Cost-effectiveness of screening high-risk HIV-positive men who have sex with men (MSM) and HIV-positive women for anal cancer

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Cost-effectiveness of screening high-risk HIV-positive men who have sex with men (MSM) and HIV-positive women for anal cancer

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NIHR Health Technology Assessment programme

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Abstract

Cost-effectiveness of screening high-risk HIV-positive men who have sex with men (MSM) and HIV-positive women for anal cancer

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Background: Anal cancer is uncommon and predominantly a disease of the elderly. The human papillomavirus (HPV) has been implicated as a causal agent, and HPV infection is usually transmitted sexually. Individuals who are human immunodeficiency virus (HIV)-positive are particularly vulnerable to HPV infections, and increasing numbers from this population present with anal cancer.

Objective: To estimate the cost-effectiveness of screening for anal cancer in the high-risk HIV-positive population [in particular, men who have sex with men (MSM), who have been identified as being at greater risk of the disease] by developing a model that incorporates the national screening guidelines criteria.

Data sources: A comprehensive literature search was undertaken in January 2006 (updated in November 2006). The following electronic bibliographic databases were searched: Applied Social Sciences Index and Abstracts (ASSIA), BIOSIS previews (Biological Abstracts), British Nursing Index (BNI), Cumulative Index to Nursing and Allied Health Literature (CINAHL), Cochrane Database of Systematic Reviews (CDSR), Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, MEDLINE, MEDLINE In-Process & Other Non-Indexed Citations, NHS Database of Abstracts of Reviews of Effects (DARE), NHS Health Technology Assessment (HTA) Database, PsycINFO, Science Citation Index (SCI), and Social Sciences Citation Index (SSCI).

Study selection: Published literature identified by the search strategy was assessed by four reviewers. Papers that met the inclusion criteria contained the following: data on population incidence, effectiveness of screening, health outcomes or screening and/or treatment costs; defined suitable screening technologies; prospectively evaluated tests to detect anal cancer. Foreign-language papers were excluded. Searches identified 2102 potential papers; 1403 were rejected at title and a further 493 at abstract. From 206 papers retrieved, 81 met the inclusion criteria. A further treatment paper was added, giving a total of 82 papers included.

Data extraction: Data from included studies were extracted into data extraction forms by the clinical effectiveness reviewer. To analyse the cost-effectiveness of screening, two decision-analytical models were developed and populated.

Results: The reference case cost-effectiveness model for MSM found that screening for anal cancer is very unlikely to be cost-effective. The negative aspects of screening included utility decrements associated with false-positive results and with treatment for high-grade anal intraepithelial neoplasia (HG-AIN). Sensitivity analyses showed that removing these utility decrements improved the cost-effectiveness of screening. However, combined with higher regression rates from low-grade anal intraepithelial neoplasia (LG-AIN), the lowest expected incremental cost-effectiveness ratio remained at over £44,000 per quality-adjusted life-year (QALY) gained. Probabilistic sensitivity analysis showed that no screening retained over 50% probability of cost-effectiveness to a QALY value of £50,000. The screening model for HIV-positive women showed an even lower likelihood of cost-effectiveness, with the most favourable sensitivity analyses reporting an incremental cost per QALY of £88,000.

Limitations: Limited knowledge is available about the epidemiology and natural history of anal cancer, along with a paucity of good-quality evidence concerning the effectiveness of screening.

Conclusions: Many of the criteria for assessing the

need for a screening programme were not met and the cost-effectiveness analyses showed little likelihood that screening any of the identified high-risk groups would generate health improvements at a reasonable cost.

Further studies could assess whether the screening model has underestimated the impact of anal cancer, the results of which may justify an evaluative study of the effects of treatment for HG-AIN.

Contents

List of abbreviations

AIDS	acquired immune deficiency syndrome
AIN	anal intraepithelial neoplasia
APE	abdominoperineal excision
AR	anterior resection
ASCUS	atypical squamous cells of undetermined significance
ASIL	anal squamous intraepithelial lesion
CIN	cervical intraepithelial neoplasia
CMT	combined modality therapy
DSS	disease-specific survival
EORTC	European Organisation for Research and Treatment of Cancer
EUS	endosonographic ultrasonography
FUMIR	5-fluorouracil, mitomycin C and radical radiation therapy
GU	genitourinary
HAART	highly active antiretroviral therapy
HDR	high dose rate
HG-AIN	high-grade anal intraepithelial neoplasia
HGD	high-grade dysplasia
HIV	human immunodeficiency virus
HPA	Health Protection Agency
HPV	human papillomavirus
HRA	high-resolution anoscopy
HSIL	high-grade squamous intraepithelial lesion
ICD-O	*International Classification of Diseases for Oncology*
ICQ	incremental cost per QALY gained
LG-AIN	low-grade anal intraepithelial neoplasia
LSIL	low-grade squamous intraepithelial lesion
MSM	men who have sex with men
NCI	National Cancer Institute
NPV	negative predictive value
NSC	National Screening Committee
OR	odds ratio
PCR	polymerase chain reaction
PPV	positive predictive value
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
RR	relative risk
RT	radiotherapy

SCC	squamous cell carcinoma	STI	sexually transmitted infection
SCCA	squamous cell cancer of the anus	TCR	Thames Cancer Registry
SCCIS	squamous cell carcinoma in situ	TNM	tumour, node, metastasis [staging system]
SEER	Surveillance Epidemiology and End Results	TRUS	transrectal ultrasound
SFGH	San Francisco General Hospital Cohort Study	UAI	unprotected anal intercourse
SFMHS	San Francisco Men's Health Study	UCSF	University of California, San Francisco
SIL	squamous intraepithelial lesion	UKCCCR	United Kingdom Co-ordinating Committee for Cancer Research
SIR	standard incidence rate	VOI	value of information
STD	sexually transmitted disease	WCISU	Welsh Cancer Intelligence and Surveillance Unit

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

Introduction

Anal cancer is an uncommon cancer. It is a disease in which cancer (malignant) cells are found in the anus. Like most cancers, anal cancer is best treated when it is diagnosed soon after it develops. Primary treatment is generally concomitant radiotherapy (RT) and chemotherapy (if tolerated) to preserve the anal sphincter, but, despite these approaches, local disease failure is considerable and requires salvage radical surgery, which is associated with high morbidity and mortality. Anal cancer is predominantly a disease of the elderly and its occurrence is near to zero in early life. The human papillomavirus (HPV) has been implicated as a causal agent of anal cancer. HPV infection, for the majority of cases, is transmitted sexually. The vulnerability of individuals with human immunodeficiency virus (HIV) to HPV infections has seen an increase the number of cases from this population presenting with anal cancer.

To decide whether the screening of groups of people for a specific condition is suitable, there are well-defined criteria that can be used to aid the decision process. The condition is an important health problem, and the natural history and epidemiology must be understood. The test itself should be safe, simple, accurate and acceptable to the general population.

Aim of the review

The aim of this review is to estimate the cost-effectiveness of screening for anal cancer in men and women who are HIV positive, and, in particular, men who have sex with men (MSM), who have been identified as being at greater risk of the disease, by developing a model that incorporates the national screening guidelines criteria.

Methods

Systematic literature reviews were undertaken of the epidemiology and natural history of anal cancer, screening technologies and screening policies, and cost-effectiveness of candidate technologies/programmes/policies. Two decision-analytical models were developed and populated to analyse the cost-effectiveness of screening in HIV-positive and HIV-negative MSM, and in HIV-positive women.

Results

The reference case cost-effectiveness model for MSM found that screening for anal cancer is very unlikely to be cost-effective. In the reference case, the individually minor, but relatively frequent, negative aspects of screening, including utility decrements associated with false-positive results and with treatment for high-grade anal intraepithelial neoplasia (HG-AIN), outweigh the larger and rarer positive effects of the prevention or early diagnosis of anal cancer.

Sensitivity analyses showed that removing the utility decrements associated with false-positive results and with treatment for HG-AIN improved the cost-effectiveness of screening. However, combined with higher regression rates from low-grade anal intraepithelial neoplasia (LG-AIN), the lowest expected incremental cost-effectiveness ratio remained at over £44,000 per quality-adjusted life-year (QALY) gained. With these assumptions in place, probabilistic sensitivity analysis showed that no screening retained over 50% probability of cost-effectiveness to a QALY value of £50,000.

The screening model for HIV-positive women showed an even lower likelihood of cost-effectiveness, with the most favourable sensitivity analyses reporting an incremental cost per QALY of £88,000.

Conclusions

From the review sections of this report, it is clear that many of the criteria for assessing the need for a population screening programme (UK National Screening Committee 2006) have not been met for anal cancer. There is limited knowledge about the epidemiology and natural history of the disease,

along with a paucity of good-quality evidence concerning the effectiveness of screening for anal cancer. The absence of such data, combined with the possible reluctance of high-risk groups to attend an anal cancer screening programme, makes introduction of population-based screening for anal cancer difficult.

The reported cost-effectiveness analyses of screening for anal cancer emphasise this conclusion. The results show little likelihood that screening any of the identified high-risk groups will generate health improvements at reasonable cost. These results could be further confirmed by updating some key parameters at little additional cost. The most efficient way to proceed would be to audit the accuracy of the cancer registries' identification of cases of anal cancer, as well as to audit the proportion of cancer cases that occur in HIV-positive men and HIV-positive women, and/or MSM. If these data show that the screening model has underestimated the impact of anal cancer in any of the populations evaluated then an evaluative study of the effects of treatment for HG-AIN may be justified.

Chapter 1
Introduction

Introduction

Anal cancer is an uncommon cancer. It is a disease in which cancer (malignant) cells are found in the anus. Like most cancers, anal cancer is best treated when it is diagnosed soon after it develops. Primary treatment is generally concomitant radiotherapy (RT) and chemotherapy (if tolerated) to preserve the anal sphincter, but, despite these approaches, local disease failure is considerable, and requires salvage radical surgery with associated high morbidity and mortality. Anal cancer is predominantly a disease of the elderly and is near to zero in early life. The human papillomavirus (HPV), has been implicated as a causal agent of anal cancer. HPV infection, for the majority of cases, is transmitted sexually. The vulnerability of individuals with human immunodeficiency virus (HIV) to HPV infections has seen an increase in the number of cases from this population presenting with anal cancer.

To decide whether the screening of groups of people for a specific condition is suitable, there are well-defined criteria that can be used to aid the decision process.[1] The condition should be an important health problem, and the natural history and epidemiology must be understood. The test itself should be safe, simple, accurate and acceptable to the general population.

Aim of the review

The aim of this review is to estimate the cost-effectiveness of screening for anal cancer in men and women who are HIV positive, and, in particular, men who have sex with men (MSM), who have been identified as being at greater risk of the disease, by developing a model that incorporates all of the above criteria.

Epidemiology

Cancer is predominantly a disease of the elderly, with overall crude rates of cancer registrations of 462 per 100,000 of the population for males and 451 per 100,000 of the population for females in England for 2003,[2] with anal cancer being no exception. Anal cancer is a rare disease; in 2003 there were 722 registrations of newly diagnosed malignant neoplasm of anus and anal canal in England, with 291 of registrations being male and 431 female.[2] Anal cancer is also very much a cancer of the elderly, with 37% (108) of males with newly diagnosed anal cancer being aged 65 or over and 56% (241) of females with newly diagnosed anal cancer being aged 65 or over.[2] For anal cancer, the rate per 100,000 of the general population in England 2003 was 1.2 per 100,000 for males and 1.7 per 100,000 for females (*Table 1*).[2]

Incidence of anal cancer

Johnson *et al.*[3] reported that the incidence rate for anal cancer in the USA was 2.04 per 100,000 for men and 2.06 per 100,000 women, based on data collected between 1973 and 2000 on diagnosis and outcomes of invasive and in situ anal cancer. The data came from the Surveillance Epidemiology and End Results (SEER) programme (see Appendix 1), a system of population-based tumour registries in the USA. The rate for US males is almost double the rate of English males, whereas the rate for US females is slightly higher than that of English females.

TABLE 1 *Anal cancer: new cases (England 2003)*

	Rate per 100,000	Total new cases	Percentage aged 65 years or over
Males	1.2	291	37
Females	1.7	431	56
Compiled from data from the Office for National Statistics.[2]			

Karandikar *et al.*[4] undertook a retrospective audit of the squamous (epidermoid) type of anal cancer diagnosed and treated in the principality of Wales over a 5-year period (1995–99), with follow-up until 2005. Patients diagnosed with anal cancer were identified from the Welsh Cancer Registry, Welsh Cancer Intelligence and Surveillance Unit (WCISU) database, and pathology records from 17 hospitals and five oncology units. Overall, 149 patients with anal cancer were identified from the WCISU and hospital pathology databases. Thirteen patients with adenocarcinoma involving the anal canal with or without involvement of the rectum, two patients with melanoma and one with a neuroendocrine tumour of the anal canal were excluded, leaving a cohort of 133 patients. The annual incidence rate of anal cancer from this audit of the principality of Wales was 1.3 per 100,000.

In 1990, Scholefield *et al.*[5] reported that anal cancer was a rare tumour in Britain, with no published epidemiology studies from this country. Scholefield *et al.*[5] reported 1988 statistics showing 250–300 cases of anal cancer per year. Scholefield *et al.*[5] undertook a retrospective study of anal cancer registrations, with colon cancer as controls, from Thames, West of Scotland and West Midlands Cancer Registries. Colorectal cancer was chosen as a control as there was no evidence that a sexual transmission agent is involved in its aetiology. Anonymous details for all anal and colorectal cancers for a 13-year period (1975–87) were obtained from the previously mentioned registries. Scholefield *et al.*[5] collected information on gender, marital status and 5-year age group.

Scholefield *et al.*[5] reported that from the Thames Cancer Registry (TCR) there were 846 cases of anal cancer and 26,359 cases of colon cancer, 182 cases of anal cancer and 9613 cases of colon cancer from the West of Scotland Registry and 288 cases of anal cancer and 11,905 cases of colon cancer from the West Midlands Cancer Registry. This gave a total of 1316 cases of anal cancer and 47,877 cases of colon cancer for the 13-year period.

In 1993, Frisch *et al.*[6] reported the findings of a descriptive epidemiological study based on data from the Danish Cancer Registry. The aim of the study was to examine long-term trends in incidence of anal cancer in a well-monitored, unselected population. The Danish Cancer Registry has recorded all cases of cancer in Denmark since 1943 (only invasive non-adenocarcinoma and non-melanoma anorectal cancers were included in the study) and 888 cases of anal cancers (303 men and 585 women) were identified.

Frisch *et al.*[6] reported that since around 1960 the incidence rates had nearly doubled in men and tripled in women. Data for 1983–7 gave incidence rates of 0.38 per 100,000 for men and 0.74 per 100,000 for women (world standardised).

Gatta *et al.*[7] gave details on survival and incidence from rare cancers (defined as those with an annual crude incidence rate of less than 2 per 100,000 for both sexes combined) in 2006, based on data of 39 adult cancer registries for 59,021 patients aged 15–99 years, diagnosed with a selected rare cancer between 1983 and 1994. Data were collected from 18 European countries. Gatta *et al.*[7] reported that for the UK (England, Scotland and Wales) there was a crude incidence rate of anal squamous cell carcinoma (SCC) of 0.73 per 100,000 and a world-standardised incidence rate of 0.51 per 100,000.

Table 2 displays the available evidence over the years of reported anal cancer incidence rates, and number of new cases. Care needs to be taken in evaluating the table as data are drawn from different sources and presented in different formats, for example age-standardised rates and non-standardised rates. Given that anal cancer is a rare disease, it would indicate that anal cancer is not a significant burden of disease in the population. The criteria for appraising screening programmes[1] (Appendix 2) identify that the first criterion to be satisfied before screening for a specific condition is that the condition should be an important health problem. Screening for anal cancer would identify only a low number of cases.

Incidence rate by age and gender

The probability of developing anal cancer rises sharply with age and the UK population is ageing. In young people, the risk is very low, but between the ages of 55 and 65 the annual incidence rate is approximately 3 per 100,000 for both males and females. Amongst those aged between 75 and 84 years, the annual incidence rate is over 5 per 100,000 and over 6 per 100,000 per year for males and females, respectively. *Figure 1* shows the age-specific incidence rate for anal cancer, based on data from the Office of National Statistics.[2]

The annual incidence rate (directly age-standardised rates) has remained constant over the last decade, remaining at around 1.0 per 100,000

TABLE 2 *Anal cancer: general population*

Study details	Study type	Country	New cases per year	Annual incidence per 100,000 population		
				General	Males	Females
Scholefield *et al.* 1990[5]	Retrospective cohort study	Britain	250–300	–	–	–
Frisch *et al.* 1993[6]	Descriptive epidemiological study	World	–	–	0.38[a]	0.74[a]
Chiao *et al.* 2005[8]	Population-based analysis	USA, 1973–81	–	0.60[b]	–	–
		USA, 1982–95	–	0.80[b]	–	–
		USA, 1996–2001	–	1.00[b]	–	–
Office of National Statistics[2]	Registry data	England, 2003	722	1.20	1.10[b]	1.30[b]
Johnson *et al.* 2004[3]	Population-based analysis	USA, 1973–2001	–	–	2.04[b]	2.06[b]
Karandikar *et al.* 2006[4]	Registry data	Wales, 1995–99	–	1.30	–	–
Gatta *et al.* 2006[7]	Registry data	UK, 1983–94	–	0.51[a]	–	–

a World standardised.
b Age standardised.

for males. For females, there has been a slight rise in directly age-standardised rates from the late 1990s, rising from around 1.0 per 100,000 to around 1.2 per 100,000 (*Figure 2*).

In 2006, Brewster and Bhatti[9] publicised the findings of their study describing secular trends in incidence of SCC of the anus in Scotland, before and during the HIV epidemic. Incidence cases of malignant neoplasms of the anus and anal canal
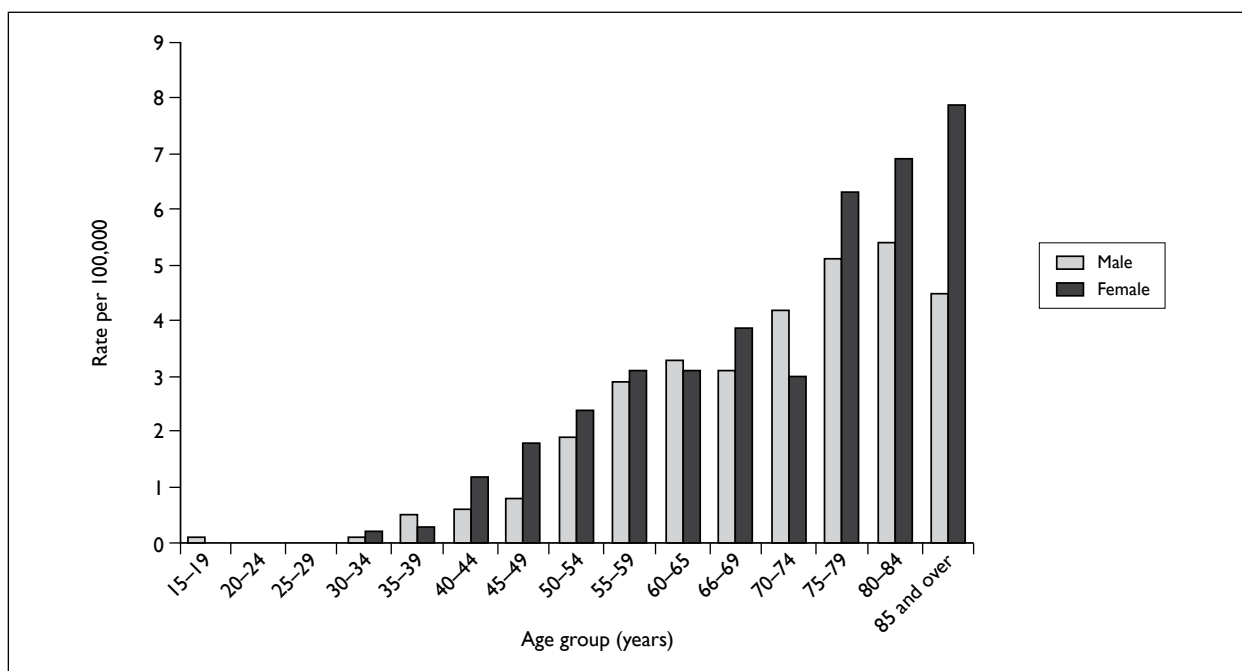
FIGURE 1 *Annual incidence rate per 100,000 for newly diagnosed anal cancer by gender and age in England 2003. Compiled from data from the Office for National Statistics.*[2]
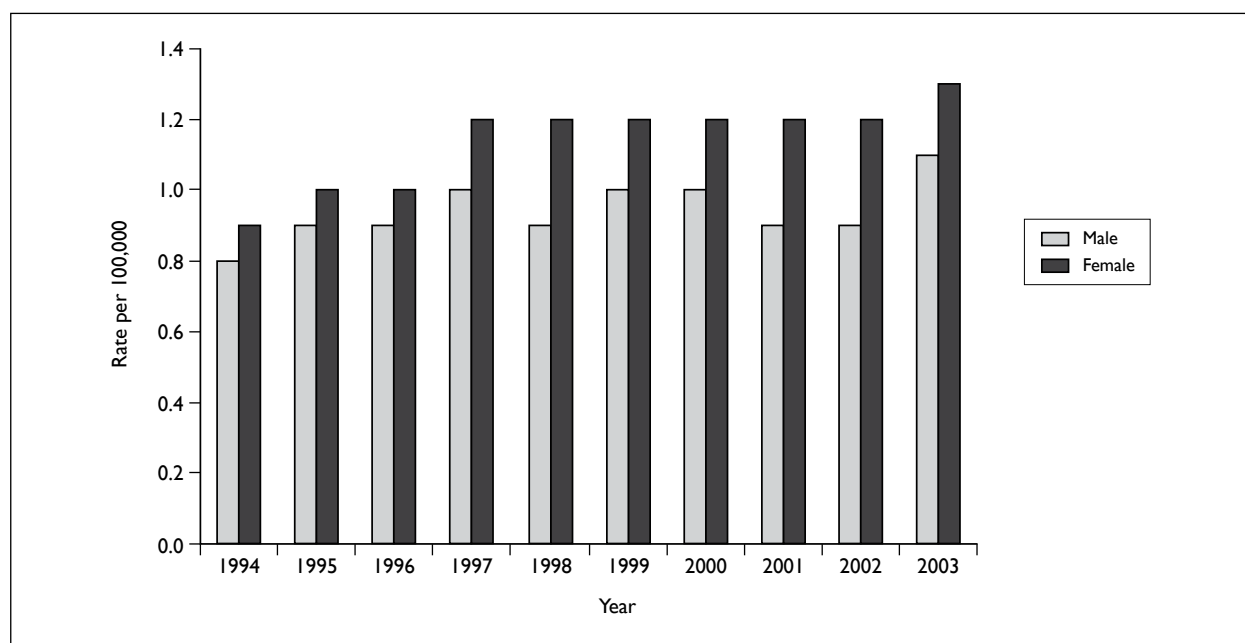
FIGURE 2 *Directly age-standardised rate per 100,000 for newly diagnosed anal cancer by gender in England 1994–2003. Compiled from data from the Office for National Statistics.*[2]

were extracted from the Scottish Cancer Registry for the years 1975–2002. Brewster and Bhatti[9] identified 757 cases of SCC (278 males and 479 females) registered, with an incident date falling within the 28-year period of the study. The authors found that in males the standardised incidence rate per 100,000 increased from 0.14 to 0.17 in the late 1970s to around 0.37 in the late 1990s, with a peak of 0.44 in the period 1993–7. For females, the incidence rate was generally higher, increasing from 0.23–0.27 in the late 1970s to a peak of 0.55 in the period 1998–2002.

