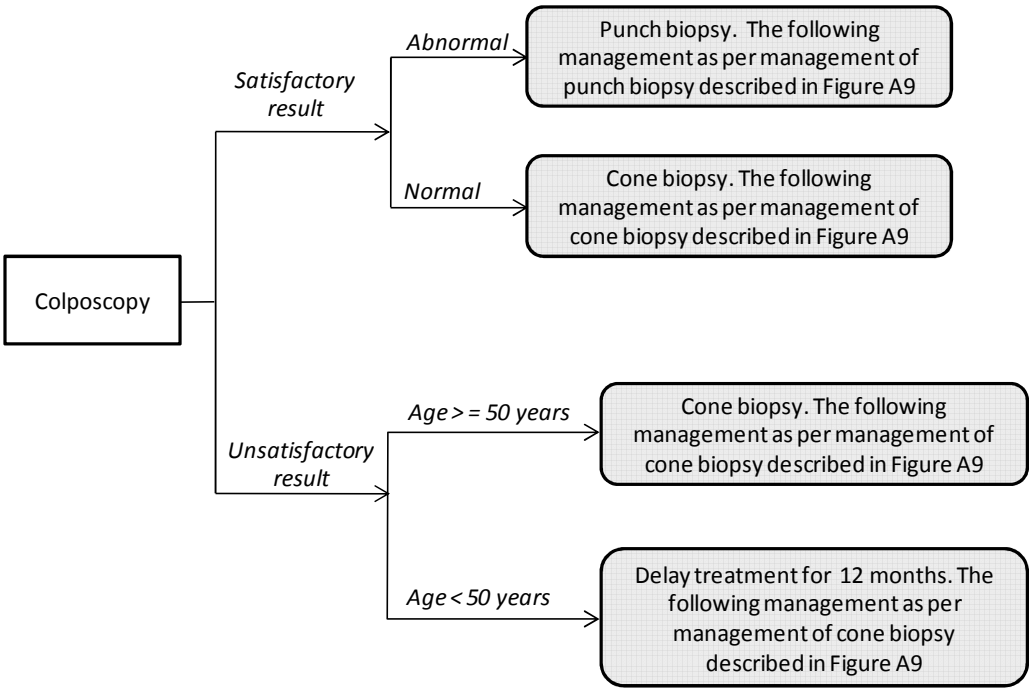
Women referred with moderate or severe dyskaryosis with a subsequent satisfactory but abnormal colposcopy were further diagnosed with punch biopsy; those with a satisfactory and normal colposcopy result or with unsatisfactory colposcopy findings were treated with cone biopsy, although women aged less than 50 years with unsatisfactory colposcopy findings were assumed to have the treatment delayed for 12 months.

Figure A9. Colposcopy management for women with borderline/mild cytology referral



* Depending on which management protocol is being modelled; see Figure A2 for cytological only follow-up; A3 for Sentinel Sites protocol; A4 for Extended Follow-up Protocol)

Figure A10. Colposcopy management for women with moderate/severe cytology referral



5. Model validation

5.1 CIN detected at the 6 month visit

Histological CIN status at 6 months post treatment was available from the HPV Sentinel Sites implementation study, and for a cohort of women treated for CIN in London, Manchester, and Aberdeen.[11] A summary of the range of CIN detection rates seen, considering in both studies, is shown in Table A5. The model predictions for CIN 1 and CIN 2+ at 6 months were within this observed range.

Table A5. Histologically detected* CIN at a follow-up visit 6 months after treatment

Group	CIN 1	CIN 2/3
All treated women	1.4 – 2.7%	0.9 – 1.2%**
Model prediction	*2.5%*	*1.2% (for CIN2+)*

Source: Kitchener 2008[11] and data from HPV Sentinel sites (personal communication Rachel Kelly, Institute of Cancer Research, London UK).

** Women were referred for colposcopy following a result of either cytology borderline dyskaryosis or worse, or a positive HPV test.*
***Based on rates of 0.4-0.6% for CIN2 and 0.5-0.6% for CIN3*

5.2 CIN detected at subsequent visits

Histological CIN status at 12 and 24 months post-treatment was available for a cohort of women treated for CIN in London, Manchester, and Aberdeen,[11] and at 6 years post-treatment for a cohort of women treated for CIN in British Columbia.[14] In order to compare model predictions with the data from British Columbia, we assumed an age and index diagnosis distribution in the treated cohort consistent with the primary analysis population (see Table A3), and restricted the comparison to exclude women treated with cryotherapy. Model predictions were consistent with these findings (Table A6).

Table A6. Histologically detected CIN 2+ at follow-up visits 12 and 24 months after treatment

Cumulative % with CIN2+ by:	Model prediction	Target	Source
12 months	*1.3 – 1.7%**	1.7%	[11]
24 months	*1.8 - 2.8%**	2.5%	[11]
6 years			
For treatment with LEEP only	*7.9%*	7.5% (95% CI: 6.6 – 8.3%)	[14]
Average for treatment with cone, LEEP, and laser		7.8%	[14]

* A range is presented based on varying compliance assumptions

Reference List

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