Incidence by marital status

Scholefield *et al.*[5] reported that the odds ratio (OR) for never-married men compared with ever-married men was 2.2 [95% confidence interval (CI) 1.8 to 2.8] and the OR for never-married women compared with ever-married women was 0.6 (95% CI 0.5 to 0.8). The authors concluded that there is a clear increase in the risk of anal cancer among never-married men.

Frisch *et al.*[6] examined incidence according to marital status, using a nested case-controlled design in which all anal cancer patients ($n = 888$) served as cases and all patients with colon cancer ($n = 54,207$) and stomach cancer ($n = 58,198$) were used as controls. The authors found that 17% (53 of 303) of men with anal cancer had never married, compared with 7% (1790 of 24,420) of never-

married men with colon cancer and 9% (2877 of 33,248) of never-married men with stomach cancer. Among women the figures were 11% (64 of 585) anal cancer, 13% (3898 of 30,787) colon cancer, and 12% (2859 of 24,062) stomach cancer. The adjusted ORs were 2.7 (95% CI 2.0 to 3.6) for men and 1.0 (95% CI 0.8 to 1.3) for women, with colon cancer as control, and 2.1 (95% CI 1.5 to 2.8) for men and 1.2 (95% CI to 0.9–1.6) for women with stomach cancer as control. The authors of this study[6] concluded that men who had never married were found at increased risk since the 1940s, indicating a potential association with male homosexuality.

Rabkin and Yellin[10] reported in 1994 the results of a study to determine the types and rates of cancers occurring in excess in the presence of HIV-1 infection. The National Cancer Institute's (NCI) SEER registry data (Appendix 1) was used to identify never-married men aged 25–54 years living in the San Francisco area and whom were HIV-1 seropositive as of late 1984. Age-, race- and sex-specific populations of San Francisco for the years 1973 to 1990 were obtained from Census data and for the period between Census dates they were estimated. For the study period of interest, there were 1,390,000 person-years of observation of the never-married men, 25–54 years of age, living in the San Francisco population. Expected cancers were calculated from age-, race- and period-specific cancer incidence rates of the entire male SEER population for the periods 1973–9 [defined

as the pre-acquired immune deficiency syndrome (AIDS) period], 1980–4, 1985–7 and 1988–90.

Rabkin and Yellin[10] study showed that in the pre-AIDS period, the incidence of anal cancer in the never-married, 25- to 54-aged San Francisco men group was 3.5 per 100,000. This was 9.9 (95% CI 4.5 to 18.7) times the expected rate of the total male SEER population for that period. By 1988–90, the standardised incidence had increased to 5.9 per 100,000 for the never-married 25- to 54-aged San Francisco men group. The SEER population rates, however, had similarly increased and the observed–expected ratio remained almost unchanged at 10.1 (95% CI 5.0 to 18.0). The authors concluded that HIV-1 is not related to the increase risk of anal cancer in homosexual men that antedated the AIDS epidemic.

Anal cancer and HIV/AIDS

In 2005, Diamond et al.[11] reported on a study that linked cancer registry data from 1988 to 2000 and AIDS registry data from 1981 to 2003 for San Diego County, USA. The authors defined 1991–5 as the pre-highly active antiretroviral therapy (HAART) era and 1996 to 2000 as the post-HAART era. The authors identified 42 men with SCC of the anus. The authors found that amongst men aged 25–64 years with AIDS, the average annual incidence of anal cancer pre-HAART was 88 per 100,000 and post-HAART, 190 per 100,000. They further reported that the annual incidence of invasive anal cancer increased from 0 per 100,000 men aged 25–64 years with AIDS in 1991 to 2224 per 100,000 in 2000. Pre-HAART, the average annual incidence of invasive anal cancer was 49 per 100,000 men aged 25–64 years with AIDS, whereas post HAART it was 144 per 100,000. It was also reported that patients diagnosed with anal cancer during the post-HAART era had a longer duration of diagnosed HIV infection (84 months vs 22 months pre-HAART).

For post-HAART anal cancer, both invasive and in situ, Diamond et al.[11] reported an average incidence of 190 per 100,000 men aged 25–64 years with AIDS (95% CI 209 to 646) compared with men without HIV/AIDS. The authors did acknowledge that the numbers of cases in the study were small but that the information had been collected for more than a decade from both registries.

In 2005, Chiao et al.[8] reported a population-based analysis of temporal trends in the incidence of squamous cell cancer of the anus (SCCA) in relation to the HIV epidemic. Chiao et al.[8] obtained data from the SEER programme, from 1973 to 2001 to characterise the primary site, histology [classified according to the *International Classification of Diseases for Oncology*, version 3 (ICD-O3)], tumour site, stage at diagnosis, initial radiation therapy, patient demographics, age, gender, race and/or ethnicity, and mortality. Tumours with anatomic sites coded C21.0 through to C21.1 and C21.8 (anus, anal canal and anorectum) were included. The analysis was limited to cases with histological types coded as invasive non-in situ epidermoid cancers according to the ICD-O3. In situ cases were included only in the analysis describing stage at diagnosis.

Chiao et al.[8] used three eras to group the years of diagnosis. As the first case definition of AIDS was adopted in 1982, the period 1973–81 was defined as the pre-HIV era. The years 1982–95 were defined as the HIV era. HAART was widely introduced in 1996, and the years 1996–2001 were defined as the HAART era. A total of 4855 cases on invasive SCCA were reported from 1973 to 2001. The overall incidence from 1973 to 2001 was 0.8 per 100,000 population, an increase from 0.6 (95% CI 0.6 to 0.7) in the pre-HIV era to 0.8 (95% CI 0.8 to 0.8) in the HIV era, and to 1.0 (95% CI 1.0 to 1.1) in the HAART era.

The conclusions reached by Chiao et al.[8] were that the incidence of SCCA has increased steadily over the past three decades, and that since the introduction of HAART the incidence of SCCA has risen particularly among men and younger individuals – the groups most affected by HIV.

Grulich et al.[12] undertook a cohort study involving an Australian nationwide linkage of HIV, AIDS and cancer registry data to describe the incidence of non-AIDS-defining cancers in people with HIV infection before and after the occurrence of AIDS, and to examine the association of cancer risk with immune deficiency. In Australia, HIV and AIDS are reported with a name code (first two letters of first and last name), date of birth and sex. The authors attempted linkage for all of those individuals who had complete data for these three fields on either the national HIV or AIDS database. The procedure of linkage with the cancer register was not fully described, but a link to a paper giving details was given. Briefly, linkage was performed using a modified version of the National Cancer Register, with full names converted to name codes. A match was accepted if there was an exact match on all three fields, or there was a near match supported by consistency between the registers in dates of death and area of residence. Linkage

was performed separately for the HIV and AIDS databases. HIV and AIDS data were available up to December 1999, and cancer data until 1995–98 depending on jurisdiction.

Grulich *et al.*[12] reported that 10 cases were observed for cancer of the anus compared with the expected number of cases of 0.27. The standard incidence rate (SIR) was 37.1 (95% CI 17.8 to 68.3), significant at $p < 0.05$. The author's conclusions were that, in this study, anal cancer rates increased from HIV diagnosis to the time around AIDS diagnosis, but there were no diagnoses more than 6 months after AIDS. Even in people with the mildest degree of immune deficiency the rates of this cancer were increased 20-fold above what was expected. The authors acknowledged that the data did not support an independent association between invasive anal cancer and HIV-associated immune deficiency but it may be that prolonged observation will be necessary.

In 2000, Frisch *et al.*[13] described a study looking at lifestyle factors associated with HPV-associated malignancies. The authors studied invasive and in situ HPV-associated cancers amongst 309,365 patients with HIV infection/AIDS in the USA, 5 years before the date of AIDS onset and 5 years after. Between 1995 and 1998, data from AIDS and cancer registries in 11 state and metropolitan locations were linked; these states and locations contained approximately one-third of the US population.

Among both male and female patients with AIDS, the majority were aged between 20 and 49 years at AIDS onset (88% and 86%, respectively). Of the males in the study, HIV infection was via homosexual contact (56%), homosexual contact and intravenous drug use (6%), intravenous drug use (26%), heterosexual contact (3%) or unknown/other (9%).

Frisch *et al.*[13] reported that invasive and in situ anal cancers were present in 360 patients (239 were invasive cancer and 121 in situ), with a mean age at onset of 41 years for invasive anal cancer and 37 years of in situ anal cancer. For invasive anal cancer, the relative risk (RR) was 6.8 (95% CI 2.7 to 14.0) for females and 37.9 (95% CI 33.0 to 43.4) for males. For in situ anal cancer, the RR was 7.8 (95% CI 0.2 to 43.6) for females and 60.1 (95% CI 49.2 to 72.7) for males.

Anal cancer and HPV

Hemminki and Dong[14] used the Swedish Family-Cancer Database to analyse the spectrum of cancers diagnosed in husbands of women with in situ or invasive cervical cancer, and compared these to second carcinogenic events in women presenting with these cancers. The author's hypothesis was that there was increased cancer susceptibility from HPV. The Swedish Family-Cancer Database (which includes all persons born in Sweden after 1934 with their biological parents, some 9.6 million individuals). From this database the authors identified 313,602 men with cancer after the birth of their last child; 6839 were men whose wife was diagnosed with in situ cervical cancer, and 2813 were men whose wife was diagnosed with invasive cervical cancer. Women (117,921 with in situ cervical cancer and 17,579 with invasive cervical cancer) were followed for second events (i.e. first cancer after in situ cancer and second primary cancer after first primary cancer) until the end of 1996, resulting in 7455 women with first cancers (after in situ cervical cancer) and 1990 women with second primaries (after invasive cervical cancer).

Hemminki and Dong[14] reported that for wives with in situ cervical cancer, the husbands had an excess of cancer at six sites: upper aerodigestive tract (including mouth, tongue, larynx and pharynx), stomach, anus, lung, kidney and connective tissue, with anal cancer showing the highest SIR of 1.75. Penile cancer showed an SIR of 1.30 (95% CI 0.91 to 1.77). These sites agreed with first cancers of women who had suffered from an in situ cervical cancer. SIRs for female cancers were high for anus (3.60), lung (2.08) and other tobacco-related sites. The authors concluded that the results suggest that female cervical cancer, probably through HPV infection, is associated with anal and, weakly, with penile cancer in husbands. There was a consistency in husbands' anal cancers irrespective of wives' in situ or invasive cervical cancer. The authors reported that the findings are consistent with the demonstrated associations between HPV infection, sexual activity and anal cancer in men and women.

In 2002, De Sanjose and Palefsky[15] undertook a review to summarise recently published epidemiological information that contributed to understanding the natural history of cervical and HPV infection and their associated lesions among HIV-infected women and men. De Sanjose and Palefsky[15] concluded that HIV-positive women and men are more likely to be infected with oncogenic HPV types and to have cervical intraepithelial

neoplasia (CIN) or anal intraepithelial neoplasia (AIN) lesions that may lead to invasive cervical and anal cancer, respectively.

Anal cancer and homosexual partnerships

In 2003, Frisch et al.[16] undertook a retrospective cohort study of 1614 women and 3391 men in Denmark for cancer from their first registration for marriage-like homosexual partnership between 1989 and 1997. The authors used data from the population-based Danish Cancer Registry to investigate the cancer profile of all men and women in Denmark who had one or more records of registered homosexual partnership between 1989 and 1997. The Civil Registration System in Denmark has kept continuously updated files on basic demographic variables of its citizens. The system uses a unique 10-digit personal identification number as key – recorded information includes name, date of birth, marital status, emigration and vital status since 1968.

Frisch et al.[16] reported that for women in registered homosexual partnerships, no incidences of anal cancer were identified and that overall cancer incidence among this group differed little from that of Danish women in general (RR = 0.9, 95% CI 0.6 to 1.4, n = 24 cancers). For men, the overall risk of cancer among 3391 men in registered homosexual partnerships increased twofold (RR = 2.1, 95% CI 1.8 to 2.5, n = 139). The authors reported that this excess was almost entirely due to high numbers of Kaposi's sarcoma (RR = 136, 95% CI 96 to 186, n = 38) and non-Hodgkin's lymphoma (RR = 15.1, 95% CI 10.4 to 21.4, n = 32) cases. A statistically significant excess was also seen for anal squamous carcinoma (RR = 31.2, 95% CI 8.4 to 79.8, n = 4).

Frisch et al.[16] concluded that apart from HIV/AIDS-associated cancers and anal squamous carcinoma in men, Danish men and women in registered homosexual partnerships appear not to be at any unusual cancer risk compared with the general population.

In 1999, Lacey et al.[17] reported on a prospective cohort study of HIV-positive homosexual men. A total of 57 subjects were recruited from a larger cohort [300 patients, 33% Centre for Disease Control and Prevention (CDC) group C] attending North Manchester General Hospital for their HIV care in January 1994 and were followed for 18 months.

The participants in the Lacey et al.[17] study were interviewed and underwent screening for sexually transmitted diseases (STDs), anal cytology and HPV at enrolment and at subsequent follow-up visits, with anoscopy and biopsy at the final visit. The study end point with anoscopy and biopsy was reached by 38 participants. The average follow-up was 17 months (range 14–21 months, total 650 months); 184 outpatient visits were attended and 184 cytology and HPV specimens were available for analysis.

Lacey et al.[17] concluded that AIN and infection with multiple oncogenic HPV types are very common among immunosuppressed HIV-positive homosexual men. Apparent progression from low to high-grade cytological changes occurred over a short follow-up period, with no cases of carcinoma. All 23 cases of high-grade anal intraepithelial neoplasia (HG-AIN) were predicted by cytology and/or anoscopy. The authors further concluded that it appears that anoscopy and cytology could be a useful screening procedure in the detection of high-grade disease in immunosuppressed HIV-positive homosexual men, but questions remain to be answered about the significance of HG-AIN in this group of patient, it seems wise to urge caution when considering screening programmes until more data about the natural history and efficacy of treatment options are known.

HPV infection

The natural history of HPV infection is complex, and clearance and persistence of viral DNA, along with progression to squamous intraepithelial lesions (SILs), vary depending on the viral type and patient characteristics, such as age and immune status.[18]

Palefsky et al.[19] reported in 1998 the findings of a cohort study to characterise the prevalence of 29 different HPV types and the mixture of 10 additional types in the anal canal among HIV-positive and HIV-negative men. Palefsky et al.[19] recruited 346 HIV-positive and 262 HIV-negative men from among homosexual and bisexual men in the San Francisco Men's Health Study (SFMHS) in the San Francisco General Hospital Cohort Study (SFGH) and the University of California, San Francisco (UCSF), responding to newspaper advertisements. The participants were interviewed regarding their medical history, prescribed drug use, X-ray exposure, hospitalisation, transfusions, history of sexually transmitted diseases, intestinal

parasites, hepatitis anal conditions (such as fissures and fistulas) and symptoms related to HIV. The participants were also asked about sexual practices, cigarette smoking, drinking and recreational drug use. Participants also tested underwent HPV testing. Palefsky *et al.*[19] reported no differences between HIV-positive and HIV-negative men.

Kreuter *et al.*[20] conducted a prospective cohort study in Germany to determine the clinical spectrum of AIN and lesional HPV colonisation in a cohort of homosexual men who were HIV-positive and had a history of receptive anal intercourse. Between December 2003 and July 2004, 103 homosexual men with a laboratory-confirmed diagnosis of HIV were recruited for a screening programme for AIN. The participants underwent a standardised interview on medical history, STDs, history of HPV-related diseases and tobacco use before screening.

Kreuter *et al.*[20] reported that of all patients 86% had anal HPV infection at their first visit. AIN was diagnosed in 20 (19.4%) of the 103 participants. The authors concluded that their data confirmed the high incidence and prevalence of inpatients with AIN who are HPV positive with HIV infection. The authors of this paper were of the opinion that standardised screening programmes for anal cancer prevention and treatment protocols for AIN in patients infected with HIV must be implemented.

Watson *et al.*[21] in 2006 reported on a prospective cohort of 72 patients (52 women, 20 men) who were diagnosed with AIN between January 1996 and December 2004. These 72 patients, from a single institution in New Zealand, were identified from a prospective database. Data collected from the database were supplemented with information from patient chart review, which included data on age, sex, HIV/AIDS infection, chronic immunosuppression, disease presentation, management and follow-up. All patients underwent biopsy or perianal skin excision between January 1996 and July 2005; 17 patients were initially diagnosed with AIN 1, 10 with AIN 2, and 45 with AIN 3 on first biopsy. A total of 42 patients also had pathological changes that were consistent with HPV infection. Seven patients were recipients of renal transplants and were on immunosuppressive therapy. Five patients were HIV positive and 10 others were on long-term immunosuppressive therapy for other causes.

Watson *et al.*[21] detailed that, during the study period, 193 procedures were carried out (127 were

biopsies only and 66 were perianal skin excisions). Eight patients progressed to develop SCC during the study period (median time 42 months). There was histological evidence of progression in 11 patients, with six patients having AIN 3 progressing to have anal SCC. Two patients with AIN 2 developed cancer and 25 patients with AIN had regression of dysplasia. The conclusion reached by Watson *et al.*[21] was that their study suggested that patients with HG-AIN are at a higher risk of developing anal SCC than previously thought and surveillance is indicated. The authors also concluded that the patients who are particularly at risk are the immunocompromised, and that the treatment available at present does not prevent AIN in some patients from progressing to invasive cancer and carries the associated risk of faecal incontinence. Watson *et al.*[21] further concluded that as a result of their study they could not recommend screening of asymptomatic high-risk populations, but that there is a need for research into more effective and less morbid treatments for this disease.

Prognosis

The staging system for anal cancer is the TNM (tumour, node, metastasis) staging system.[22] The TNM staging system is useful for surgical purposes, such as providing guidelines on the extent of resection, it is described in more detail below.

The TNM staging system is based on the anatomical extent of spread, where, T refers to the extent of the primary tumour, N refers to the extent of nodal metastases and M refers to the presence or absence of distant metastases. Each of these three factors is given a number: for T, the number indicates how large the tumour is; for N, the number informs which lymph nodes have cancer cells in them; and for M, the number informs as to whether the cancer has spread to other parts of the body – in general, the higher the number, the more serious the cancer. There are five stages of tumour size in the current TNM classification of anal cancer: T1–T4 and a very early stage called Tis or carcinoma in situ. Anal cancers are not usually found at this very early stage, as they do not cause any symptoms when they are so small. Below are descriptions of each T stage for anal cancer:

- *Tis or carcinoma in situ* The earliest stage of anal cancer, when the cancer cells are found

only inside the lining of the anus and have not spread elsewhere.

- *T1* The tumour measures 2 cm across or less.
- *T2* The tumour is larger than 2 cm but smaller than 5 cm.
- *T3* The tumour is larger than 5 cm.
- *T4* The cancer can be any size, but is growing into the surrounding tissues or organs, such as the urethra, the vagina or bladder.

Staging is a process that tells the clinician how widespread the cancer may be at the time of diagnosis. It will show whether the cancer has spread and how far. The treatment and outlook for anal cancer depends, to a large extent, on its stage.

In 2004, Johnson *et al.*[3] reported 5-year survival figures of 58% for males and 64% for females, based on data collected between 1973 and 2000 on diagnosis and outcomes of invasive and in situ anal cancer. The data came from the SEER programme in the USA. Lower 5-year survival figures were reported by Bower *et al.*[23] for a cohort of English patients with HIV (25 MSM and 1 heterosexual woman) with confirmed cases of invasive anal cancer. Bower *et al.*[23] reported a 5-year overall survival figure of 47%.

In 2006, Karandikar *et al.*[4] reported a 5-year overall survival figure of 45%, based on a cohort of patients with anal cancer who were identified from a 5-year audit (1995–9) of anal cancer in Wales.

Also in 2006, Jeffreys *et al.*[24] reported the results of a study that was based on all first, primary, invasive malignant cancers of the rectum and anus – excluding anal margin and skin – that were diagnosed in adults (15–99 years) and registered in the National Cancer Registry for England and Wales between 1986 and 1999. The aims of the study were to investigate the effects of tumour and patient characteristics on trends in the survival of patients with cancer of the anus or rectum in England and Wales. A total of 132,542 adults who were diagnosed during the 14 years were followed up to 2001 through the National Health Service Central Register. Results were given for patients diagnosed during the calendar periods 1986–90, 1991–5 and 1996–9. Relative survival up to 5 years after diagnosis was estimated, using deprivation-specific life tables. Five-year relative survival rose by about 10% overall, from 38% (1986–90) to 48% (1996–9) in men, and 39% (1986–90) to 51% (1986–90) in women.

Gatta *et al.*[7] gave details on survival and incidence from rare cancers using data collected from 18 European countries. They reported that the overall 5-year relative survival for anal SCC was good at 53.1% (95% CI 51.5 to 54.8); the authors also reported absolute survival figures, with 53.1% (95% CI 51.7% to 54.4%) for 3-year survival and 43.3% (95% CI 41.9% to 44.6%) for 5-year survival.

For the UK, Gatta *et al.*[7] reported a 5-year relative survival of 51.9% (95% CI 49.7% to 54.2%). Data for the UK (England, Scotland and Wales) came from national cancer registries or from regional cancer registries.

Quality of life

Allal *et al.*[25] undertook a study to assess long-term quality of life (QoL) in patients treated by RT with or without chemotherapy. The study population was drawn from 165 patients with anal carcinoma who received sphincter-conserving treatment using RT, with or without chemotherapy, between January 1976 and December 1994. Patients were considered for the study's QoL assessment if they were 80 years old or less and were alive without disease activity at least 3 years after completion of treatment with a functioning anal sphincter. In total, 52 patients satisfied the inclusion criteria – 49 patients were contacted by telephone to request their participation in the study and three were contacted by mail. Of these patients, 46 patients agreed to participate, one refused, two were assessed to be ineligible because of serious comorbidities and the three contacted by mail did not respond. Among the 46 patients who received the two questionnaires, five refused to complete them for different reasons (two 'unclear', two 'number of questions', one 'questions relating to sexual aspects'). This left 41 patients for the analysis.

The QoL questionnaires used by Allal *et al.*[25] were developed by the QoL Study Group of the European Organisation for Research and Treatment of Cancer (EORTC). One was a validated questionnaire assessing cancer-specific QoL (EORTC QLQ-C30) (Aaronson *et al.* 1993) and one assessing site-specific (colorectal) QoL (EORTC QLQ-CR38), which at the time of the study was in the process of validation.

The EORTC QLQ-C30 is a patient self-rating questionnaire that comprises six multi-item function scales measuring physical, role, social, emotional and cognitive functions, along with overall QoL. Separate symptom scales are included to assess pain, fatigue and emesis, and five single

items to measure gastrointestinal symptoms, dyspnoea, appetite loss and sleep disturbances. A final item evaluates the perceived economic consequences of the disease.

The EORTC QLQ-CR38 is a patient self-rating questionnaire that comprises 38 questions, of which 19 are completed by all patients and the remaining by a subset of patients (males or females, patients with or without a stoma). The general structure comprises four multi-item/single-function scales, seven multi-item symptom scales and one single symptom item. The functioning scales assess effects on micturition, chemotherapy, side effects, gastrointestinal general symptoms, defecation problems, stoma-related problems and sexual dysfunction in males or females. The single symptom item assesses weight loss.

The result reported by Allal *et al.*[25] for the EORTC QLQ-C30 questionnaire was that the physical function scale scores did not differ significantly in the subgroups, although older patients tended to report lower scores ($p = 0.08$). For the role function scale, while non-significant, the severity of late complications and poor MSK (Memorial Sloan-Kettering Center anal function criteria) anal function appear to have a negative effect ($p = 0.08$ for both). For the emotional and the social function scales, no significant differences were noted between the different subgroups. However, the overall QoL score was significantly affected by the severity of late complications ($p = 0.005$) and the anal function score ($p = 0.04$). This score did not differ with the current age and pain symptom scales, particularly according to the length of follow-up.

The results of the EORTC QLQ-CR38 questionnaire used by Allal *et al.*[25] were that body image function score was significantly lower only in patients with advanced T stage ($p = 0.003$). For the future perspective function scale, no significant differences were noted between subgroups, while lower scores were reported in patients with higher grade of late complications ($p = 0.1$). The sexual functioning score was significantly lower only in the advanced-age subgroup ($p = 0.01$). None of the function scale scores seemed to be influenced by the length of follow-up. A significantly higher defecation problems score was reported in patients who were treated with brachytherapy for the boost ($p = 0.03$).

Allal *et al.*[25] concluded that in patients treated with sphincter conservation for anal carcinomas, long-term QoL, as measured by the EORTC QLQ-C30 and QLQ-CR38, appeared to be acceptable, with the exception of diarrhoea and, perhaps, sexual function. The subset of patients who presented with severe complications and/or anal dysfunction showed poorer scores in most scales.

In 2005, Pachler and Wille-Jorgensen[26] reported on a systematic review of QoL after rectal resection for cancer, with or without permanent colostomy. The objective of the review was to evaluate the QoL in patients treated for rectal cancer with either abdominoperineal excision (APE), with a permanent stoma or rectal anastomosis anterior resection (AR) with preservation of the sphincter function.

The criteria for considering studies to use in the review by Pachler and Wille-Jorgensen[26] were:

- All controlled clinical trials and observational controlled studies in which QoL in patients with rectal cancer, having either APE or AR were studied using a multidimensional QoL instrument.
- The participants were individuals with verified cancer of the rectum, which had been treated with either APE or AR.
- No discriminatory criteria concerning age, gender, race or social status.
- Quality-of-life assessments using validated multidimensional questionnaire, self-reported questionnaires completed by the patient – a relative or independent rater was considered eligible for inclusion.
- Assessments of functional results or one-dimensional aspects of QoL (e.g. sexual function, urinary function, pain) were not included in the review.

Pachler and Wille-Jorgensen[26] reported that 30 potential studies were identified, 11 of these, including 1412 participants (range 23–372), met the inclusion criteria. None was randomised, nine were retrospective and two prospective. Overall, six studies found that patients undergoing APE did not have poorer QoL than patients undergoing AR. One study found that a stoma only slightly affected the patient's QoL; four found that after APE patients had significantly poorer QoL than after AR. The authors concluded that it was not possible to draw conclusions whether the QoL measures of stoma patients are poorer than for non-stoma patients. However, the results challenge the assumption that people with stoma fare less well than non-stoma patients.

Chapter 2

Methods

Systematic reviews were conducted to identify and assess all literature relating to the screening of anal cancer in high-risk groups.

Search strategies

A comprehensive literature search was undertaken in January 2006 (updated in November 2006) to identify relevant literature pertaining to screening high-risk groups for anal cancer. Four major searches were conducted, which were designed to retrieve papers:

- describing the epidemiology of anal cancer
- on the effectiveness of screening technologies for anal cancer
- on the effectiveness of different screening programmes/policies for anal cancer
- on the cost-effectiveness and comparative costs of candidate technologies/programmes/policies identified from effectiveness searches. Searches were also undertaken to retrieve papers on the effectiveness of different treatments for anal cancer.

The following electronic bibliographic databases were searched:

1. Applied Social Sciences Index and Abstracts (ASSIA)
2. BIOSIS previews (Biological Abstracts)
3. British Nursing Index (BNI)
4. Cumulative Index to Nursing and Allied Health Literature (CINAHL)
5. Cochrane Database of Systematic Reviews (CDSR)
6. Cochrane Central Register of Controlled Trials (CENTRAL)
7. EMBASE
8. MEDLINE
9. MEDLINE In-Process & Other Non-Indexed Citations
10. NHS Database of Abstracts of Reviews of Effects (DARE)
11. NHS Health Technology Assessment (HTA) Database
12. PsycINFO
13. Science Citation Index (SCI)
14. Social Sciences Citation Index (SSCI).

Attempts were also made to identify 'grey' literature by searching appropriate databases (e.g. the King's Fund, DH-Data) current research registers [e.g. National Research Register (NRR), Current Controlled Trials (CCT) register]. A general internet search was also conducted using a standard search engine (Google) and a meta-search engine (Copernic).

The reference lists of included studies and relevant review articles were also checked.

No date or language restrictions were applied to these searches. The search strategies used in MEDLINE (Ovid) are displayed in Appendix 3.

All prospective and retrospective primary studies groups who were at high risk of anal cancer were included in the review. An assessment was conducted of published literature identified by the search strategy by all four reviewers. All publications were divided into the following broad categories based initially on their titles and abstracts (where available): cost-effectiveness, natural history, prevalence, diagnosis, epidemiology, screening, treatment, risk, QoL, and not relevant – excluded. A paper could be included in more than one category. The reviewers then obtained copies of all papers not excluded. Some papers were reclassified after reading the full text, additional papers were subsequently excluded. Each paper not excluded after the initial readings was given a unique identifier. Hand searching of included papers was conducted to identify any relevant papers not detected by the electronic searches. A quality of reporting of meta-analyses (QUOROM) trial flow chart is displayed in Appendix 4.

Inclusion/exclusion criteria

Papers were selected if they met the following inclusion criteria:

- contained data on population incidence, effectiveness of screening, health outcomes or screening and/or treatment costs of anal cancer
- described defined suitable screening technologies
- prospectively evaluated a test, or a combination of tests, to detect anal cancer.

Papers were excluded if they were a foreign language publication.

Data abstraction

Data from all of the studies meeting the inclusion criteria were extracted into data extraction forms by the clinical effectiveness reviewer.

Chapter 3
Results

Screening

This section reviews studies that evaluated screening procedures for the detection of AIN, anal squamous intraepithelial lesion (ASIL) or anal cancer. Ten studies were identified for inclusion on screening; *Table 3* shows the studies characteristics and Appendix 5 gives details on study quality. Nine studies were cohort studies[27–35] and one was a systematic review.[36]

The reporting quality of the screening studies is generally poor, making it difficult to assess the true quality of the work undertaken. Only one of the studies is randomised. The remaining studies are cohort studies. The data tend not to be analysed on an intention-to-treat basis and assessors are not blinded.

Anal cytology

De Ruiter *et al.*[27] reported on a cohort study that recruited 215 homosexual/bisexual men. The perianal area and anal canal were then examined using a colposcope, and areas macroscopically suggestive of intraepithelial neoplasia were biopsied.

The anal cytology and histology methods used by De Ruiter *et al.*[27] were:

- *Cytology* Patients were examined in the lithotomy position. Anal smears were obtained by blindly inserting a cytobrush 1.5–2.0 cm into the anal canal, rotating through 360°, transferring to a glass slide and fixing with 96% ethanol.
- *Histology* An oblique-viewing Graeme Anderson proctoscope was inserted into the anal canal.

The findings from De Ruiter *et al.*[27] were:

- *Cytology* A total of 126 (81.8%) of the 154 patients had macroscopic anal condylomata and 28 (18.2%) had no macroscopic evidence of anal condylomata; 46 patients were found to have features of both HPV and AIN, 85 (55.2%)

had evidence of HPV alone and 23 (14.9%) were found to be negative.
- *Histology* A total of 169 (78.6%) had macroscopic anal condylomata, 46 (21.4%) did not have macroscopic anal condylomata and 176 (81.9%) were biopsied; 76 patients (35.4%) had histological evidence of both HPV and AIN, 91 (42.3%) had features suggestive of HPV alone and 9 (4.2%) were normal.
- *Comparison between anal cytology and histology* Of the 154 patients with an adequate anal smear, 56 (36.4%) had both HPV and AIN on histology; 67 (43.5%) had evidence of HPV alone; and 31 (20.1%) were negative.

The conclusions reached by De Ruiter *et al.*[27] were that anal cytology is a sensitive but non-specific method of identifying patients with biopsy-proven AIN if cytological features of HPV alone are included as abnormal smears. The authors reported that specificity is improved by restricting abnormal smears to those with features of both HPV and AIN but it markedly lowers the sensitivity of the test. The authors further concluded that at the time of the study, anoscopy and histology are required in addition to anal cytology to differentiate between patients who simply have anal condylomata and those who also have AIN.

The cohort members of the 1997 cohort study by Palefsky *et al.*[28] were participating in a natural history study of ASIL, using anoscopically directed anal biopsy as the standard. Overall, 658 homosexual or bisexual male subjects were studied: 407 (62%) were HIV positive and 251 were HIV negative. The mean age of HIV-positive men was 41 years, range 21–66 years, whereas for HIV-negative men the mean was 44 years with a range of 25–73 years.

Palefsky *et al.*[28] reported that, defining abnormal cytology as including atypical squamous cells of undetermined significance (ASCUS) and ASIL, the sensitivity of anal cytology for detection of biopsy-proven ASIL in HIV-positive subjects was 69% (95% CI 60 to 78), specificity 59% (95% CI 53 to 65), the positive predictive value (PPV) was 38% (95% CI 31–45) and the negative predictive value (NPV) was 84% (95% CI 79–89). A PPV is the proportion

TABLE 3 *Screening studies characteristics*

Study details	Objective	Population	Inclusion/ exclusion criteria	Study type	Screening test
de Ruiter 1994[27]	To compare anal cytology with histology as a method of detecting AIN	Homosexual or bisexual men (*n* = 215)	Homosexual and bisexual men attending a central London department of GU medicine for routine follow-up of their HIV infection or with newly diagnosed anal condylomata	Cohort study	Anal cytological smear performed under standard conditions
Palefsky *et al.* 1997[28]	To assess the sensitivity, specificity, and positive and NPVs of anal cytology	HIV-positive (*n* = 407) and HIV-negative (*n* = 251) homosexual and bisexual men	HIV-positive and HIV-negative homosexual and bisexual men, who were participating in a natural history study of ASIL	Cohort study	Anoscopically directed anal biopsy as standard. Anal cytology results were classified using standard Bethesda criteria[38] for cervical cytology
Mathews *et al.* 2004[29]	To estimate agreement between consecutive anal cytological examinations, between concurrent cytological examination and histopathology, and between HRA visual impression and histopathology and to estimate the prevalence of severe dysplasia by concurrent cytological category	Patients with HIV (*n* = 1864)	HIV-infected patients receiving anal dysplasia screening as part of routine care for HIV at the University of California at San Diego Owen Clinic, with a history of anal receptive intercourse, anogenital warts or anal/cervical dysplasia	Prospective observational cohort study	Anal Pap test with a repeat Pap test and biopsy performed for patients with a screening Pap diagnosis of ASCUS, LSIL or HSIL
Panther *et al.* 2004[30]	To determine the accuracy of anal Pap smear as a predictor of paired anal histology results, as well as whether HIV serostatus had an impact on findings	MSM (*n* = 153)	MSM referred to an anal dysplasia clinic	Cohort study	Anal Pap smears
Fox *et al.* 2005[37]	To establish whether anal cytology has value as a screening tool and to validate the Palefsky method based on a UK population	Homosexual/ bisexual males who underwent high-resolution anoscopy (*n* = 99)		Cohort study	Dacron swab was inserted blindly 3 cm into the anal canal and rotated using a spiral motion
Arain *et al.* 2005[31]	To assess the usefulness and limitations of anal smears in screening for ASILs	Males that had anal smears collected in liquid medium (*n* = 198)	Anal smears retrieved from files of the pathology department at Cedars-Sinai Medical Centre, Los Angeles	Cohort study	Anal smears collected in liquid medium compared with results of surgical biopsies or repeat smears
Friedlander *et al.* 2003[32]	To evaluate anorectal cytology as a screening tool and to correlate anorectal cytology with anoscopic and histological findings	Patients that had anorectal specimens on file (*n* = 51)	Anorectal specimens retrieved from the files of the cytology service at Memorial Sloan-Kettering Cancer Center, New York	Cohort study	Retrieved smears stained with Papanicolaou stain

TABLE 3 *Screening studies characteristics (continued)*

Study details	Objective	Population	Inclusion/ exclusion criteria	Study type	Screening test
Lampinen *et al.* 2006[33]	To compare self- vs clinician-collection procedures with respect to specimen adequacy for cytological evaluation	HIV-1 seronegative MSM aged 18–30 years (*n* = 222)	Men involved in a study of HIV incidence and risk behaviours among young HIV-1 seronegative MSM conducted in Vancouver	Cross-sectional study	Self- and clinician-collected anorectal Dacron swabs for liquid-based cytological evaluation were collected
Cranston *et al.* 2004[36]	To assess the performance of results collected by study participants at home compared with samples collected by experienced research clinicians in a clinic of MSM with a high prevalence of AIN	HIV-positive and HIV-negative MSM (*n* = 125)	HIV-positive and HIV-negative MSM, enrolled at the University of California at San Francisco Anal Neoplasia Study; criterion: who previously had an anal cytology sample taken by a practitioner	Cohort study	Self-collection kit and standard clinician-collected samples
Varnai *et al.* 2005[36]	To examine methods that may enable the routine diagnosis of HPV-induced changes in the anal rim and the consequences of such detection of a more sensitive diagnosis of AIN	Patients that had tissue samples from anal lesions, which had been archived (*n* = 87)	Patients who had been diagnosed with the following: invasive anal carcinoma, AIN of varying severity and condylomatous lesions	Cohort study	Tissues samples from anal lesions, which had been archived, were retrospectively examined, for histological examination; the tissue was completely embedded in paraffin and processed according to the usual methods of diagnostic histology
Chiao *et al.* 2006[36]	To evaluate and summarise indirect evidence concerning anal Pap smear screening for HIV-infected patients	HIV-infected individuals	Studies were excluded if they did not include HIV-infected individuals or did not include original data	Systematic review	Anal Pap smear

ASCUS, atypical squamous cells of uncertain significance; GU, genitourinary; HRA, high-resolution anoscopy; HSIL, high-grade squamous intraepithelial lesion; LSIL, low-grade squamous intraepithelial lesion; NPV, negative predictive value.

of those with a positive test who actually have the disease, whereas a NPV is the proportion of those with a negative test who actually do not have the disease.

For HIV-negative subjects, Palefsky *et al.*[28] reported that, using the previous definition, the sensitivity of anal cytology for detection of biopsy-proven ASIL was 47% (95% CI 26–68), specificity 92% (95% CI 89–95), the PPV 35% (95% CI 15–54) and the NPV was 95% (95% CI 93–98). The authors concluded that anal cytology may be a useful screening tool

to detect ASIL, particularly in HIV-positive men. The grade of disease on anal cytology did not always correspond to the histological grade, and anal cytology should be used in conjunction with histopathological confirmation.

Between July 2000 and September 2003, Mathews *et al.*[29] identified 1864 patients who underwent 2918 Pap tests: 8.4% were female, 11.5% were black, 21.5% were Hispanic, 60.4% were white and 6.6% from other ethnic groups; 68.4% were MSM, 15.4% related to injection drug abuse, 9.4% were related

to heterosexual transmission and 6.8% were related to other risk factors. Median age was 39 years (35–45 interquartile range). The authors suggested that the reproducibility of key screening measures is moderate at best but of similar magnitude to that of other studies of anal and cervical dysplasia screening.

Panther et al.[30] accounted the results of a study that looked at comparing the pathological diagnoses obtained by anal Pap smear with those obtained by anal biopsy or by surgical excision for 153 MSM. The medical histories, high-resolution anoscopy (HRA) findings and pathology reports of these MSM were recorded. Of the 153 MSM, 100 (65%) were HIV positive and 53 (35%) were HIV-negative. The basis for referral was an abnormal screening anal Pap smear finding [24 (24%) of 100 HIV-positive and 22 (42%) of 53 HIV-negative subjects], HG-AIN on pathological examination of surgically removed anogenital condylomata [19 HIV-positive subjects (19%) and six HIV-negative subjects (11%)], or a history of internal and/or external anal condylomata for 40 HIV-positive subjects (40%) and 14 HIV-negative subjects (26%). The remainder of the cohort was referred for anal bleeding, palpable internal and/or external anal mass, or screening.

Panther et al.[30] stated that the detection of high-grade squamous intraepithelial lesion (HSIL) on an anal Pap smear had a sensitivity of 47% (95% CI 35–59) and specificity of 90% (95% CI 81–96) for detection of a high-grade histological finding (AIN level 2, AIN level 3 or SCC) in the paired specimen. Panther et al.[30] believe that the cross-sectional data presented in their article independently confirmed a substantial incidence of histologically proven high-grade anal dysplasia in MSM who present with minimally abnormal anal Pap smear findings. The authors also stated that their study independently confirmed that a substantial proportion of low-grade dysplasia on anal Pap smears occurs with HG-AIN in MSM, and that it confirmed that abnormal anal cytological findings of any grade should suggest the possibility of high-grade histological findings.

Fox et al.[37] prospectively collected data from 99 consecutive homosexual/bisexual male patients who underwent HRA at the Chelsea and Westminster Hospital anoscopy clinic. Data from follow-up visits on this group of patients were also included in the study. The anoscopy procedure used by Fox et al.[37] utilised the cytology method developed by Palefsky, whereby a Dacron swab

was inserted blindly 3 cm into the anal canal and rotated, using a spiral motion, outward pressure was applied on the anal canal and the swab was gradually withdrawn. They reported that 160 anoscopic procedures were reviewed from 99 homosexual or bisexual men in whom both cytological and histological examinations were planned. Eighty-nine (90%) patients were HIV positive and 10 were known to be HIV negative. They concluded that anal cytology by the Palefsky method is simple to undertake, and can therefore be used as the basis of a pilot screening project in centres with large cohorts of HIV-positive homosexual men who have a high risk of developing anal carcinoma. HPV genotyping is not a useful adjunct to cytological screening.

Arain et al.[31] studied the cytomorphological features of 200 consecutive anal smears collected in liquid medium from 198 patients, and the findings were correlated with results of surgical biopsies and/or repeat smears that became available for 71 patients within 6 months. They concluded that liquid based anal smears had a high sensitivity (98%) for detection of ASIL but a low specificity (50%) for predicting the severity of the abnormality in subsequent biopsy, and suggested that all patients with a diagnosis of ASCUS should be recommended for HRA with biopsy.

Anorectal cytology

Friedlander et al.[32] collected 78 consecutive anorectal specimens representing 51 patients: 33 patients were HIV positive (27 males, six females). All HIV-positive females also had a history of gynaecological (vulvar, vaginal or cervical) intraepithelial neoplasia. The mean age of the patients was 43 years (range 26–74 years). The results from this study were that with histology as the gold standard, the sensitivity of cytology to distinguish benign from dysplasic or malignant lesions was 92% but the specificity was only 50%. Friedlander et al.[32] concluded that anorectal cytology is an accurate method for screening patients for anal squamous lesions. Atypical parakeratotic cells represent a potential pitfall. Anoscopy is important in confirming the presence of a lesion, but only a biopsy can accurately determine the grade of a lesion.

Self-screening

In 2006, Lampinen et al.[33] evaluated self-screening for anal cancer by MSM. Paired self- and clinician-collected anorectal Dacron swabs for liquid-based

cytological evaluation were collected in random sequence from this cohort of young MSM. Each participant provided at the same study visit two anorectal swab specimens: one self-collected and one collected by the study clinician. Specimens collected by clinicians were more adequate than those collected by men who were wholly naive to the procedure; however, it was found that the vast majority of self-collected anorectal swab specimens from MSM were adequate for cytological evaluation. The conclusion reached by Lampinen *et al.*[33] was that self-collection of anorectal swab specimens for cytological screening in research and possibly clinical settings appears feasible, particularly if specimen adequacy can be further improved. The severity of biopsy-confirmed anorectal disease is seriously underestimated by cytological screening, regardless of collector.

A total of 125 MSM were invited to take part in the study by Cranston *et al.*,[34] and 102 were included in the analysis: 82 were HIV positive and 20 HIV negative. The participants in the study by Cranston *et al.*[34] were given a cytology self-collection kit, with written instructions for use, and requested to collect the sample 1 month after the clinic visit. Cranston *et al.*[34] reported that the sensitivity of any grade of anal cytology abnormality for detection of AIN 1, AIN 2, or AIN 3 was comparable between clinician-collected (70%) and self-collected (68%) samples. The sensitivity of any grade of anal cytology abnormality for detection of a high-grade lesion (AIN 2 or 3) was also comparable between clinician-collected (74%) and self-collected (71%) samples. The sensitivity of anal cytology to detect AIN in self-collected samples was higher among HIV-positive men than among HIV-negative men. Among the 57 HIV-positive men, anal cytology to detect AIN overall or AIN 2 or 3 specifically was also higher for HIV-positive men in the clinician-collected samples, and the magnitude of these differences in sensitivity was similar to those seen in self-collected samples ($p = 0.15$ for AIN overall; $p = 1.0$ for AIN 2 or 3). The conclusions reached by Cranston *et al.*[34] were that MSM with biopsy-proven AIN can self-collect anal cytology samples with sensitivity comparable with that of experienced clinicians, and that this may facilitate screening for AIN.

Histological markers

Varnai *et al.*[35] retrospectively examined biopsy samples from 87 patients for microscopic indications of HPV infection. After microdissection, additional HPV analysis via polymerase chain reaction (PCR) was carried out. Varnai *et al.*[35] reported that in 38 of 47 cases of anal carcinoma, HPV DNA could be detected via PCR (80.9%), the majority of which were HPV 16 (33 out of 38 = 86.8%). In 29 of the 33 cases of AIN, HPV DNA was detected (87.9%), most of these in AIN 3 (15 out of 16 = 93.8%). Histological markers of HPV infection were detected in all 87 cases. The authors recommended any histological reports on excision of anal lesions to include a statement as to whether histological markers of HPV infection were detected. In individual cases, that, validation via HPV PCR must be considered.

Anal Pap smear screening for HIV-infected patients

Chiao *et al.*[36] systematic review of the English-language literature published from July 1996 through to July 2005 noted that the natural history of progression from anal intraepithelial neoplasia to anal cancer is unknown, and although low-grade anal dysplasia has been shown to progress to high-grade dysplasia (HGD) in a majority of HIV-infected men within 2 years after initial diagnosis, the true rate of progression from HGD to invasive anal cancer remains unclear.

Chiao *et al.*[36] commented that the data published to date highlight limitations to current anal Pap smear screening-related research, no randomised or cohort studies exist to determine if there are improved survival or outcomes for those who have been screened with anal Pap smears, and that there have been no ecological studies to correlate use of screening and the incidence or outcomes of SCCA.

Screening summary/discussion

The sensitivity, specificity, PPV and NPV (where given) of the studies reported in Chapter 3 (see Screening) are displayed in *Table 4*. The PPV will depend on the prevalence rate of the disease: if the disease (such as anal cancer) has a low prevalence rate then we would expect to have a low PPV. Where reported, 95% CIs are included.

Since the late 1990s, the sensitivity and specificity of reported screening tests for anal cancer appear to have improved (*Table 4*). Within recent years, sensitivity values of 70–98% have been reported,[31,34,35] which would highly suggest that screening techniques have improved. However, the reported PPVs are mixed while a number of studies fail to report these values (*Table 4*). This reflects

the relative rarity of anal cancer. Large numbers would need to be screened to identify a relatively small number of affected individuals. *Table 4* allows comparisons to be made between the historical data and the positive and NPVs. ROC (receiver operating characteristic) curves have not been generated for this review.

The two studies by Lampinen *et al.*[33] and Cranston *et al.*[34] reported that self-collected samples (anorectal swabs or anal cytology) are adequate for interpretation, although further research is needed before using self-collected samples in a screening programme. However, both the De Ruiter *et al.*[27] and Palefsky *et al.*[28] studies put forward that anal cytology should be used in conjunction with histopathological confirmation.

Treatment

Six studies[40–45] were identified and included in this review: *Table 5* displays characteristics of the studies and Appendix 6 gives details on study quality. The criteria of the National Screening Committee (NSC) for appraising the viability, effectiveness and appropriateness of a screening programme (Appendix 2) states that 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. Therefore, survival from treatment options is of interest. For completeness, comments from an editorial[38] and *Effective Health Care* bulletin issued in March 2004[39] are included at the end of this section.

TABLE 4 *Sensitivity, specificity, PPVs of anal screening tests*

Study details	Screening test	n	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
de Ruiter *et al.* 1994[27]	Anal cytology	154	88	16	37	70
	Histology	215	34	73	41	66
Palefsky *et al.* 1997[28]	Anal cytology (ASCUS and above) HIV-positive patients	407	69 (95% CI 60 to 78)	59 (95% CI 53 to 65)	38 (95% CI 31 to 45)	84 (95% CI 79 to 89)
	Anal cytology (ASCUS and ASIL) HIV-negative patients	251	47 (95% CI 26 to 68)	92 (95% CI 89 to 95)	35 (95% CI 15 to 54)	95 (95% CI 93 to 98)
	Anal cytology ASIL, HIV-positive patients	407	46 (95% CI 36 to 56)	81 (95% CI 76 to 85)	46 (95% CI 36 to 57)	80 (95% CI 76 to 85)
	Anal cytology ASIL, HIV-negative patients	251	26 (95% CI 5 to 47)	98 (95% CI 96 to 100)	56 (95% CI 22 to 89)	94 (95% CI 91 to 97)
Fox *et al.* 2004[37]	Anal cytology	99	83	38	86 (95% CI 78 to 91)	33 (95% CI 19 to 51)
Cranston *et al.* 2004[34]	Self-collected anal cytology samples	102	68	Not reported	Not reported	Not reported
	Clinician-collected anal cytology samples	102	70	Not reported	Not reported	Not reported
Panther *et al.* 2004[30]	Anal Pap smear (HG-AIN)	153	47 (95% CI 35 to 59)	90 (95% CI 81 to 96)	81 (95% CI 66 to 92)	65 (95% CI 55 to 74)
	Anal Pap smear (LSIL)		68 (95% CI 56 to 78)	48 (95% CI 36 to 59)	59 (95% CI 48 to 69)	57 (95% CI 44 to 70)
Arain *et al.* 2005[31]	Anal Pap smear	71	98	50	Not reported	Not reported
Varnai *et al.* 2006[35]	Histology	87	94	80	85	91

CI, confidence intervals (not all papers reported the CI); LSIL, low-grade squamous intraepithelial lesion.

TABLE 5 *Treatment studies details*

Study details	Study type	Design	Patient group	Study objectives
UKCCCR Anal Cancer Working Party 1996[40]	RCT	Multicentre RCT with a main end point of local failure whether due to disease or complications of treatment, as indicated by the need for major surgical intervention. Five-year survival was a secondary end point. Eligible patients had epidermoid carcinoma (squamous, basaloid or cloacogenic) of the anal canal or margin, no evidence of major hepatic or renal dysfunction, and normal blood counts From 856 patients considered for entry to the multicentre trial, 585 patients were randomised to receive initially either 45-gray (Gy) RT in 20 or 25 fractions over 4–5 weeks (290 patients) or the same regimen of RT combined with 5-FU by continuous infusion during the first and final weeks of RT and mitomycin (12 mg/m^2) on day 1 of the first course (295 patients). Clinical response was assessed 6 weeks after initial treatment: good responders were recommended for boost RT and poor responders for salvage surgery. The main end point was local failure rate ($\geq$6 weeks after initial treatment); secondary end points were overall and cause-specific survival. Analysis was by intention to treat	Any patient with anal cancer	To compare the most promising regimens of RT alone with CMT
Cummings *et al.* 1984[41]	Case series	A subset (25 patients) of 51 anal canal carcinoma patients treated by radical external beam radiation alone (RT) between 1958 and 1978, were compared with 30 patients with anal canal carcinoma treated by combined 5-FU, mitomycin C and radical radiation therapy (FUMIR) between 1978 and 1982	Any patient with anal cancer	The results and toxicity of treatment of anal canal carcinoma by radiation therapy or radiation therapy and chemotherapy in a single centre
Doniec *et al.* 2006[42]	Case series	From 1993 to 2001, 50 patients with histologically confirmed primary cancer of the anal canal (n = 38) and the anal margin (n = 12) without evidence of distant metastases were treated at the University Clinic Kiel with curative intention. Prior to treatment, all patients underwent staging, consisting of digital and EUS investigation of the anus and the rectum (7-MHz transducer, BandK Medical), sphincter manometry, total colonoscopy, ultrasound of the abdomen and the inguinal region, and CT scan of the pelvis. Forty-five patients were admitted and examined	Any patient with anal cancer	To optimise local tumour control by TRUS-guided brachytherapy and thereby minimise the risk of local recurrence, resulting in a reduced rate of salvage abdominoperineal resection
Brown *et al.* 1999[43]		Between 1989 and 1996, 46 patients were identified with HG-AIN; 34 underwent local excision of all macroscopically abnormal disease and the resulting defect was left open, closed primarily or skin grafted. Regular follow-up subsequently included anoscopy and biopsy of any suspicious lesions. All patients diagnosed in one hospital with HG-AIN between 1989 and 1996 were included	Any patient with anal cancer	

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TABLE 5 *Treatment studies details (continued)*

Study details	Study type	Design	Patient group	Study objectives
Edelman and Johnstone 2006[44]	Case series	Retrospective review of the records of 17 HIV-positive patients with anal SCC treated with CMT of RT and concurrent chemotherapy, between 1991 and 2004, at a single institution	HIV-positive patients	To report the toxicity and survival data of HIV-positive patients with anal SCC treated with CMT of RT and concurrent chemotherapy
Place *et al.* 2001[45]	Case series	This was a retrospective cohort study, which identified 73 patients with anal SCC, treated at the University of Texas Southwestern Medical Center-affiliated hospitals; 23 were HIV positive. In the HW-positive group, nine had in situ squamous carcinomas and 14 had invasive SCCs. Data collected included age, CD4 count, treatment, complications and survival	HIV-positive patients	To determine the outcome of HIV-positive patients with anal SCCs

5-FU, 5-fluorouracil; CD4, cluster of differentiation 4; CMT, combined modality therapy; EUS, endosonographic ultrasonography; FUMIR, 5-FU, mitomycin C and radical radiation therapy; RCT, randomised controlled trial; RT, radiotherapy; TRUS, transrectal ultrasound; UKCCCR, United Kingdom Co-ordinating Committee for Cancer Research.

RT alone vs a combination of RT/chemotherapy

Two studies reported on the treatment of anal cancer by RT alone or a versus combination of RT/chemotherapy: there was one randomised controlled trial (RCT)[40] and one cohort study.[41]

In 1996, the United Kingdom Co-ordinating Committee for Cancer Research (UKCCCR) Anal Cancer Working Party[40] reported on a trial to compare combined modality therapy (CMT) with RT alone in patients with epidermoid anal cancer. The aim was to compare the most promising regimens of RT alone with CMT, within a multicentre RCT. The main end point of the trial was local failure whether due to disease or complications of treatment, as indicated by the need for major surgical intervention, with 5-year survival as a secondary end point. Patients were eligible if they had epidermoid carcinoma (squamous, basaloid or cloacogenic) of the anal canal or margin, no evidence of major hepatic or renal dysfunction, and normal blood counts. The Working Party[40] reported that from 856 patients considered for entry to the multicentre trial, 585 patients were randomised to receive initially either 45 Gy RT in 20 or 25 fractions over 4–5 weeks (290 patients) or the same regimen of RT combined with 5-fluorouracil (5-FU) (1000 mg/m^2 for 4 days or 750 mg/m^2 for 5 days) by continuous infusion during the first and the final weeks of RT and

mitomycin (12 mg/m^2) on day 1 of the first course (295 patients). Clinical response was assessed 6 weeks after initial treatment: good responders were recommended for boost RT and poor responders for salvage surgery.

The UKCCCR Anal Cancer Working Party[40] findings were that, after a median follow-up of 42 months (interquartile range 28–62), 164 of 279 (59%) patients receiving RT had a local failure compared with 101 of 283 (36%) of patients receiving CMT. This gave a 46% reduction in the risk of local failure in the patients receiving CMT (RR 0.54, 95% CI 0.42 to 0.69, $p < 0.0001$). The risk of death from anal cancer was also reduced in the CMT arm (0.71, 95% 0.53 to 0.95, $p = 0.02$). There was no overall survival advantage (0.86, 95% CI 0.67 to 1.11, $p = 0.25$). Early morbidity was significantly more frequent in the CMT arm ($p = 0.03$), but late morbidity occurred at similar rates. There was no statistically significant difference in overall survival between the two groups, with a 58% 3-year survival rate for the RT arm and 65% for the CMT arm.

The authors reported that the UKCCCR Anal Cancer Working Party trial[40] showed that the standard treatment for most patients with epidermoid anal cancer should be a combination of RT and infused 5-FU and mitomycin, with surgery reserved for those who fail on this regimen.

In 1984, Cummings *et al.*[41] reported on the results and toxicity of treatment of anal canal carcinoma by radiation therapy or radiation therapy and chemotherapy in a single centre. In this study, a subset (25 patients) of 51 patients with anal canal carcinoma, treated by radical external beam radiation alone between 1958 and 1978, were compared with 30 patients with anal canal carcinoma treated by combined 5-FU, mitomycin C and radical radiation therapy (FUMIR) between 1978 and 1982.

Cummings *et al.*[41] reported that the uncorrected 5-year survival rate in each group was approximately 70%, but primary tumour control was achieved in 93% (28 of 30 patients) in the FUMIR group compared with 60% (15 of 25 patients) treated with RT. The authors further reported that colostomies were needed as part of treatment for residual carcinoma or for the management of treatment-related toxicities in 11 of the 25 patients treated by radiation alone, and required (at the date of the study) in 4 out of the 30 patients treated by FUMIR.

The conclusion reached by Cummings *et al.*[41] was that the improvement in the primary tumour control rate, and the reduction in the number of patients requiring colostomy when compared with the results of RT, favour combined chemotherapy and radiation as the initial treatment for anal canal carcinoma.

RT combined with chemotherapy

One prospective cohort study[42] and two retrospective cohort studies[44,45] reported on patients treated with RT combined with chemotherapy.

Doniec *et al.*[42] reported using CMT of anal cancer and transrectal ultrasound (TRUS)-guided high dose rate (HDR) after-loading therapy on 50 patients with histologically confirmed primary cancer of the anal canal ($n = 38$) and the anal margin ($n = 12$) with curative intention. Prior to treatment, all patients underwent staging consisting of digital and endosonographic ultrasonography (EUS) investigation of the anus and the rectum (7-MHz transducer, BandK Medical), sphincter manometry, total colonoscopy, ultrasound of the abdomen and the inguinal region, and CT scan of the pelvis. All patients underwent follow-up examination 3 months after completion of brachytherapy, including clinical examination and TRUS. This was repeated at 3-month intervals for 1 year, followed by 6-month intervals during the second year, and annually thereafter. The median follow-up was 34 months (range 6–96). Relapse rates, disease-specific survival and overall survival were calculated according to the Kaplan–Meier method.

Doniec *et al.*[42] reported a 5-year overall survival rate of 74% for 50 patients with anal cancer and treated by combination radiochemotherapy; the specific disease-related 5-year survival rate was 82%. The conclusion reached by Doniec *et al.*[42] was that EUS-guided brachytherapy for anal cancer may decrease the side effects of conventional brachytherapy.

Edelman and Johnstone[44] conducted a retrospective review of the records of 17 HIV-positive patients with anal SCC who were treated with CMT of RT and concurrent chemotherapy at a single institution. The objective of the study was to report the toxicity and survival data of these patients. For these patients the actuarial 18-month survival was 67%.

Place *et al.*[45] conducted a retrospective analysis of 73 patients with anal SCC of these 73 patients, 23 were HIV-positive and included in the study. Of these 23 patients, 9 had SCC in situ (SCCIS) and 14 had SCCA. All 23 were homosexual men. Mean age was 40 (range 28–58) years, with a mean age of 42 years for the patients with SCCA and 36 years for the patients with SCCIS ($p = 0.05$). The 1- and 5-year mortality rates of HIV-positive patients with SCCA with follow-up of at least 1 year (which excluded all new patients receiving HAART) were 40% and 80%, respectively. The 1- and 5-year mortality rates of HIV-positive patients with SCCIS were 17% and 50%, respectively.

Radiation therapy and chemotherapy were offered to 13 of the 14 patients with SCCA. The remaining patient had a T2 margin tumour and was offered wide local excision with radiation therapy. For the 13 patients who were offered chemotherapy, 11 received 5-FU and cisplatinum, one received 5-FU and mitomycin C, and one declined therapy. Standard fraction external beam radiation therapy was given to 12, with two declining therapy. Six of 14 patients with SCCA and 8 of 9 patients with SCCIS received antiretroviral therapy before their anal malignancy diagnosis, and all continued it during treatment. The nine patients with SCCIS received local excision only.

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Place *et al.*[45] concluded that HIV-positive patients with in situ carcinomas present at an earlier age than those with infiltrating lesions. The authors also concluded that because these patients appear to succumb to their HIV status and not the anal disease, anal SCC should be included with cervical SCC as an AIDS-defining illness. HIV-positive patients, particularly patients with AIDS, with invasive anal cancers and without effective antiretroviral therapy obtain little benefit and significant toxicity from current radiation therapy and chemotherapy.

Surgery

Brown *et al.*[43] reported in 1999 on a study that looked at intermediate and long-term follow-up of these patients, with particular reference to the incidence of recurrent disease and the associated surgical morbidity. Patients diagnosed in one hospital with HG-AIN between 1989 and 1996 were included in the study.[43] Thirty-four underwent local excision of all macroscopically abnormal disease and the resulting defect was left open, closed primarily or skin grafted. Regular follow-up subsequently included anoscopy and biopsy of any suspicious lesions.

The median follow-up reported by Brown *et al.*[43] was 41 months (range 12–104); 19 patients had histological evidence of incomplete excision at the time of initial resection. Some 12 of the 19 had histologically proven recurrent HG-AIN within 1 year. Even with microscopically complete excision, 2 of 15 patients subsequently developed recurrent HG-AIN at 6 and 32 months after operation. It was reported that no patient developed invasive anal cancer, although it was not clear whether this was due to surgery and intensive follow-up or because of the low risk of anal cancer.

Brown *et al.*[43] concluded that although no definite recommendations can be made for the treatment of HG-AIN, the results illustrated some potential drawbacks of surgical excision with a high potential for incomplete excision and persistent disease, even after complete excision in some patients and a high morbidity rate.

Treatment summary/discussion

Anal cancer is usually treated aggressively with a combination of chemotherapy and RT (chemoradiation), but the treatment can have very unpleasant side-effects. Surgery can be used to remove precancerous and cancerous cells from the anus; however, the precancerous or cancerous cells may recur. Surgery is more likely if the cancer is small and near the anal margin. The chemotherapy treatment will be a combination of mitomycin C and 5-FU during the first and final weeks of the RT course.

Table 6 shows the survival results from the above studies; for completeness, survival data from cohort studies and registry data are also present in the table, although treatment given is not known. The study by Cummings *et al.*[41] reports only an approximation of the uncorrected 5-year survival rate. The UKCCCR Anal Cancer Working Party reports only a 3-year survival rate. Johnson *et al.*[3] reported 5-year survival figures of 58% for males and 64% for females, based on data collected between 1973 and 2000 on diagnosis and outcomes of invasive and in situ anal cancer. The data came from the SEER programme in the USA. Lower 5-year survival figures were reported by Bower *et al.*[23] for a cohort of English HIV-positive patients (25 MSM and one heterosexual woman) with confirmed cases of invasive anal cancer. Bower *et al.*[23] reported a 5-year overall survival figure of 47%.

In 1997, Myerson *et al.*[46] reported on a study to review the patterns of presentation, care and outcome reflected in data from the National Cancer Data Base, which represented a broad range of medical centres. Data on patients with anal carcinoma (on 1050 patients from 1988 and 1289 patients from 1993) were reviewed for patterns of care and presentation. The 1988 cases were also reviewed for outcome data. Records of patients with anal carcinoma were extracted on basis of anatomic site (ICD-O2 site code of C21) and histology (ICD-O2 histology codes of M801–67 and M894). Other eligibility criteria included an accession year of 1988 or 1993, and diagnosis and/or treatment having taken place at the reporting hospital.

Myerson *et al.*[46] reported that the mean age at diagnosis decreased slightly between 1988 and 1993 – from 62.8 years to 61.8 years. The gender distribution of patients changed little, with 64.3% being female in 1988 compared with 62.5% in 1993. It was also reported that there was an increase in the use of chemotherapy between 1988 and 1993 (from 61.6% to 67.2%) and that substantial differences were observed in the management of epidermoid carcinomas and adenocarcinomas. The majority of epidermoid carcinomas were managed non-surgically,

TABLE 6 *Anal cancer: survival*

Study details	Study type	Treatment	5-year survival rate (%)	3-year survival rate (%)
Hospital-based studies				
Cummings *et al.* 1984[41]	Cohort study	RT alone, $n=25$	≈70[a]	Unknown
		CMT, $n=30$	≈70[a]	Unknown
UKCCCR Anal Cancer Working Party 1996[40]	RCT	RT alone, $n=285$	Unknown	58[b]
		CMT, $n=292$	Unknown	65[b]
Bower *et al.* 2004[23]	Prospective cohort study	Unknown	47[b]	Unknown
Doniec *et al.* 2006[42]	Cohort study	Combined radiochemotherapy	74[b]	Unknown
Population-based studies				
Johnson *et al.* 2004[3]	Registry data, 1973–2000	Unknown	58[b] (men), 64[b] (women)	Unknown
Karandikar *et al.* 2006[4]	Registry data, 1995–9	Unknown	45[b]	Unknown
Jeffreys *et al.* 2006[24]	England and Wales Registry data, 1986–99	Unknown	48%[b] (men), 51%[b] (women)	Unknown
Gatta *et al.* 2006[7]	European Registry data, 1983–94	Unknown	43[b]	53[b]

a Actuarial survival.
b Overall survival.

principally with combined chemotherapy and radiation, whereas three-quarters of patients with adenocarcinoma underwent surgery. The authors reported that the most important factors for favourable 5-year survival were early stage (ranging from 71.3% for stage 1 to 23.1% for stage 4), epidermoid carcinoma histology (57.6%, compared with 41.3% for adenocarcinoma), and female gender (56.2%, compared with 49.6% for males).

The conclusion reached by Myerson *et al.*[46] was that their study confirmed a trend in patterns of care favouring non-surgical management with radiochemotherapy for epidermoid carcinomas of the anus. For adenocarcinomas, there had been a trend towards increasing use of multimodality therapy with surgery and adjuvant radiochemotherapy. Survival data from the 1988 cases confirm the efficacy of conservative treatment with radiation plus chemotherapy for epidermoid carcinomas.

The *Effective Health Care* bulletin[39] issued in March 2004 reported that two large RCTs comparing RT alone with chemoradiotherapy (CRT) have demonstrated a highly statistically significant reduction in local failure. Both saw improvements in colostomy-free survival and reduction in deaths from anal cancer with CRT. Neither showed any significant effect on overall survival. A third RCT tested the benefit of adding mitomycin C to 5-FU and RT. This also demonstrated statistically significant improvements in colostomy-free and disease-free survival. Other forms of treatment, such as surgical excision, may be considered by anal cancer multidisciplinary teams, but surgery is usually reserved for salvage.

In 2005, James *et al.*[38] presented an editorial on the current status of the Second UK Phase III Anal Cancer Trial, the ACT II study. The RT schedule in the ACT II trial is a continuous schedule of 50.4 Gy in 28 fractions with either 5-FU and mitomycin C (5-FU/MMC) or 5-fluoroacil and cisplatin (5-FU/CDDP). The authors reported that analysis on early trial data were highly encouraging, and showed that the chemoradiation regimen and maintenance chemotherapy could be given without interruption and had acceptable toxicity.

A study by Adjani *et al.*[47] reported in 2008, while this review was in completion, giving results from the USA. The large trial of 682 patients compared two chemoradiation therapies: the first, fluorouracil plus mitomycin and RT; the second, fluorouracil plus cisplatin and RT. The primary end point was 5-year disease-free survival; the secondary end point was the overall survival and time to relapse. The 5-year local recurrence for mitomycin-based treatment was 25% (95% CI 20 to 30) and 33% (95% CI 27 to 40). The 5-year overall survival rate was 75% (95% CI 67 to 81) in the mitomycin arm and 70% (95% CI 63 to 76) in the cisplatin arm. In their report it was noted that there was an increased colostomy rate in the cisplatin group and it was recommended that this combination should be avoided in the treatment of localised anal cancer. They also note that there has been little improvement in the survival outcomes for patients since the 1990s. Of interest to this current review is the finding that the mitomycin group of patients suffered a higher degree of haematological toxicity. Although this is the treatment modality used in the model it is worth noting that this study specifically excluded patients with HIV. These patients do present a problem, as they often have increased toxicity to chemotherapy.

Treatment summary/discussion

Published studies of treatment can be helpful in developing estimates of effect as part of a screening model. However, not all treatment studies give the information in such a way that it can be used for modelling. For example, reporting that an intention to treat analysis was undertaken but not reporting fully on these results makes it more difficult to incorporate the results into the model. Some studies were excluded for this reason.

The ideal treatment study for a screening evaluation would take patients identified through screening and randomise them into treatment and watchful waiting groups. This could then be used to estimate the true benefits of treatment in patients otherwise not presenting with disease.

A study that looks at patients that present with symptoms may have useful information regarding the effect of treatment at different stages of disease but will be biased towards patients with overt symptoms.

When considering including a treatment study in evaluating screening for use in the UK, consideration should be given to the population under investigation, how they were identified for randomisation, and how the control group were monitored. Whereas the biological level of differences between populations may be small when comparing outcomes, the structural differences in health-care systems can greatly affect the use of data from other settings.

The construction of an evaluation of a screening programme makes little use of the specifics of treatment. In effect, the evaluation is concerned with the outcome (good or bad) of treatment for those identified as having the disease.

Some of the treatment studies are used to estimate the natural history of the disease process. This is an important first step in evaluating the effect of screening, as those not diagnosed through the usual clinical pathway will have the outcomes of natural history (no treatment) unless screening identifies them.

In the following model, we have used broad estimates of the effects of treatment, based on a selection of studies that cover a range of treatment variations. In fact, it is the relative benefit of treatment over the health state that would have been experienced if the treatment had not been initiated that gives the benefit of the screen detection.

By not linking the screening evaluation too closely to a particular treatment modality the evaluation can be considered robust even if the treatment of choice changes, provided that the sensitivity analysis applied covers the range of outcomes expected.

In this specific case, the effect of systematic screening the at-risk population would be expected to bring forward the start of treatment, rather than expose cases to treatment they would not otherwise have had. As such, this means the effect of screening is measured in the effect of the earlier treatment. In this study we have included some papers that cite local recurrence rates from the reported treatment modalities. The emphasis in this model was, as previously stated, to look at bringing forward the start of treatment rather than wait until individuals were symptomatic. The assumption being that early treatment following screening would prevent the problems found in treating symptomatic patients.

The following model considers several scenarios for the effect of this change, with the noted above trials falling within these parameters.

Chapter 4
Risk of anal cancer

In Chapters 1 and 3 risk is used in a descriptive and general sense; in this chapter, risk is used in the context of modelling and does not necessarily draw upon the same evidence.

Anal cancer is a rare neoplasm that affects the epithelium of the anal canal. The increased incidence in men, particularly in the USA is etiologically related to a sexually transmitted agent.[48] HPV has been implicated as a causal agent of anal cancer.

Risk of anal cancer is near to zero in early life. Sexual activity is virtually essential for transmission of HPV. Multiple partners bring the risk of a greater variety of strains, and, in turn, a greater chance of a more dangerous strain (with regard to anal cancer). Other genitourinary (GU) infections may be a marker of multiple sexual partners, sex with infected individuals and high-risk behaviour. There may be some potential of HPV infection with some other GU infections. The criteria for appraising screening programmes[1] list the importance of there being a detectable risk factor when considering implementing a screening programme.

Once HPV infection occurs, the dysplastic process at the anal margin follows more frequently with certain types of HPV, and appears to be seen more frequently where receptive anal intercourse occurs.

Infection with HIV has a profound effect on the immune system. It is the immune system that fights infection but also this same system guards against dysplastic changes. It is this latter role that explains much of the increased cancer risk in patients with HIV and AIDS.

Kim *et al.*[49] undertook a retrospective cohort study, comparing HIV-positive and HIV-negative patients with respect to treatment tolerance and outcome. HIV-positive and HIV-negative patients were compared by age, gender, sexual orientation, stage at diagnosis, treatment provided, response to treatment, tolerance and survival.

Kim *et al.*[49] reviewed the records of 98 patients with anal neoplasms. Seventy-three patients had invasive anal epidermoid (squamous or cloacogenic) carcinoma and formed the study group.

Of the 73 patients, 13 were HIV-positive and 60 were HIV-negative. Biopsies were performed on all primary tumours. Preoperative staging was performed using examination, anal ultrasound, chest X-rays and computerised tomography (CT) scanning. After completion of primary therapy, patients were seen every 2–3 months for 3 years, every 6 months until the end of the fifth year, and then annually. Post-treatment evaluation included a careful clinical examination with digital palpation and anoscopy at each visit.

The findings by Kim *et al.*[49] were that the HIV-positive and HIV-negative groups differed significantly by age (42 vs 62 years, $p < 0.001$), male gender (92% vs 42%, $p < 0.001$) and homosexuality (46% vs 15%, $p < 0.05$). The authors found that there were no differences by stage at diagnosis or radiation dose received. Acute treatment major toxicity differed significantly (HIV-positive 80% vs HIV-negative 30%, $p < 0.005$). Kim *et al.*[49] reported that only 62% of HIV-positive patients were rendered disease free after initial therapy versus 85% of HIV-negative patients ($p = 0.11$), and that the median time to cancer-related death was 1.4 vs 5.3 years ($p < 0.05$). A survival model did not show age, gender, stage or treatment to be independent predictors.

Kim *et al.*[49] found that HIV-positive patients with anal carcinoma seemed to be a different population from HIV-negative patients by age, gender and sexual orientation. They have a poorer tolerance for combined therapy and a shorter time to cancer-related death. A strong trend to poorer initial response rate was also seen.

Once dysplasia has occurred, progression to higher levels of dysplasia [from low-grade squamous intraepithelial lesions (LSILs) to HSILs] takes place over time. This progression is seen at an increased rate in persons with HIV (regardless of how contracted).

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Once anal cancer is present, prognosis is better in patients with an intact immune system. Patients with HIV and AIDS have a poorer prognosis despite having developed the cancer at a younger age.

The first diagram in Appendix 7 summarises the life course model for this condition. The second diagram shows how this model is modified for HIV-negative women.

Model parameters

There are four groups that can possibly be modelled:

- A men with HIV
- B men who have sex with men (without HIV)
- C women with HIV
- D women with high risk of anal cancer.

A Men with HIV
After onset of HIV, incidence of HPV infection, dysplasia and cancer will be greater than in the general population. There may be differences between men with HIV who acquired HIV through anal intercourse compared with others. This is a closed group in that there is no transition to any other group. Prognosis once cancer has developed is likely to be the same regardless of mode of acquisition of HIV. HAART can be seen to increase life expectancy over those not treated.

B Men who have sex with men (without HIV)
Incidence of HPV infection, dysplasia and cancer will be greater than the general population but less than that for group A. Risk will increase with time, as risk of contracting a more oncogenic strain will be increased (through repeated exposure and multiple partners). Persons in this group can move to group A if HIV is acquired.

C Women with HIV
After onset of HIV, incidence of HPV infection, dysplasia and cancer will be greater than in the general population. There may be differences between women with HIV acquired through sexual exposure compared with others. This is a closed group. Prognosis once cancer develops is likely to be the same regardless of mode of acquisition of HIV. HAART can be seen to increase life expectancy over those not treated.

D Women with high risk of anal cancer
For example, women with known cervical cancer. Incidence of HPV infection, dysplasia and cancer will be greater than the general population, but less than that for group C. Evidence suggests risk does not increase greatly with time, as new sexual partners are less frequently acquired after 30 years of age. Persons in this group can move to group C if HIV is acquired.

For each of the previous defined groups, the available literature and findings are present in the following sections.

High-risk groups

Men who have sex with men may identify themselves as homosexual or bisexual, and these men are at increased risk for STDs such as HIV infection, HPV and anal cancer. Knight[50] reported that many men are engaging in dangerous sexual practices that may jeopardise their health. These sexual practices include anal sex without a condom ('bare backing'), oral sex without a condom, oral stimulation of the anus ('rimming') without protection, multiple sex partners at one time and use of illicit drugs.

Halperin[51] reported in 1999 the results of a review examining the practice of anal sex among heterosexual population, related sociocultural factors and risk of associated health problems. Halperin[51] stated that heterosexual anal sex remained understudied, but that analysis of available evidence suggesting that this stigmatised behaviour is not so rarely practised among heterosexuals. The review reported that surveys from North America, Europe and Australia suggest that between 7% and 25% of the population reported practising heterosexual anal intercourse. For men, surveys from the late 1980s and early/mid 1990s suggest that approximately 2–5% of men reported having a same-sex experience, although only a small proportion of these engage in receptive anal intercourse.

Dodds *et al.*[52] reported the findings of an annual behavioural survey of homosexual men (from 1996 to 2000) who socialised in gay venues across London. Participants completed a short anonymous self-completion questionnaire covering demographic details, sexual health service use, HIV testing history, self-perceived HIV status

and sexual behaviour. The authors found that the proportion of men having unprotected anal intercourse (UAI) increased significantly each year from 30% in 1996 to 42% in 2000 ($p < 0.001$).

In 1997, Frisch *et al.*[53] reported on a population-based case–control study, undertaken in Denmark and Sweden to examine if the incidence of anal cancer had increased, particularly amongst women. The authors conducted telephone interviews with 324 women and 93 men in whom invasive or in situ anal cancer was diagnosed between 1991 and 1994, 534 controls with adenocarcinoma of the rectum and 554 population controls. The interviews covered a wide spectrum of possible risk factors for anal cancer. ORs were calculated by logistic regression. Specimens of anal cancer tissue and samples of rectal adenocarcinomas were tested for HPV DNA using PCR.

Frisch *et al.*[53] searched national cancer registries in Denmark and Sweden to identify all incident cases of histologically verified invasive or in situ anal or rectal epidermoid carcinoma (anal cancer) reported during the period from 1991 to 1994. Danish patients were considered eligible for the study if the tumour was rectum, anal canal, anus, anorectum or perianal skin. Swedish patients were eligible if the topography was anus or rectum. The authors also included two control groups, with one group consisting of patients with adenocarcinoma of the rectum, who were chosen as controls to minimise any possible bias due to differential recall between patients with anal cancer and controls. The other control group consisted of persons from the general population. For the men, we tried to match two patients with rectal adenocarcinoma and two population controls to each patient with anal cancer, and for the women, a 1:1:1 match was sought. Controls were frequency matched within each country for sex and age (in 5-year intervals, except for the youngest patients in the cancer control group, because of the rarity of rectal cancer in young persons), and the patients with rectal adenocarcinoma were matched for the year of the diagnosis.

Overall, 417 patients with anal cancer (93 men and 324 women), 534 controls with adenocarcinoma of the rectum (191 men and 343 women), and 554 population controls (205 men and 349 women) were interviewed. The participation rate was 78–79% among female patients (cases and cancer controls) and 71–73% among male patients. Participation rates were 60–61% among population controls of both sexes.

Frisch *et al.*[53] found that, for men, indicators of sexual promiscuity were positively correlated with the risk of anal cancer. Among men who reported ever having had heterosexual intercourse, there was a statistically significant trend towards an association between the lifetime number of female sexual partners and the risk of anal cancer, with men reporting a total of two or three partners at lowest risk (*p*-value for trend = 0.004). Men with 10 or more female partners had 2.8 times the risk of those with two or three partners. Twenty-three per cent of patients with anal cancer, compared with 15% of controls, reported having visited a prostitute [OR 1.8 (95% CI 0.99 to 3.2)]. Unmarried men were at high risk for anal cancer: among those who did not report a current heterosexual relationship, the OR was 3.3 (95% CI 1.5 to 7.3), and among those who lived with a female partner, the OR was 8.7 (95% CI 3.1 to 25.0).

Men with HIV

Increased risk of HPV and other infections

Bjorge *et al.*[54] in 2004 reported on a case–cohort study examining the relationship between HPV infection and the subsequent risk of anal and perianal skin cancer, using Finnish and Norwegian cancer registries. The Finnish and Norwegian cancer registries are nationwide and population based. The data files of the serum banks and cancer registries were linked on the basis of the personal identification number to identify anal, perianal, and head and neck cancers.

Bjorge *et al.*[54] identified 28 anal and perianal cancer cases [25 anal cancer (20 in Norway, five in Finland); three perianal cancer, all in Norway]. These 28 cases and 1500 controls were analysed for the presence of immunoglobin G (IgG) antibodies to HPV types 16, 18, 33 or 73, and ORs of developing anal and perianal skin cancer were calculated. The authors reported ORs that showed an increased risk of developing anal and perianal skin cancer among subjects who were seropositive for HPV 16 (OR 3.0, 95% CI 1.1 to 8.2) and HPV 18 (OR 4.4, 95% CI 1.1 to 17). In total, 29% of anal and perianal cancer cases were positive for HPV 16 compared with 8% of controls.

In 2005, Van Der Snoek *et al.*[55] undertook a study to establish the prevalence of HPV infection in relation to being HIV-positive in a group of Dutch MSM; 286 MSM were recruited between February 1999 to February 2003. The cohort participants

were tested for STDs and HIV every 6 months over a period of 3 years. HPV specimens were taken on the third and sixth visits only. At the sixth visit, 213 MSM were tested: 17 were HIV positive and 196 HIV negative. Van Der Snoek et al.[55] found that persistence of HPV 31 at the perianal region was significantly more often seen in HIV-positive MSM ($p = 0.036$), whereas the incidence of HPV 16 may be associated with HIV positivity ($p = 0.059$).

In 2004, Sobhani et al.[56] reported on a cohort study of 228 patients with anal cancer condylomas the incidence of HGD. Patients referred to a department of coloproctology in Paris between June 1993 and June 2002 were recruited for a prospective cohort study. Patients with invasive anal cancer at baseline were excluded. A total of 228 consecutive patients (164 HIV positive) were included, after curing of their lesions. Patients were interviewed using a standardised questionnaire and underwent proctological examination at baseline, 1 month later and every 3–6 months thereafter. Overall, 199 patients underwent all of the examinations required and were included in the analysis.

Sobhani et al.[56] reported that HGD was detected in 38 (19%) patients: 32 HIV-positive patients and six HIV-negative patients in at least one examination. A positive HIV test at baseline was identified as an independent risk factor for cancer and HGD. In HPV-infected patients, the incidence of HGD was 15.5% and for invasive carcinoma was 3.5%.

Palefsky et al.[57] reported in 1998 on the incidence of anal cancer amongst HIV-positive and HIV-negative homosexual and bisexual men: 346 HIV-positive and 262 HIV-negative men were enrolled in this prospective cohort study. Participants were interviewed and asked about their current status regarding HIV-related diseases and conditions, medications, sexually transmitted diseases, anal conditions and behavioural topics – such as smoking, drinking, substance use and sexual practices – that might be associated with anal disease. HIV-positive subjects were interviewed every 6 months and HIV-negative subjects every year. Subjects were followed for 4 years. Anal swabs for cytology and HPV studies were obtained, followed by biopsies of visible lesions.

Palefsky et al.[57] found that HIV-positive men were more likely to develop HSIL than HIV-negative men with a RR of 3.7 (95% CI 2.6 to 5.7). The authors concluded that HIV infection and HPV

infection were associated with high rates of incident HSIL among homosexual men.

Time with HIV

Fagan et al.[58] in 2005 reported on a retrospective cohort study of 14 HIV-positive patients diagnosed with anal neoplasms. These patients were identified from the records of all HIV-positive patients diagnosed with either AINs (group 1) or anal carcinoma (group 2), between January 1998 and November 2004 at a veteran medical centre in Texas, USA. Seven patients in each group were included in the analysis. The authors concluded that the most significant factor for the development of invasive anal carcinoma in patients with HIV is duration of disease. The authors reported that with the advent of HAART, HIV has changed from a terminal illness to a chronic disease, and as a result of improved long-term survival secondary to new HIV therapy, anal invasive carcinoma will become an increasing problem.

Effect of HAART

In 2005, Palefsky et al.[59] reported the findings of a point-prevalence analysis in a prospective cohort study, in which 357 HIV-positive MSM with no history of anal cancer completed a questionnaire detailing behaviours and medical history, anal cytology and HPV testing, and HRA with biopsy for detection of AIN. Participants had a clinical examination, consisting of an anal swab for cytology and another anal swab for anal HPV testing. The participants were interviewed and asked about lifetime history of medical conditions, common HIV conditions, lifetime use of antiretroviral medication, cigarette use, alcohol consumption, recreational drug use and sexual behaviour factors (receptive/insertive anal intercourse, rimming and use of objects in the anus).

The findings from this study by Palefsky et al.[59] was that prevalence of AIN remained high among this cohort of HIV-positive MSM since the introduction of HAART therapy in 1996, indicating that HAART is not associated with a reduced prevalence of AIN. However, the study was carried out on a group of men with a high proportion that had been HIV-positive for a number of years, and may not be generalisable to people who have only been HIV-positive for a few years.

In 2001, Palefsky et al.[60] reported the findings of an analysis of study participants who were HIV-

positive MSM, enrolled in two anal neoplasia cohort studies[61,62] and treated with HAART continuously for at least 3 months, while participating in the studies, between the years 1991 and 1994. A total of 98 HIV-positive MSM were followed for at least 6 months before initiation of HAART, and results confirmed with data collected during follow-up, 6 months after HAART initiation.

Of the 98 MSM included in the analysis by Palefsky *et al.*,[60] the mean age at HAART initiation was 46 years (range 30–69). The conclusions by the authors were that 6 months' treatment with HAART had relatively little impact on the natural history of ASIL and anal HPV infection. In the absence of screening and treatment of anal HSIL, the longer survival owing to HAART may increase the risk of progression to cancer as most of these lesions persist after HAART initiation.

The findings from Palefsky *et al.*[59,60] were supported by another study conducted by Piketty and Kazatchkine[63] in 2005. In a review of published studies that assessed the impact of HAART on cervical and anal disease, Piketty and Kazatchkine[63] suggest that HAART has little impact on the incidence of HPV-related cervical and anal cancer.

A study was undertaken by Oehler-Janne *et al.*[64] to investigate the outcome of HIV-seropositive patients, under HAART, with anal cancer treated with RT alone or in combination with standard chemotherapy. Overall, 81 HIV-seronegative patients and 10 consecutive HIV-seropositive patients under HAART that were treated with RT were retrospectively analysed. Ten TNM stage- and age-matched HIV-seronegative patients were compared with the 10 HIV-seropositive patients. The main findings from Oehler-Janne *et al.*[64] were that despite high response rates to organ-preserving treatment with RT with or without chemotherapy, local tumour failure seems to be high in HIV-positive patients receiving HAART.

Proportion affected

Palefsky *et al.*[65] in 1990 reported the findings of a cohort study of male homosexuals with AIDs and HIV. Each participant was asked about anal symptoms and history of receptive anal intercourse. A smear for anal cytology was obtained using a Dacron swab inserted into the anorectal junction. The conclusions reached by

the authors indicated that immunosuppressed male homosexuals have a high prevalence of anal HPV infection and AIN, and that this population may be at significant risk for the development of anal cancer. However, it should be noted that these conclusions were based on the results of 97 participants of a highly selected population.

Palefsky *et al.*[66] in 1992 reported the findings of a study on 37 homosexual men with group IV HIV, who were attending an outpatient clinic. These 37 men were originally in the earlier study by Palefsky *et al.*[65] and received a 17-month follow-up visit. This subsample of the original study may not be a very representative sample of homosexual men. The authors of the 1992 study[66] found that during the 17-month period, the proportion of subjects with abnormal anal cytology increased from 27% to 65% from the original findings, and that the proportion with AIN increased from 8% to 32%. It was also found that the proportion of the group with anal HPV infection also increased from 58% to 89%. The authors concluded that the results indicated that this particular population may be at significant risk of developing anal cancer. Both of the above studies were carried out in San Francisco, which has a high population of homosexuals.

In 1998, Critchlow *et al.*[67] reported on a longitudinal study of 287 HIV-seronegative and 322 HIV-seropositive men attending a community-based clinic in the USA. The study objective was to identify risk factors for the detection of prevalent and incident of HPV infection, and HPV persistence among HIV-seropositive and seronegative homosexual men.

To be eligible for the study by Critchlow *et al.*,[67] subjects had to be men reporting having sex with other men and were at least 18 years of age. Of the 910 men enrolled, 287 HIV-seronegative and 322 HIV-seropositive men were seen for at least two visits, at which specimens adequate for the detection of anal HPV DNA were obtained. At enrolment, subjects underwent a standardised interview and were asked questions concerning demographic characteristics, sexual behaviour, other behavioural characteristics and health status. Self-administered questionnaires were completed at each return visit, with information obtained regarding recent sexual behaviour, use of antiretroviral therapies, and occurrence of symptoms associated with AIDS, anal disease or other STDs. At enrolment, and at each subsequent

visit, participants underwent a standardised physical examination, and a standardised unaided and colposcopic anal examination.

Critchlow et al.[67] reported that HIV seropositivity was associated with increased levels of high risk, but not low or intermediate risk HPV types. The authors wrote that risk of anal HPV infection appears to increase with sexual exposure, epithelial trauma, HIV infection and immune deficiency. Incident infection may result from recent sexual exposure or reactivation of latent infection.

In 2003, Piketty et al.[68] reported on a cross-sectional study that compared the prevalence of and risk factors for abnormal anal histological or cytological findings in HIV-positive men who had sex with men with male HIV-positive injection drug users who reported no history of anal intercourse. Participants in the study by Piketty et al.[68] were interviewed by using a standardised, comprehensive, self-administered questionnaire that included questions on age, education status, professional activity, tobacco use, route of HIV infection, medical history, history of sexually transmitted diseases, history of HPV-related disease, history of treatment for anal disease, drug use, age at first intercourse, total number of sexual partners, total number of receptive and insertive anal intercourse, and history of commercial sex work with men. The questionnaires were self-administered, and the investigators were blinded to the results to better ensure patient privacy and accuracy of the data. Participants had a thorough anal examination that included insertion of a Dacron swab for anal cytological and HPV testing.

The study by Piketty et al.[68] included 50 male HIV-1 positive injection drug users and 67 HIV-1 positive men who had sex with men. Human papillomavirus 16 was the most common high-risk genotype found in the two groups (30% in the men who had sex with men and 22% in the injection drug users; $p > 0.2$). Human papillomavirus 18 was found in 16% of the men who had sex with men and 4% of the injection drug users; $p > 0.2$.

The findings from Piketty et al.[68] were that anal HPV infection and ASIL may be acquired in the absence of anal intercourse in HIV-positive men, and that prevalence of HSIL is high among HIV-positive injection drug users.

Forty-five HIV-infection MSM from the previous study[68] were analysed in a later study by Piketty et al.[69] and the results reported in 2004. These 45 MSM had previously received HAART treatment and protease inhibitors for at least 6 months. Anal cytology was abnormal in 32 (72%) of the cohort, which included four participants with ASCUS, 22 with LSIL and six with HSIL; HPV DNA was detected in 36 (80%) of the cohort. The authors concluded that their results demonstrated a high prevalence of ASIL, including high-grade SIL, and anal HPV infection in HIV-infected MSM, despite immune restoration under HAART. The authors speculated that if HAART exhibits little or no effect on the restoration of specific immunity against HPV, there would be more time for HSIL to progress to cancer. That could lead, in turn, to an increase in anogenital cancer among patients receiving HAART because they are living longer.

In 1998, Palefsky et al.[70] reported on the parameters of incidence and progression of ASIL in HIV-positive and HIV-negative homosexual men, with the same population from another of their studies.[57] They found that the incidence of HSIL within 2 years was 20% in HIV-positive men and 8% in HIV-negative men, for ASIL the incidence was 52% in HIV-positive men and 17% in HIV-negative men who had no evidence of lesions at baseline. However, the Palefsky[70] data only included 2 years of follow-up. As progression from HSIL to anal cancer may take several years, HIV-positive individuals on HAART may be at increased risk of progression to anal cancer if HAART prolongs their lifespan but does not lead to HSIL regression.

Summary

The available evidence has been carried out mainly on HIV-positive males who are homosexual or bisexual, indicating that this is a particular high risk group of interest. *Table 7* shows the results of some studies examining the risk to HIV-positive males of HPV infection. An indirect comparison to the sample of HIV-positive heterosexual males in the study by Piketty et al.[68] shows that HIV-positive homosexuals/MSM have a high rate of HPV infection. The majority of studies also have a higher rate of HPV infection when an indirect comparison is made to the group of HIV-negative MSM in the study by Critchlow et al.[67]

MSM (without HIV)

In 1982, Daling et al.[71] reported on a study looking at whether characteristics that are correlated

TABLE 7 Risk of infection to HIV-positive males

Study details	Population	n	AIN	HPV	LSIL	HSIL
			Proportion (%) with:			
Palefsky et al. 1990[65]	HIV-positive homosexual men	97	15	54		
Palefsky et al. 1992[66]	HIV-positive homosexual men (subgroup of the above study, followed up after 17 months)	37	32	89		
Critchlow et al. 1998[67]	HIV-positive MSM	322		92		
	HIV-negative MSM	287		66		
Palefsky et al. 1998[70]	HIV-positive homosexual men	346				20
	HIV-negative homosexual men	262				8
Piketty et al. 2003[68]	HIV-positive heterosexual males	67		46	16	18
	HIV-infected MSM	50		85	49	18
Piketty et al. 2004[69]	HIV-infected MSM	45		80	42	22

with male homosexual behaviour are associated with the incidence of cancer. The authors linked patients' names on a population-based cancer reporting system covering 13 Washington counties in the USA, with names on the Washington State Department of Social and Health Services syphilis registry, as syphilis was believed to be correlated with homosexual activity. Of 47 men identified to have anal cancer, eight were considered to have syphilis, when the authors expected 0.4, based on the proportion of syphilis cases among men with other sites of cancer, thus suggesting that anal intercourse may be a risk factor for anal cancer.

Daling et al.[71] did state that the incidence of anal cancer was not high, either in men in general (approximately 1.1 per 100,000) or in homosexual men (the rate of which was unknown). The report authors, assuming that homosexual men have an anal cancer risk of 25–50 times that of heterosexual men, believed the annual incidence of anal cancer in homosexual men would be only between 12.5 and 36.9 per 100,000.

Chin-Hong et al.[72] reported findings from the EXPLORE study on age-related prevalence of HPV infection in HIV-negative MSM in 2004 and 2005. The authors reported on age-related prevalence of anal cancer precursors in HIV-negative MSM. The EXPLORE study, a randomised clinical trial of the efficacy of a behavioural intervention to reduce the risk of HIV acquisition in sexually active HIV-negative MSM, recruited participants from four cities in America (Boston, Denver, New York and San Francisco). Males were eligible for inclusion into the study if aged 16 years or older and reported as having receptive or insertive

anal intercourse with one or more men within the preceding year. The study recruited 1409 men, with a median age of 37 years (interquartile range 31–43) and the median age at first receptive anal intercourse was 20 years (interquartile range 17–24). During the 6 months preceding entry into the study, the participants reported a median of eight sexual partners (range 4–20) and 77% reported having receptive anal intercourse.

In 2004, Chin-Hong et al.[72] reported on 1218 participants of the EXPLORE study: 8% reported a history of injection drug use and 49% were current smokers or had smoked in the past. Using PCR testing, the authors found that 57% of the HIV-negative MSM were HPV positive, and that 26% were infected with a high-risk HPV type, indicating that a high proportion of HIV-negative MSM may be at risk for developing anal cancer.

In 2005, Chin-Hong et al.[73] reported on a cross-sectional analysis of prevalence and determinants of ASIL in 1262 of 1409 HIV-negative MSM recruited to the EXPLORE study, for whom anal cytology and behavioural data were obtained. From an earlier analysis of participants of the EXPLORE study, it was believed that HIV-negative MSM are a population that is at an increased risk for the development of invasive anal cancer compared to the general population. It was reported that factors statistically significantly associated with ASIL were having more than five receptive anal sex partners compared with fewer than two receptive anal sex partners during the previous 6 months [OR 1.8 (95% CI 1.1 to 2.8), $p = 0.018$], older age at first receptive anal intercourse [OR 1.3 per 10-year increase in age

(95% CI, 1.0 to 1.7), $p = 0.045$], injected drug use two or more times per month compared with no use in the previous 6 months [OR 17 (95% CI 1.2 to 223), $p = 0.035$], PCR evidence of an anal HPV infection [OR 2.5 (95% CI 1.3 to 4.9), $p = 0.008$] and anal HPV infection with increasing numbers of HPV type ($p < 0.001$ for linear trend). Although neither age nor smoking status were statistically significantly associated with ASILs in univariate analysis, the authors included both factors in the final multivariate model because previous studies had indicated that they are important risk factors for anal cancer.

In summary, the findings of these three studies indicate that HIV-negative MSM are at an increased risk of anal cancer due to receptive anal intercourse.

Females with HIV

In 1999, Hankins *et al.*[74] reported on a study undertaken to explore risk factors for HPV infection in HIV-positive women using data from the Canadian Women's HIV Study, a prospective open cohort study that recruited HIV-positive women at 28 sites across Canada. HPV test results were available for 375 women, with a median age of 32.5 (range 16.5–77.3) years. It was reported that sexual transmission was the most frequent source of HIV infection (69.9%, $n = 262$); 14.1% ($n = 53$) were infected through injection drug use and 9.1% ($n = 34$) through the receipt of infected blood or blood products. Overall, two-thirds (67.2%, 252 out of 375) of the women were positive for HPV, with 28.8% having more than one HPV type. The global prevalence of high-risk oncogenic HPV types (16, 18, 45 and 56) and of intermediate-risk oncogenic HPV types (31, 33, 35, 39, 51, 52 and 58) in the cohort was 32.3%.

The findings from this study[74] indicated, when HPV prevalence was examined by age, a consistent inverse relation between the presence of HPV and age ($p = 0.006$). HPV infection was found in 74.6% (141 out of 189) of women under the median age of 32.5 years, as compared with 59.7% (111 out of 186) of older women ($p = 0.002$).

In 2001, Holly *et al.*[75] reported on a study that evaluated HPV-related abnormalities in 251 HIV-positive women and 68 HIV-negative women from the San Francisco Bay Area site of the multicentre Women's Interagency HIV study between the years

1995 and 1997. Questionnaire data on medical history and relevant sexual practices was obtained and study participants underwent a physical examination. The study was conducted before HAART therapy became widely available.

Holly *et al.*[75] found that their study indicated that HIV-positive women were at higher risk of abnormal anal cytology than high-risk HIV-negative women. Risk factors for abnormal cytology in HIV-positive women included detection of anal HPV DNA, a lower number of CD4 cells, a higher plasma level of HIV ribonucleic acid (RNA), a history of receptive anal intercourse and concurrent abnormal cervical cytology.

The two studies in this section suggest that that women who are HIV-positive, particularly younger HIV-positive women, are of high risk of HPV infection.

Females with higher risk of anal cancer

Sexual behaviour

In 1997, Frisch *et al.*[53] reported on a population-based case–control study (undertaken in Denmark and Sweden) on factors positively correlated with the risk of anal cancer. Telephone interviews were conducted with 324 women in whom invasive or in situ anal cancer was diagnosed and 343 controls with adenocarcinoma of the rectum and 349 population controls.

Of the women participating in the survey,[53] approximately 1 out of 10 reported having had anal intercourse at least once. This practice was more common in the group of women with anal cancer than in either control group [OR 2.2 (95% CI 1.4 to 3.4)]. Having had anal intercourse for the first time at or after the age of 30 years was not associated with an increased risk of anal cancer. In contrast, women who had experienced anal intercourse before the age of 30 were clearly at increased risk of anal cancer (OR 4.4), lifetime number of anal-sex partners was positively correlated with the risk of venereal diseases. Women with anal cancer were also significantly more likely than controls to have had gonorrhoea (OR 4.4), trichomoniasis (OR 2.2) and prior cervical neoplasia (OR 2.6). No other venereal disease occurred significantly more frequently among women with anal cancer, but they had been tested for HIV more often than controls (OR 2.0).

Frisch *et al.*[53] also reported that fewer female patients with anal cancer (70%) than controls (82%) were married or widowed, and female patients with anal cancer reported more sexual promiscuity among their partners. The risk of anal cancer among women whose partners had experienced three or more other sexual partners was twice as high as the risk among women whose partners had experienced no other sexual partners. The significant trend towards an association between the number of male partners and the risk of anal cancer persisted after adjustment for differences in smoking status and education. Anal intercourse remained associated with an elevated risk, but the OR was reduced from 2.2 to 1.6 after adjustment for differences in the lifetime number of male partners, smoking status and education. Female subjects who had a history of anogenital warts, gonorrhoea or cervical neoplasia, those who had been tested for HIV, and those whose partners had experienced sexually transmitted infections (STIs) remained at significantly increased risk.

HPV infection

Moscicki *et al.*[76] reported in 1999 on a cohort study undertaken in March 1994, recruiting women who were participating in an ongoing natural history study of HPV. Women aged 13–20 years were screened for cervical HPV DNA detection, those women who tested positive for cervical HPV DNA were recruited. Women who consented had samples obtained for anal HPV DNA and anal cytology. The study reported the prevalence and risks for anal cytological abnormalities over a 1-year period.

The study[76] group comprised 442 women, with an average age of 22.5 years (± 2.3 years), with 49.3% of women in the study reported ever having had anal intercourse. A total of 269 samples were analysed for HPV DNA status: 66.7% were positive for HPV within 1 year prior to the visit at which they were diagnosed. The factors the authors found to be significantly associated with abnormal anal cytology were a history of anal sex [OR 6.90 (95% CI 1.7 to 47.2)], a history of cervical SILs [OR 4.13 (95% CI 1.3 to 14.9)] and a current anal HPV infection [OR 12.28 (95% CI 3.9 to 43.5)]. There was a strong association between anal intercourse and the development of HPV-induced SILs, which supports the role of sexual transmission of HPV in ASILs.

In 2001, Palefsky *et al.*[77] presented results from the same study as Holly *et al.*,[75] which showed that anal HPV infection is under-recognised in HIV-positive and HIV-negative women. The study found that 76% (170 out of 223) HIV-positive women and 42% (24 out of 57) HIV-negative women had anal HPV infection.

In 2003 Chan *et al.*[78] reported on a study that evaluated factors that predict regression of untreated CIN2 and CIN3. A cohort of 93 women with untreated CIN2 or CIN3, from a prospective, double-blinded, randomised, placebo-controlled trial of -carotene, were prospectively analysed. The cohort was analysed by age, race, parity, smoking history, oral contraceptive use, marital status, lesion grade, sexual history and HPV status. At enrolment into the study, HPV infection was detected in 84% (78 out of 93) women and most patients had HPV types that were considered high risk for progressing to cancer. Chan *et al.*[78] reported that in multivariate analysis, HPV status and the number of sexual partners remained as significant independent predictors of regression of untreated CIN2 and CIN3.

In 2005, Hernandez *et al.*[79] reported on the findings of a cohort study which sought to characterise anal HPV infection in a cohort of Hawaiian women. Women were eligible to take part if they were ≥ 18 years of age; women were ineligible if they had been pregnant within the past year, had blood-clotting disorders or could not speak/understand English. A total of 2392 ethnically diverse women were recruited from five clinic sites in Honolulu, Hawaii, and followed with repeat visits at 4-monthly intervals. Of these 2392 women, 88% (1378) agreed to provide anal specimens and had sufficient specimens. Overall, 27% (372 out of 1378) of women were positive for anal HPV DNA.

Of the 2392 participants in this study,[79] 826 did not have an anal specimen collected and 1566 did. When asked about anal intercourse, women providing anal specimens were more likely to have engaged in anal intercourse compared with women who did not provided anal specimens (21% compared with 11.6%).

Other factors

In 2003, Evans *et al.*[80] reported the findings of a retrospective cohort study that examined the occurrence of second primary cancers in women in the area covered by the TCR, who had been diagnosed with either CIN3 or invasive cervical cancer, compared with the expected cancer incidence derived from registered age- and period-

specific incidence rates for all women in the same population. The TCR is a population-based cancer registry that started in 1960 and, at the time of the study by Evans *et al.*,[80] covered a population of 14 million in South East England.

Evans *et al.*[80] identified a cohort of women with CIN3 (ICD-10 D06) who were diagnosed prior to any invasive cancer between 1960 and 1999, and, in addition, a second cohort of women with a first cancer diagnosed in the uterine cervix (ICD-10 C53) between 1960 and 1999 was also identified. A total of 21,703 women were identified with an initial cervical cancer diagnosed between 1960 and 1999, and 98 of these were excluded because they had a different cancer diagnosed on the same day. Approximately 5% of the remaining 21,605 women had a further cancer diagnosed (1055 women had two cancers, 51 had three, and four women had four cancers each).

Evans *et al.*[80] calculated SIRs for subsequent cancer sites after CIN3 and invasive cervical cancer. Women who were diagnosed with CIN3 had a significantly increased risk of developing subsequent cancer at the following six sites: anus (SIR 5.9, 95% CI 3.7 to 8.8), lung (SIR 1.8, 95% CI 1.5 to 2.1), cervix uteri (SIR 2.8, 95% CI 2.4 to 3.2), vulva (SIR 4.4, 95% CI 2.8 to 6.6), vagina

(SIR 18.5, 95% CI, 13.0 to 25.5) and kidney (SIR 1.6, 95% 1.0 to 2.4). None of the cancer sites had a significantly decreased incidence. The increase in anal cancer was only significant 10 or more years after the initial diagnosis of CIN3. Women who were diagnosed with cancer of the cervix uteri had a significantly increased risk of developing subsequent cancer at the following eight sites: rectum (SIR 1.4, 95% CI 1.1 to 1.9), anus (SIR 6.3, 95% CI 3.7 to 10.0), lung (SIR 2.5, 95% CI 2.2 to 2.8), connective tissue (SIR 2.7, 95% CI 1.2 to 5.3), vulva (SIR 1.9, 95% CI 1.0 to 3.3), vagina (SIR 8.0, 95% CI 4.4 to 13.5), bladder (SIR 1.7, 95% CI 1.3 to 2.3) and kidney (SIR 1.9, 95% CI 1.2 to 2.8). Cancers of the rectum and anus were significantly raised within 4 years of the initial diagnosis and then again after 15 years. The results of this study supported the hypothesis that cancers of the cervix, anus, vulva and vagina share common risk factors, such as HPV and smoking.

In summary, there is little available research on women with anal cancer, and while HIV-positive women were at higher risk than HIV-negative women, the current available evidence points to women being at significantly less risk of anal cancer than MSM in general, and HIV-positive MSM are the group with the greatest risk of developing anal cancer.

Chapter 5
Modelling methods for the cost-effectiveness analysis of screening for anal cancer

This section reports the decision modelling methods that informed the cost-effectiveness analysis of multiple alternative screening programmes for the early detection of anal cancer and precancerous AIN lesions. The analysis focuses on MSM as an aggregate group of individuals who are at significantly increased risk of developing anal cancer. However, the analysis separates this aggregate group into MSM with diagnosed HIV infection, and MSM who are HIV negative or have undiagnosed HIV infection. Alternative screening programmes target at the former group, and at both groups of MSM are analysed. As MSM have been identified at the group at greatest risk the cost-effectiveness analysis focuses on this group. If cost-effectiveness of a screening programme is not cost-effective in the highest-risk group then it will not be cost-effective in groups with a far lower risk of disease.

The analysis is undertaken from the perspective of the UK National Health Service (NHS), and presents the results of the analysis with respect to the health service costs incurred and quality-adjusted life-years (QALYs) gained as a result of the implementation of each screening programme, as well as a 'no screening' option. Costs and QALYs are discounted at 3.5%.

Only two previous papers describing cost-effectiveness analyses of screening for anal cancer were identified.[81,82] Both were undertaken by the same set of authors and used a cohort Markov model to assess screening for anal cancer in HIV-negative and HIV-positive MSM, respectively. These studies are not reviewed explicitly, rather specific issues and approaches adopted by Goldie et al.[81,82] are critiqued at relevant points in the description of the methods used to develop and populate the model used in the current analysis. The following section describes the model structure used to evaluate screening for anal cancer. The subsequent sections describe the data, analyses and assumptions used to populate the model.

Anal cancer screening model structure

The anal cancer model structure develops the published models used by Goldie et al.[81,82] to evaluate anal cancer screening in HIV-negative and HIV-positive MSM. The model describes progression of anal cancer from no AIN lesions, to either low or HG-AIN lesions, and from HG-AIN lesions to anal cancer. Individuals' low-grade anal intraepithelial neoplasia (LG-AIN) lesions may either regress to a healthy state or progress to the high-grade lesion state.

Figure 3 presents the structure of the model used in the current analysis. The major difference to the Goldie model[81,82] is that the current model structure combines HIV-negative, undiagnosed HIV-positive, and diagnosed HIV-positive MSM in the same model. Goldie et al.[81,82] modelled HIV-negative and HIV-positive MSM separately so that their model did not allow for the transition from HIV negative to HIV positive, and it was not clear how undiagnosed HIV-positive MSM were modelled (the implicit assumption was that all HIV-positive MSM were diagnosed).

Thus, the baseline (natural history) model allows for the parallel description of the incidence and progression of HIV infection (through three decreasing CD4 count categories), the incidence and progression of anal cancer and its precursors (including the regression of LG-AIN), the diagnosis of HIV infection and the diagnosis of anal cancer and its precursors.

Another difference is that Goldie et al.[81,82] described the existence of ASCUS as a separate state that was handled by assuming that 24% of men in this state had underlying LSILs and 18% had underlying HSILs. It was not clear how this aspect was handled practically, for example did these proportions move to these states and the others to a normal state? In the current model, it is assumed that an ASCUS screening results is a positive test results, and screening test
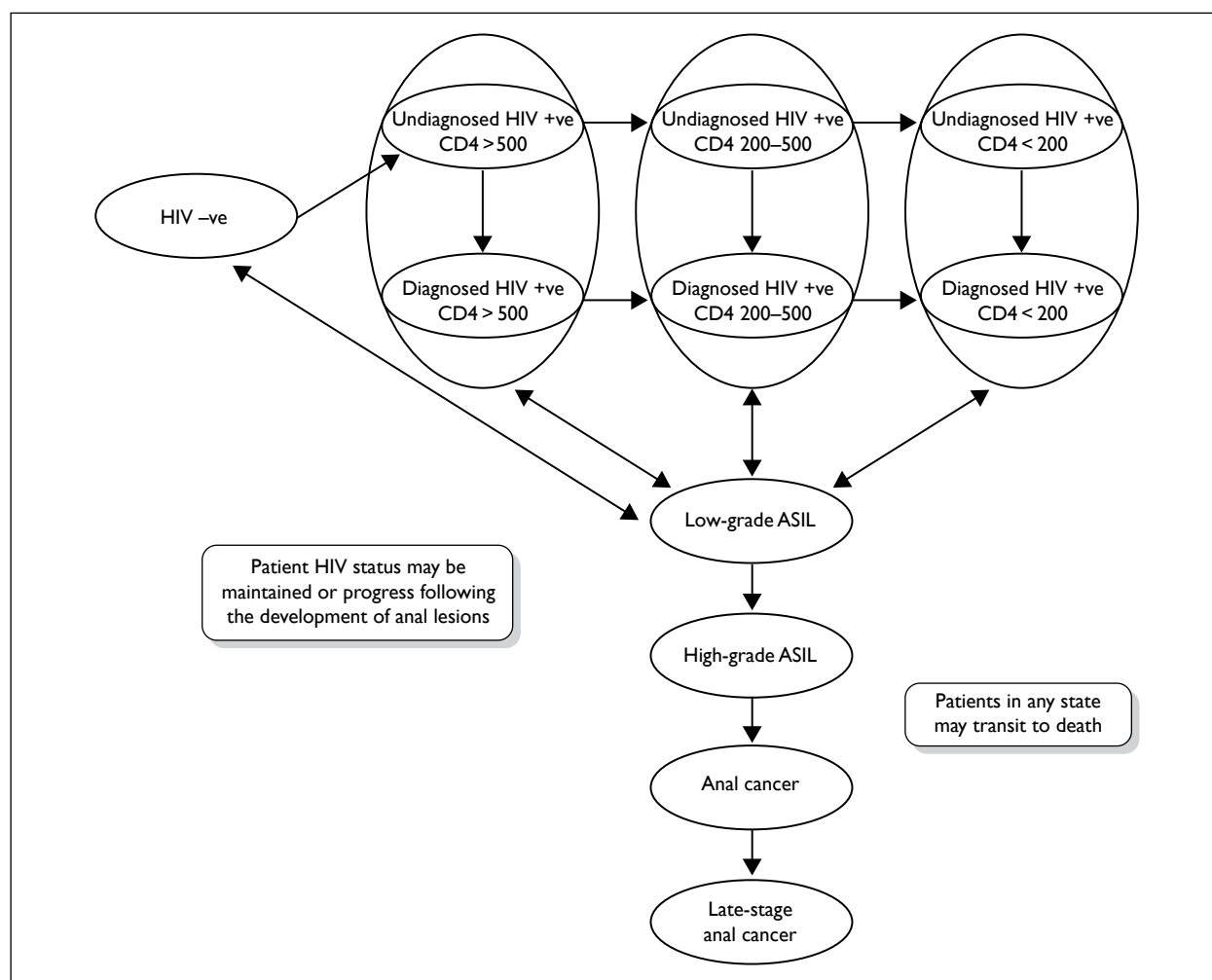
FIGURE 3 *Anal cancer model structure.*

characteristics (i.e. sensitivity and specificity) are estimated accordingly. The resource implications of the differential processing of ASCUS and more definitive positive test results are assumed to be minor.

Alternative screening programmes are overlaid on the natural history, which act to increase the likelihood of detection of anal cancer in individuals eligible for screening in the years in which screening is offered.

The main screening model was developed as a cohort Markov model, so exact estimates of costs and benefits were estimated for each set of input parameters analysed. It was implemented in Microsoft EXCEL spreadsheets, with associated macros. Submodels (as described below) were also developed as cohort Markov models in Microsoft EXCEL.

The model moved forward in cycles of 1 year. It is recognised that disease may progress through multiple stages within a single year, but, as an annual screening programme was the shortest interval tested, the improvements in accuracy from reducing the cycle length were not considered to justify the necessary increase in model complexity. The time horizon of the model followed MSM to a maximum age of 100 years. The starting age of the model was varied to reflect the current distribution of MSM (this aspect is explained in more detail in the following section).

Model population

The subsequent sections describe the data, analyses and assumptions used to populate the model. The separate sections describe the estimation of the age-specific size of the MSM

population; the incidence and progression of HIV infection; the incidence and progression of AIN lesions; the effects of treatment of precancerous and cancerous AIN lesions; the model's screening-related parameters (screening attendance, as well as test sensitivity and specificity); and costs and utility weights associated with different events and states included in the model.

Age-specific prevalence of MSM

The prevalence of MSMs within each age range was estimated using UK life table data to estimate the mean annual prevalence of men in each age range over the period 1990–2005, and data from the National Survey of Sexual Attitudes and Lifestyles (NATSAL) II.[83] NATSAL II was a cross-sectional study of a multistage stratified random sample of 12,110 men and women, aged 16–44 years, living in private households in Great Britain in 2000–1. A range for the proportion of men who are MSM was based on answers to the questions about whether male respondents had experienced sex with a man in the last year (upper estimate) and in the last 3 months (lower estimate). Rates in the 46–55, 56–65, 66–75 and 76+ age ranges were not informed by the NATSAL and so were assumed to be 95%, 75%, 5% and 0% of the rates estimated for the 35–44 age range.

Age-specific MSM prevalence was then calculated by multiplying the estimated prevalence proportions by the mean male population size in each age range. The resulting ranges are presented in *Table 8*.

HIV incidence and progression in MSM

The following sections describe the estimation of the HIV-related parameters included in the anal cancer screening model. The analysis of the HIV parameters used the common categorisation of HIV as CD4 counts of '> 500', '200–500' and '< 200'.

Age-specific prevalence of diagnosed and undiagnosed HIV (by CD4 count) in MSM

Data describing the number of diagnosed HIV-positive MSM (in 2005) were directly informed by data provided by the Survey Of Prevalent HIV Infections Diagnosed (SOPHID) team at the HPA, with only minor adjustments required to assign those cases for which CD4 count was not reported.

The SOPHID team did not have quantitative information on the age or CD4 distribution of undiagnosed HIV-infected MSM, although they estimated the number of MSM aged 15–59 living in the UK with undiagnosed HIV-infection to be 9000 (range 6600–12,400). A log-normal distribution was used to represent the uncertainty in this aggregate figure. Qualitatively, the SOPHID team stated that it is likely that the proportion of undiagnosed cases decreases with age, as men are

TABLE 8 Estimation of age-specific numbers of MSM

| Age (years) | *n* | Proportion of MSM | | Male population | No. of MSM | |
		Lower bound	Upper bound		Lower bound	Upper bound
16–17	372	0.005	0.009	–	–	–
18–19	312	0.000	0.004	–	–	–
20–24	826	0.016	0.018	–	–	–
16–24	1510	0.010	0.013	3,019,907	30,151	38,927
25–34	2132	0.026	0.027	3,460,727	89,979	93,440
35–44	2033	0.017	0.020	3,635,349	61,801	72,707
46–55[a]		0.016	0.019	3,219,359	51,993	61,168
56–65[a]		0.013	0.015	2,553,926	32,563	38,309
66–75[a]		0.00085	0.001	1,921,442	1633	1921
>75[a]		0	0	1,361,287	0	0

a Rates in 46–55, 56–65, 66–75, and ≥76 age ranges assumed to be 95%, 75%, 5% and 0% of the rates estimated for the 35–44 age range.

increasingly likely to develop symptoms or attend a genitourinary medicine clinic.

To allocate the estimated number of undiagnosed HIV-positive MSM by age and stage, relative likelihoods of remaining undiagnosed were assigned to individuals of different ages, based on clinical opinion. Individuals in the youngest age groups (15- to 25- and 26- to 35-year-olds) were assigned a relative value of 1; 36- to 45- and 46- to 55-year-olds, 0.5; and 56- to 65-year-olds, 0.25. An aggregate undiagnosed HIV-positive MSM population and a set of age-specific diagnosed HIV-positive MSM populations were sampled from relevant Poisson distributions. For each iteration, the non-adjusted numbers of undiagnosed HIV-positive MSM (aggregate undiagnosed cases multiplied by proportion of diagnosed cases in each age group) in each age group were multiplied by the relative likelihood weights, which were then adjusted proportionately so that the aggregate number of undiagnosed individuals equalled the sampled value from the range estimated by the SOPHID team.

The stage distribution was estimated by applying clinical opinion-based relative likelihoods that individuals in each of the three CD4 stages would remain undiagnosed (< 200 CD4, 0.05; 200–500 CD4, 0.1; > 500 CD4, 1), and then adjusting to equal the estimated aggregate number of undiagnosed HIV cases.

Finally, the estimated numbers of diagnosed and undiagnosed HIV-positive MSMs were converted to prevalence rate ranges by dividing the lower and upper estimates of the numbers by the upper and lower estimates of the relevant age-specific numbers of MSM in the general population, respectively. The resulting figures and presented in *Table 9*.

Transition probabilities for movement between the HIV states

Separate sets of transition probabilities were required for diagnosed and undiagnosed individuals. For undiagnosed individuals, mean estimates of the transition probabilities between the three defined states have been reported by Sweeting *et al.*[84] Goldie *et al.*[82] report transition

TABLE 9 *Modelled prevalence rates for HIV infection by CD4 count category in MSM*

CD4 count	Age group (years)	Diagnosed		Undiagnosed	
		Lower est.	Upper est.	Lower est.	Upper est.
< 200 CD4 count	15–25	0.0010	0.0023	0.0001	0.0002
	26–35	0.0034	0.0044	0.0002	0.0005
	36–45	0.0090	0.0122	0.0003	0.0007
	46–55	0.0060	0.0088	0.0002	0.0005
	56–65	0.0045	0.0074	0.0001	0.0002
	66–75	0.0052	0.0126	0.0000	0.0000
200–500 CD4 count	15–25	0.0090	0.0142	0.0013	0.0032
	26–35	0.0244	0.0275	0.0033	0.0066
	36–45	0.0555	0.0695	0.0038	0.0084
	46–55	0.0364	0.0470	0.0025	0.0056
	56–65	0.0242	0.0333	0.0009	0.0019
	66–75	0.0346	0.0557	0.0000	0.0000
> 500 CD4 count	15–25	0.0053	0.0089	0.0080	0.0194
	26–35	0.0169	0.0193	0.0234	0.0458
	36–45	0.0440	0.0554	0.0299	0.0664
	46–55	0.0269	0.0352	0.0187	0.0415
	56–65	0.0158	0.0224	0.0057	0.0127
	66–75	0.0148	0.0282	0.0000	0.0000

est., estimate.

data that aim to reflect the impact of HAART. The reported transition times from the two sources are similar for the highest CD4 count state, with a small difference estimated for the mean time spent in the intermediate CD4 state (4 years vs 3.63 years by Sweeting *et al.*[84] and Goldie *et al.*,[82] respectively). The transition probabilities used in the model are presented in *Table 10*; the lower and upper CIs are informed by multiplying the mean duration in each state by 1.25 and 0.75, respectively.

Clinical presentation rates by CD4 count state

Sweeting *et al.*[84] present an application of Bayesian back-calculation to estimate median estimates of the quarterly probabilities of diagnosis (with 95% credibility intervals) for each of the three CD4 count states for homosexual men between 1984 and 2002. These data are assumed to inform clinical presentation rates in MSM. *Table 11* presents the estimated ranges of the annual probabilities of clinical presentation, which were based on lowest and highest intervals between 1991 and 2002 as estimated by Sweeting *et al.*[84] These ranges were presented by uniform distributions in the calibration analysis.

Age-specific clinical presentation rates were estimated by applying subjectively defined weights that increased the likelihood of older MSM presenting clinically and reduced the probabilities in younger MSM.

Age-specific incidence rates of HIV

Sweeting *et al.*[84] also present aggregate annual estimates of the incidence of HIV in homosexual men from 1981 to 2002. A separate Markov model was developed in order to estimate age-specific HIV incidence rates using a range of alternative data sources.

The HIV incidence submodel assumes that:

- all individuals developing an HIV infection start in the '> 500' CD4 count category
- all individuals who developed HIV prior to 1990 were dead by the year 2005
- age-specific incidence rates of HIV have remained constant since 1990
- HIV progression from the '> 500' CD4 count category is not affected by treatment.

The estimation process involves the following stages. For individuals entering the '> 500' CD4 count state at every age between 15 and 84 years, the submodel estimates the probability that individuals remain in the '> 500' state at each subsequent age. Individuals may leave the '> 500' state due to transition to another CD4 state (informed by transition probabilities described above) or death (informed by UK male life tables as a CD4 count > 500) has been shown to have little effect on mortality.[85] The mean duration in the '> 500' state prior to transition to another CD4 state for both diagnosed and undiagnosed

TABLE 10 *Annual transition probabilities between HIV states*

		95% CI	
	Mean	**Lower**	**Upper**
Undiagnosed			
> 500 to 200–500 CD4 count	0.166	0.135	0.215
200–500 to < 200 CD4 count	0.221	0.181	0.283
Diagnosed			
> 500 to 200–500 CD4 count	0.166	0.135	0.215
200–500 to < 200 CD4 count	0.241	0.198	0.307

TABLE 11 *Annual probabilities of clinical presentation with HIV by CD4 count*

HIV category	Lower bound	Upper bound
CD4 count > 500	0.060	0.091
CD4 count 200–500	0.189	0.381
CD4 count < 200	0.570	0.984

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cases was estimated to be 5.5 years (transition probability = 0.166).[82,84] In the absence of empirical estimates, duration in the '> 500' state was assumed to be normally distributed with a subjective standard deviation of 1 year.

A simulation exercise was undertaken to identify the combinations of input parameter values (including age-specific HIV incidence rates) that best predicted the estimated age-specific prevalence of diagnosed and undiagnosed HIV-infected MSM with a CD4 count of > 500. Outputs from each iteration of the submodel were inputted to the following equation, which was solved for ages 15–84 years and combined into the seven age categories used by the HPA,

$$N(\text{CD4} > 500/\text{age\_in\_2005}) = \sum_{x=1}^{15} I_{(age-x)} \cdot P_{(age-x)}$$

where:

- x = 2005 minus current year of incidence (1990–2005)
- $I_{(age-x)}$ = incidence of HIV infected individuals with a CD4 > 500 at 'age in 2005–x' years
- $P_{(age-x)}$ = probability of incident cases at 'age in 2005–x' years remaining in the '> 500' state at 'age in 2005' years.

The calibration process identified 2451 of the 5000 eligible iterations that predicted aggregate numbers of HIV-infected MSM within the 95% CI estimated from the HPA data (11,722–15,718). Probabilities representing the likelihood that each of the 2451 parameter sets was the most relevant set were estimated using the following process:

1. For each model iteration, the sum of differences between the age-specific incidence estimates informed by the submodel and the bounds of the respective HPA-based 95% CIs were estimated.
2. The proportion of the sum of differences contributed by each iteration were estimated.
3. The reciprocals of the proportions of the sum of differences contributed by each iteration were estimated (no iterations had a sum of differences of zero).
4. The reciprocals were divided by the sum of the reciprocals to estimate the probability that each of the 2451 parameter sets was the most relevant set.

The calibrated age-specific annual incidence of HIV-infected MSMs were converted to incidence rates based on the number of MSM at risk of HIV

infection within each age range. These parameters were estimated as the prevalence estimate of all MSM (in each age range) minus the sum of prevalent HIV-infected MSMs at the start of each age range and one-half of all incident cases across each age range. The prevalence of HIV infected MSMs at the start of each age range was estimated by assuming that 90%, 85%, 80%, 75%, 70% and 65% of incident cases in the previous two age ranges (i.e. the previous 20 years) remain alive at the start and throughout the 15–25, 26–35, 36–45, 46–55, 56–65, 66–75 and 76+ age ranges, respectively.

This process was undertaken for each set of HIV incidence parameters that were included following the calibration of the HIV incidence model (as described above). The estimates for age groups over 66 years using the above process were unstable due to small numbers (e.g. estimated incidence probabilities ranged from negative values to 6.51). As the incident numbers were so small for these age groups, incidence rates of zero are assumed.

Mortality rates in HIV-positive individuals

Two studies were identified that assessed the RR of death in HIV-positive cohorts compared to mortality in the general population.[86,87] A third study presented quantitative estimates of the effects of CD4 count on the incidence of AIDS and non-AIDS related serious illnesses.[88]

Ormaasen *et al.*[86] evaluated HIV related and non-HIV related mortality compared with the general population before and after introduction of HAART. Median follow-up for 398 patients with HIV who were receiving HAART was 38 months. The RR for 5-year mortality compared with an age-matched Norwegian general population was 3.96 (95% CI 2.25 to 6.97) in the post-HAART era.

Martínez *et al.*[87] prospectively followed-up consecutive HIV-infected adults who were prescribed HAART in a Catalonian hospital between January 1997 and December 2004 or until death, loss to follow-up or discontinuation of HAART. RRs for all-cause mortality compared with an age-matched Catalonian general population were estimated from the figures presented by Martínez *et al.*, and are shown in *Table 12*. Mortality rates decreased over time in HIV-infected patients ($p < 0.001$, chi-squared test for trend), although the rate remained between four and seven times higher than that for the age-matched general population. The proportion of

AIDS-related deaths decreased significantly over time – from 84% in 1997 to 7% in 2004.

Baker *et al.*[88] found that the risk of non-AIDS defining illnesses decreased by around 16% for every 100 cell increment in CD4 cell count (hazard ratio 0.84, $p < 0.01$), while the risk of AIDS-defining events fell by 43% for every 100 cell increment in CD4 cell count (hazard ratio 0.57, $p < 0.01$). They calculated the risk of these events through a multivariate analysis, which adjusted for the latest viral load and CD4 cell count, age, gender, prior AIDS diagnosis, hepatitis co-infection and injecting-drug use.

Based on the above studies, the following parameter estimates were derived:

- relative risk for death of HIV patients compared with the general population = 4–7 (uniform distribution)
- proportion AIDS-related deaths = 0.07
- relative risk of AIDS for 100 CD count increment = 0.57 (subjective 95% CI 0.46 to 0.68)
- proportion non-AIDS-related deaths = 0.93
- relative risk of non-AIDS illness for 100 CD count increment = 0.84 (subjective 95% CI 0.73 to 0.95)
- distribution of CD4 < 200, 200–500, > 500 categories = 0.25, 0.5, 0.25, respectively.

A simulation process was applied to estimate the distributions of the RRs of death compared with the general population for patients in each of the three defined CD4 count categories (*Table 13*). First, RRs for mortality for the 200–500 and > 500 CD4 count categories, relative to the < 200 category, were informed by sampled values of the RRs for AIDS and non-AIDS-related illnesses. Second, the Solver function in EXCEL was used to fit the RR of death in patients with a CD4 count of < 200 to a sampled value for the overall RR of death for patients with HIV. This process was

TABLE 12 *Annual mortality rates in a HAART-treated HIV-infected cohort and an age-matched Catalonian general population, and associated RRs*

| Year | Mortality rate per 100 person-years | | RR |
	HIV positive	General population	
1997	4.497	0.200	22.49
1998	2.694	0.200	13.47
1999	1.618	0.200	8.09
2000	0.895	0.200	4.47
2001	0.925	0.200	4.62
2002	1.030	0.200	5.15
2003	1.236	0.200	6.18
2004	1.317	0.200	6.58

TABLE 13 *Relative risks of death for HIV-positive individuals by CD4 count and diagnosis status*

| CD4 count | Mean | Percentile | |
		2.5th	97.5th
Treated			
< 200	8.56	5.89	11.62
200–500	5.24	3.57	7.16
> 500	3.01	1.49	5.41
Untreated			
< 200	53.37	39.51	69.88
200–500	16.07	10.65	22.64
> 500	4.35	1.36	10.52

repeated 1000 times to obtain a joint distribution of the RRs for the three CD4 count categories.

A similar process was undertaken for non-diagnosed HIV patients based on the combined RR for death observed in 1997 (uniform distribution 17.5–27.5) and the proportion of AIDS-related deaths in 1997 (84%), which was assumed to be representative of the pre-HAART era.

Anal cancer epidemiology and natural history

Values for the following anal cancer transition probabilities were required:

- no AIN to LG-AIN
- no AIN to HG-AIN
- progression from LG-AIN to HG-AIN
- progression from HG-AIN to early stage invasive cancer
- progression from early stage invasive cancer to late stage invasive cancer
- regression from LG-AIN to no AIN
- regression from high-grade to LG-AIN.

The estimation of these parameters is discussed in the following sections, as well as in the model calibration section.

Data sources for incidence and progression up to HG-AIN

Two studies, published in the mid- to late 1990s, inform parameter estimates of the natural history of anal cancer in HIV-negative and positive homosexual men.[57,61,70,89] Other studies were excluded on account of the absence of any histological follow-up, for example Sayers *et al.*[90] report a study based in Edinburgh, which followed up 20 HIV-positive men with dyskaryosis that was suggestive of AIN.

Critchlow *et al.*[89] undertook a prospective study beginning in January 1991, which followed 158 HIV-positive and 147 HIV-negative men in Seattle, Washington. This study excluded men with any positive cytology at baseline. *Figure 4* describes the pathway to the final study sample. The mean follow-ups were 20.2 and 22.1 months for HIV-negative and positive men, respectively.

The other main study recruited a prospective cohort of homosexual and bisexual men in San Francisco between November 1991 and March 1994.[57,61] Analyses from the study are presented after 2-year[70] and 4-year follow-up[57] periods. The pathways to inclusion for these two analyses are presented in *Figures 5* and *6*.
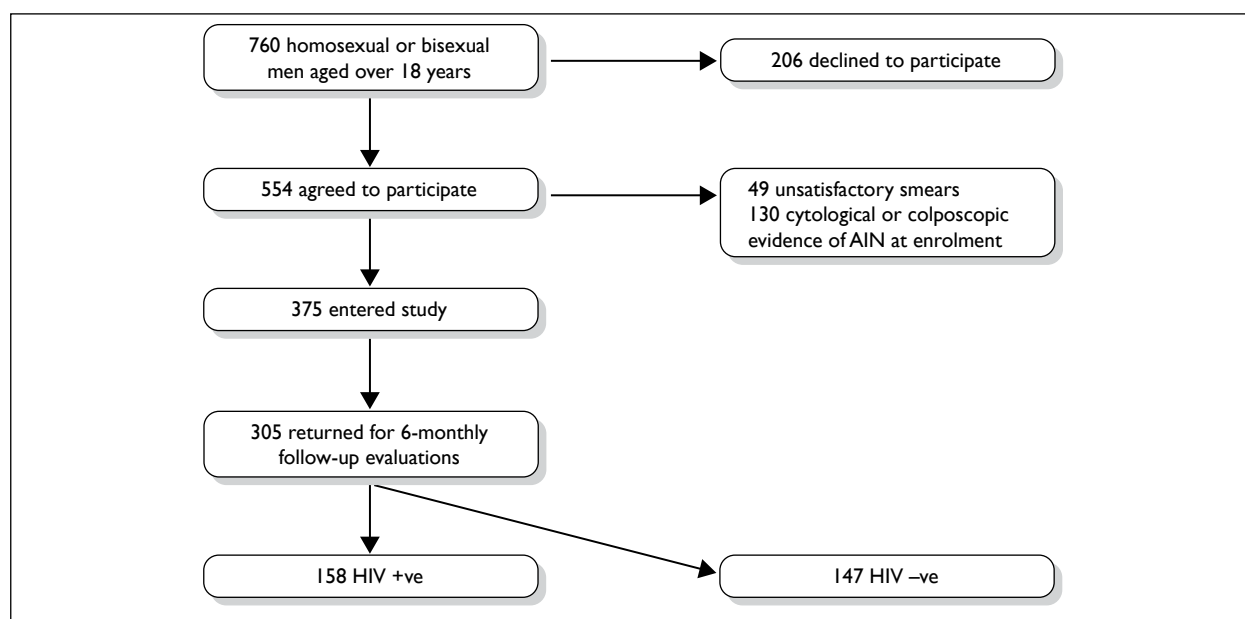
FIGURE 4 *Seattle study: pathway to study sample.*
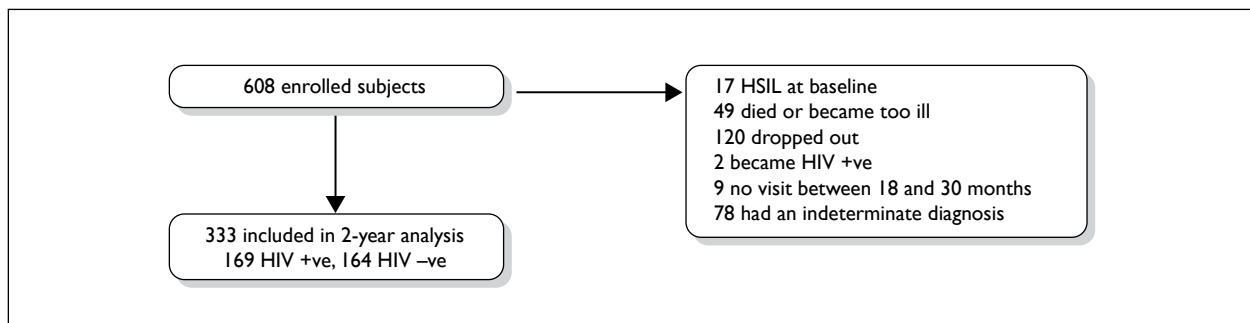
FIGURE 5 *San Francisco study, 2-year analysis: pathway to study sample.*
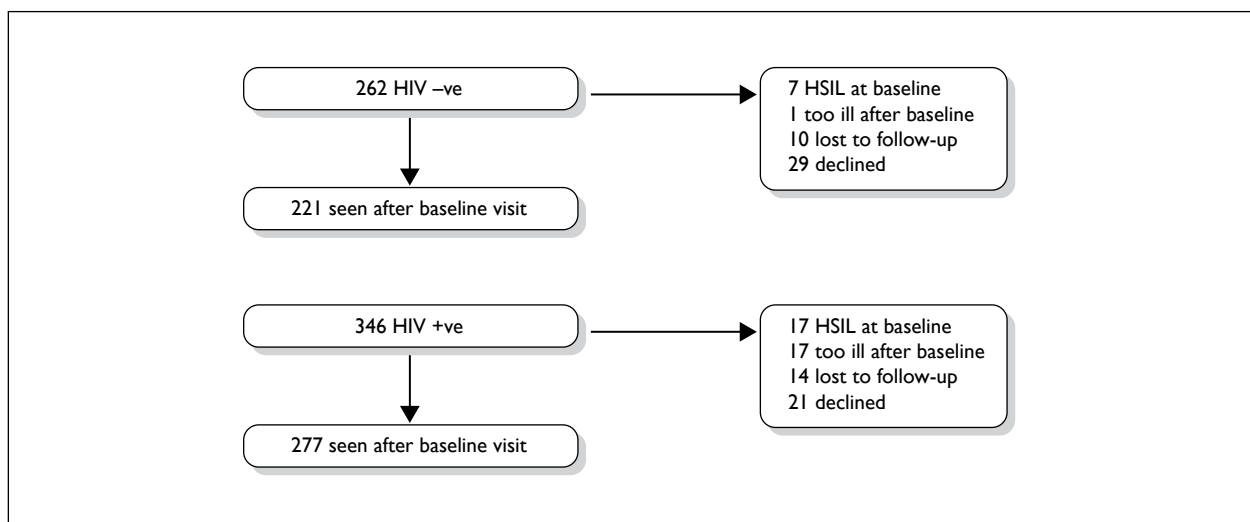
FIGURE 6 *San Francisco study, 4-year analysis: pathway to study sample.*

Analyses of the Seattle and San Francisco cohort studies

The data from the two natural history studies were analysed using methods that are categorised as either complex or simple. The complex analysis used literature-based sources to control for false-negative and false-positive results in 'cytology alone'-detected cases, the unobserved development of low-grade disease prior to high-grade disease, the timing of events and incomplete follow-up. The simple analyses treat the data 'as is' and restrict the application of assumptions to a minimum. The

complex analyses are described first, followed by the simple analyses.

Table 14 presents the relevant results from the Seattle study.

To estimate the direct transition probability from normal to HG-AIN, the numbers of incident HG-AIN cases (direct from no AIN) were adjusted to account for the sensitivity and specificity of cytology. The follow-up times were adjusted to account for the cases developing LG-AIN prior to

TABLE 14 *Seattle study: AIN incidence*

HIV status	n	Mean follow-up	HG-AIN incidence	LG-AIN prior to HG-AIN	HG-AIN diagnosis	
					Histology	Cytology
HIV positive	158	20.2	24	14	13	11
HIV negative	147	22.1	8	4	4	4

HG-AIN. The following assumptions and analyses were undertaken:

- Of the 15 cytologically detected cases, nine did not undergo biopsy and six did receive biopsy but could not locate areas of high-grade disease. In eight of the nine cases without biopsy, the cytological findings did not return to normal over a mean 16.5 additional months; in five of the six cases with biopsy, the cytological findings did not return to normal over a mean 23.8 additional months. The implication that the number of true-positives is between 9 and 13 (60–87% specificity). Palefsky *et al.*[57] state that they found that 70% of cytologically identified HG-AIN cases were confirmed histologically when a lesion was seen (for HIV-positive men), although the data reported in the referenced paper indicate that the rate is between 57% and 60%.[28] No cytological high-grade cases were reported in HIV-negative men in the screening study paper.[28]
- Based only on high-grade cytological screen results, the data presented by Palefsky *et al.*[57] indicate a sensitivity rate for the detection of histologically defined HG-AIN of 27% (3 out of 11) in HIV-positive men, and 0% (0 out of 1) in HIV-negative men. Panther *et al.*[30] stated that the detection of HSILs on an anal Pap smear had a sensitivity of 47% (95% CI 35 to 59) and specificity of 90% (95% CI 81 to 96%) for detection of a high-grade histological finding.
- In the Seattle study, subjects with cytological evidence of HG-AIN *or* visible evidence of abnormalities of the internal anal canal were referred for biopsy. Thus, sensitivity is likely to be markedly increased compared with the use of cytology alone, while specificity may be reduced. Based on the above data describing test characteristics, a range of 60–87% was assumed for specificity, and a range of 80–90% was assumed for sensitivity for the Seattle study observations of HG-AIN that were not detected histologically.
- Based on the Palefsky *et al.* screening study,[28] sensitivity rates of 48.5% and 27.8% were defined for the detection of LG-AIN for HIV-positive and negative men, respectively. Specificity rates of 43.8% and 55.6% were defined for LG-AIN for HIV-positive and negative men, respectively. These estimates were used to adjust the numbers of HG-AIN cases detected in the absence of prior low-grade disease.

- The mean follow-up time was re-estimated to exclude the time post development of LG-AIN (LG-AIN was assumed to occur at the mid-point of the mean follow-up). This will still overestimate the mean follow-up time, as it was not possible to exclude follow-up time in men developing LG-AIN who did not subsequently develop HG-AIN.

Observed transition matrices for HIV-negative and positive men between baseline and 2 years in the San Francisco study are presented in *Table 15*. *Table 16* presents the relevant data published from the 4-year analysis:

- The San Francisco data were simplified by assuming that the ASCUS cases were normal. The numbers of high-grade cases were re-estimated using the same methodology and sensitivity and specificity rates as used for the analysis of the Seattle data (including the number of normal to high-grade cases that passed through LG-AIN based on the Seattle data, by HIV status). In the 2-year analysis, the proportions of normal to HSIL, and LSIL to HSIL cases detected histologically were assumed to be the same as reported for the 4-year analysis.[57]
- The 2-year data included only men who were observed over the full 2-year study period, and it was assumed events occurred at the mid-point.
- The 4-year data presented in *Table 16* report the numbers of observed cases of HG-AIN over the 4-year follow-up period, but do not indicate the mean follow-up time, assuming a 4-year follow-up period would underestimate the incidence figures. Total person-years at risk are presented for HIV-negative and HIV-positive men for the estimation of RRs of developing HG-AIN.[57] Dividing the person-years by the respective numbers of HIV-negative and HIV-positive men estimates mean follow-up times of 2.4 and 2.7 years, respectively.
- Presented life table analysis of the 4-year data predicted that 49% of HIV-positive men would develop HG-AIN at 4 years' follow-up[57] compared with the 38% estimated from the data reported in *Table 16*. Applying the monthly progression rate implied by the 49% event rate at 4 years (1.4%), the mean follow-up time at which 38% progression would be expected to be observed is 34 months (2.8 years). This analysis provides some evidence that the progression rate is approximately stable.

TABLE 15 *San Francisco study: transition matrices between baseline and 2 years*

Status at baseline[a]	Status at 2 years[a]			
	Normal	**ASCUS**	**LSIL**	**HSIL**
HIV positive				
Normal	28	14	28	17
ASCUS	5	3	10	9
LSIL	0	0	21	34
HIV negative				
Normal	101	13	12	11
ASCUS	6	3	3	1
LSIL	4	1	4	5

a Based on the highest grade of lesion determined by cytology and histology.

TABLE 16 *San Francisco study: incidence of HG-AIN by baseline status*

Status at baseline	*n*	Incident HSIL during 4-year follow-up		
		Cytological	**Histological**	**Either**
HIV positive				
Benign	115	20	28	34
Indeterminate	27	4	8	10
ASCUS	45	8	15	15
LSIL	90	27	43	47
Total	277	59	94	106
HIV negative				
Benign	173	9	16	20
Indeterminate	14	0	3	3
ASCUS	17	2	4	4
LSIL	17	6	6	7
Total	221	17	29	34

- The 2-year data indicates zero regression from LG-AIN to no AIN in HIV-positive men, and a 36% LG-AIN regression rate in HIV-negative men. Other observations may have passed through two states prior to their status at 2 years, for example a case in LSIL at baseline and 2 years may have regressed to normal and then progressed back to LSIL.

Separate sets of simpler analyses were also undertaken that did not adjust for test sensitivity and specificity, that estimated person-years at risk assuming individuals experiencing an AIN event had one-half of the follow-up of those not experiencing an event, and that one-half of the observed cases of HG-AIN (in individuals with no AIN at baseline) experienced prior LG-AIN.

Outputs from the Seattle and San Francisco cohort studies analyses

The results of the complex data analyses are presented in *Table 17*. Transition probabilities from no AIN to LG-AIN show that HIV-positive men are significantly more likely to develop LG-AIN, whereas HIV-negative men are more likely to regress back to a normal state once they have developed LG-AIN.

The CIs from all three analyses of the direct transition probabilities from no AIN to HG-AIN overlap in both HIV-positive and HIV-negative men. No significant difference is observed between HIV-positive and HIV-negative men.

More divergence is noted in the transition probabilities between LG-AIN and HG-AIN that were based on the 2- and 4-year San Francisco data. The 2-year data lead to a significantly higher estimate of the transition probabilities, which may be partially explained by differential disease severity profiles in the two cohorts. Higher proportions of men in the 4-year analysis had CD4 counts of < 200 (29% vs 19%) and < 500 (71% vs 66%). Thus, the higher estimated transition probabilities in the 2-year data are unlikely to be due to increased disease severity. Indeed, regarding the 2-year analysis, Palefsky *et al.*[70] state that 'the true incidence in HIV-positive men may have been underestimated, because subjects with the most advanced immunosuppression were less likely to have been included in the 2 year analysis' (p. 318).

Uncertainty around the follow-up times may also affect the comparison. For example, although the 4-year data analysis is informed by a clearer aggregate estimate of the timing of events, it was not possible to define separate follow-up intervals by baseline AIN status. In HIV-positive men, the mean follow-up to detection of HG-AIN (or the end of the study follow-up period) was 2.4 years, but the mean follow-up in men with LG-AIN at baseline would likely be significantly less. If follow-up in this cohort was reduced by one-third to 1.6 years, the resulting transition probabilities would have been 0.366 (original value 0.595) and

0.281 (original value 0.35) in HIV-positive and HIV-negative men, respectively.

Table 18 presents the results of the simplified analyses of HG-AIN incidence by HIV status and AIN at baseline status, based on the 4-year San Francisco data. *Table 19* presents incidence rates of LG-AIN by HIV status, based on the 2-year San Francisco data. The simplified analyses generally produce lower progression estimates than the more complicated analyses presented in *Table 17*.

As a result of the uncertainties and assumptions involved in the above analyses, it was decided to base the initial calibration analyses on the relevant estimates produced by the simplified analyses of the 2- and 4-year San Francisco data, as presented in *Tables 18* and *19*. Estimates of the regression rates from LG-AIN were informed by the complex analysis of the 2-year San Francisco data, as presented in *Table 17*.

AIN progression by HIV status

The 2- and 4-year analyses of the San Francisco study both present estimates of the RRs for anal lesion progression (including progression from normal to any grade AIN, and from LG-AIN to HG-AIN) for HIV-positive men with differing CD4 counts (> 500, 200–500, < 200) compared with HIV-negative men. The RRs are presented in *Table 20*. The results show that HIV status and CD4 count are significant predictors of anal cancer progression (the *p*-value test for trend was < 0.0005).

None of the observed increases in RR between the 2- and 4-year follow-up was statistically significant,

TABLE 17 *Annual transition probabilities from the complex analyses of AIN incidence and progression*

| | HIV positive | | | HIV negative | | |
| | | San Francisco | | | San Francisco | |
Transition	Seattle	2-year data	4-year data	Seattle	2-year data	4-year data
Normal to LG-AIN	–	0.523 (0.413 to 0.632)	–	–	0.072 (0.034 to 0.122)	–
Normal to HG-AIN	0.027 (0.004 to 0.056)	0.069 (0.008 to 0.152)	0.041 (0.005 to 0.085)	0.021 (0.008 to 0.040)	0.057 (0.024 to 0.103)	0.037 (0.019 to 0.058)
LG-AIN to normal	–	0.017 (0.000 to 0.063)	–	–	0.071 (0.002 to 0.236)	–
LG-AIN to HG-AIN	–	0.595 (0.464 to 0.716)	0.260 (0.197 to 0.331)	–	0.350 (0.129 to 0.599)	0.180 (0.075 to 0.322)
95% CIs are shown in parentheses.						

TABLE 18 *Annual incidence rates for HG-AIN by HIV status and AIN at baseline status from the simple natural history analyses*

	n	No HG-AIN	HG-AIN	Person-years	Person-years at risk[a]	
					Per non-HG-AIN case	Per HG-AIN case
Summary data						
HIV negative	221	188	33	671	3.3	1.65
HIV positive	277	170	107	593	2.7	1.35
LG-AIN to HG-AIN annual transition probabilities						
LSIL at baseline	n	No HG-AIN	HG-AIN		Total person-years at risk	Mean (95% CIs)
HIV negative	17	10	7		44.3	0.158 (0.068 to 0.278)
HIV positive	90	43	47		218.2	0.215 (0.164 to 0.272)
Normal to HG-AIN annual transition probabilities						
Normal at baseline	n	No HG-AIN	HG-AIN	HG-AIN without prior LG-AIN	Total person-years at risk	Mean (95% CIs)
HIV negative	204	178	26	13	626.7	0.021 (0.011 to 0.033)
HIV positive	187	127	60	30	515.1	0.058 (0.040 to 0.080)

a Person-years at risk per individual who did and did not develop HG-AIN were fitted to the observed person-years at risk, assuming years at risk in individuals experiencing HG-AIN were one-half of those in individuals not developing high-grade disease.
CIs estimated by describing the observed data as beta distributions.

TABLE 19 *Low-grade AIN incidence by HIV status from the simple natural history analyses*

	Status at 2 years			Revised status at 2 years[a]			Normal to LG-AIN annual transition probabilities: mean (95% CIs)
Status at baseline	Normal (+ASCUS)	LSIL	HSIL	Normal (+ASCUS)	LSIL	Pys[b]	
HIV positive							
Normal	28	28	17	28	36.5	92.5	0.395 (0.298 to 0.496)
Normal + ASCUS	50	38	26	50	51	151	0.338 (0.265 to 0.415)
HIV negative							
Normal	101	12	11	101	17.5	219.5	0.080 (0.048 to 0.119)
Normal + ASCUS	123	15	12	123	21	267	0.079 (0.050 to 0.114)

a Observed status at 2 years revised to account for the assumed 50% of HG-AIN cases that would have developed LG-AIN initially.
b Person-years estimated by assuming that patients remaining in the normal state had 2 years' follow-up and patients developing LG-AIN had 1-year follow-up.
CIs estimated by describing the observed data as beta distributions.

although the increase in CD4 < 200 approached significance. As it is not possible to disentangle the specific effects, if the observed increase is a true result it may be an indication that incidence increases with age (within the age range of the study cohort) and/or AIN progresses at an increasing rate in HIV-positive MSM. It is also noted that the analysis of the 4-year cohort was not an extension of the 2-year analysis – different

TABLE 20 *Relative risks for HG-AIN by HIV status*

HIV status	RRs (95% CIs)		
	2-year follow-up	4-year follow-up	Model inputs
HIV negative	1	1	1
HIV positive CD4 >500	1.8 (1.2 to 2.6)	2.1 (1.1 to 3.5)	2.1 (1.1 to 3.5)
HIV positive CD4 200–500	2.7 (2.0 to 3.6)	3.3 (2.1 to 5.3)	3.3 (2.0 to 5.3)
HIV positive CD4 <200	3.1 (2.3 to 4.1)	5.8 (3.7 to 9.3)	5.8 (2.3 to 9.3)

inclusion criteria led to significant differences in the disease severity profiles of the two cohorts.

Given the uncertainty around the time dependence of the AIN progression parameters in HIV-positive MSM, the model did not incorporate this aspect. The RRs (and CIs as presented in *Table 20*) were used to adjust aggregate transition probabilities to HG-AIN for HIV-positive patients by CD4 count.

Progression from HG-AIN to invasive anal cancer

Marchesa *et al.*[91] report on 47 patients with HG-AIN treated surgically between 1972 and 1993 (retrospectively followed up). Three cases of invasive anal cancer were observed in the conservatively treated group (20 patients). The duration of follow-up in the radical and conservative groups is not stated, although the overall median duration was 104 months (range 16–273). In addition, 35 patients who were symptomatic at the time of detection of HG-AIN had experienced symptoms for a mean duration of 19 months (range 1–120).

Other relevant studies reported no incidence of anal cancer, including the Seattle and San Francisco studies and prospective studies of patients treated for HG-AIN.[43,92]

Given the limited data informing progression from HG-AIN to anal cancer, alternative uniform distributions for this transition probability were tested during the full model calibration process.

No evidence of increased progression rates in HIV-positive MSM was identified and so separate transition probabilities for HIV-negative and HIV-positive MSM were not estimated. However, the probability of transition to anal cancer was assumed to increase with age. The rationale behind the use of age-specific transition probabilities was that an increasing likelihood of

transition with increased lesion duration has been observed in other cancer models (e.g. colorectal cancer[93]). Infeasible increases in model complexity prevented the direct modelling of time dependent transition probabilities, so the use of age increasing transition probabilities acted as a proxy for this potential relationship.

Aggregate transition probabilities (sampled from a uniform distribution) were converted to age-specific probabilities assuming RRs of transition (compared with age group 15–25 years) of 1, 1.5 and 5 for ages 26–35, 36–45 and over 45 years. Weighted aggregate RRs (estimated using the estimated numbers of MSM in each age category) were fitted to sampled aggregate transition probabilities. The reference case transition probabilities are presented in *Table 21* (the calibration process is described in Chapter 6).

In the earlier cost-effectiveness analysis of anal cancer, Goldie *et al.*[81,82] fitted an annual transition probability of approximately 5% in HIV-positive MSM and 3.6% (range 0.36% to 6%) in HIV-negative MSM. This is a major area of difference in the current study and potential reasons are explored in the model sensitivity analyses.

Treatment of AIN lesions

Chin-Hong and Palefsky[94] state that AIN 1 (LG-AIN) is treated to reduce risk of further spread or enlargement to the point at which topical therapy is no longer possible. They also present treatment algorithms describing treatment pathways for AIN 1 and AIN 2 or 3. In both cases, small lesions are treated topically (common therapies are liquid nitrogen and 80% trichloroacetic acid). Medium or large AIN 1 lesions are surgically removed only if symptomatic. AIN 2 or 3 lesions are treated whenever possible. They also state that treatment of HIV-positive patients with AIN is more challenging as lesions are often larger and recur at a higher rate or are never eliminated at all.

TABLE 21 *Annual transition probabilities from untreated HG-AIN to anal cancer*

Age (years)	Mean (95% CIs)
15–35	0.0009 (0.0006 to 0.0012)
36–45	0.0014 (0.0009 to 0.0018)
45+	0.0045 (0.0032 to 0.0060)

We contacted Dr Chin-Hong to try to ascertain the proportion of AIN 2 or 3 lesions that present as small lesions that may be treated topically, as no indication of the proportion of AIN 2 or 3 lesions that are amenable to topical treatment was identified in the literature. He responded that parameter estimates will depend on whether the patient is HIV positive or negative. In general, for AIN 2/3, only about 10–20% present as small lesions and the rest (80–90%) have to be referred to surgery. If small enough, topical therapy will be effective in about 65–75% of cases.

Dr Chin-Hong pointed out that his experience is based on a clinic population that probably has a higher proportion of more complex cases. It is possible that a general clinic-based population will have a higher proportion of men with smaller lesions. He also talked about the use of an outpatient method called infrared coagulator (IRC), where many of these lesions can be treated very effectively as outpatients (regardless of size). The impact of this change could lead to only 10% of these lesions being referred to surgery. However, the extent to which this technology is being used in the UK is unclear.

Chang *et al.*[92] undertook a prospective study of 37 patients treated surgically for large-volume HSILs. Eight HIV-negative patients were followed up for a mean period of 32.3 ± 20.6 months, during which time zero recurrences were observed. Twenty-nine HIV-positive patients were followed up (28.6 ± 12.9 months) with 23 recurrences occurring. Mean time to recurrence was 12 months. The Kaplan–Meier analysis demonstrates that risk of recurrence approaches 100% by 50 months. However, recurrent HSIL can be retreated and no cases of anal cancer were reported in this cohort. In a survey of side effects, 16 out of 29 reported uncontrolled pain for a mean of 2.9 weeks (range 1 day to 4 months).

Brown *et al.*[43] followed up 34 patients who received surgical intervention for HG-AIN. The paper implies that 24 patients underwent a local excision, while the remaining 10 patients received a complete excision±grafting. After a median follow-up of 41 (range 12–104) months, 14 patients (41%) developed recurrent HG-AIN; 13 of the 14 recurred within 1 year, while 4 of the 14 patients experienced more than one excision of recurrent disease – two in one patient, four in two patients and seven in one patient. No patient developed carcinoma but five had complications of anal stenosis or faecal incontinence.

Marchesa *et al.*[91] report on 47 patients with HG-AIN, who were treated between 1972 and 1993 (retrospectively followed up). Patients receiving radical operations (27 patients) (wide local excision/abdominoperineal resection) had a statistically significantly lower recurrence rate than those receiving conservative operations (20 patients) (local excision/laser vaporisation): Kaplan–Meier 7-year recurrence rates of approximately 23% versus 70%.

On the basis of these data, treatment of LG-AIN was not modelled because treatment effectiveness is not established and the proportion of potentially treatable LG-AIN is unknown.

All detected HG-AIN lesions are assumed to receive treatment. It is assumed that 20–30% of detected HG-AIN is small enough to be treated non-surgically. The remainder was assumed to receive the seemingly more effective radical surgery, defined as wide local excision. The effectiveness of both forms of treatment was assumed to be similar, with a RR of between 0.2 and 0.4 for progression to anal cancer. The high rate of effectiveness incorporates the treatment of recurrences, with the average HIV-positive patient assumed to receive treatment for recurrence every 2 years. Recurrences in HIV-negative patients were assumed to be less common, occurring once every 10 years.

Progression of treated and non-treated anal cancer

The anal cancer model was initially specified to differentiate between early-stage (primary) and late-stage (metastatic) anal cancer. Evidence informing the progression of early-stage anal cancer following treatment was identified from selected treatment papers. Only two studies[42,96] presented any information regarding progression from early- to late-stage disease, and these data were of limited value, as the absolute rate of progression was unclear and no information on

the timing of progression was presented. No data describing prognosis in patients with metastatic anal cancer were identified.

Assumptions of similar progression rates, and effects of metastatic disease, to those reported for other cancer locations (e.g. breast or cervical cancer) were considered. However, similar data limitations and/or significant additional assumptions and uncertainties precluded this approach.

As most studies presented survival rates following treatment of early-stage anal cancer, the model structure was adapted and the distinction between early-stage and late-stage anal cancer was removed. The final model structure described transition to death from a single anal cancer state.

The review section presented the reported mortality rates in treatment studies of early stage anal cancer, from which relevant studies were selected to populate the model. Most studies included patient populations that are unlikely to be representative of the population of MSMs with anal cancer.

Survival is therefore estimated in two parts. First, non-anal cancer-related mortality rates are estimated separately for HIV-positive and HIV-negative patients. HIV-negative patients were assumed to have the same mortality rate as the general population, while an additional cause of mortality (RR between 4 and 7) was assumed in HIV-positive patients (see Chapter 5, Mortality rates in HIV-positive individuals).

Second, anal cancer-specific mortality was estimated from the reviewed papers. *Table 22* summarises the study characteristics and relevant survival estimates. Disease-specific survival (DSS) in treated patients was informed by the more effective chemoradiation (CMT) arm of the UKCCCR trial. The UKCCCR trial included patients with metastatic disease, although only 15 out of 585 patients were identified as having metastases at trial entry.[40] In the chemoradiation arm, 77 out of 111 (69%) deaths were related to anal cancer or treatment for anal cancer (7 out of 77). The presented Kaplan–Meier analyses for deaths from anal cancer show 5-year survival of 52% and 64% in the RT and CMT arms, respectively. A subjective 95% CI of 0.54 to 0.74 was assumed around the mean 5-year DSS of 0.64.

Oehler-Janne *et al.*[64] matched 10 HIV-positive patients treated with HAART with 10 HIV-negative patients based on TNM stage (80% T1/2), age (44.5 years) and grading (80% G1/2). Overall survival at 1 year was 90% and 100% in the HIV-positive and negative groups, respectively. At 5 years, survival was 70% and 69%, respectively. Although based on a very small sample, in the current era of HAART, these data were used to inform an assumption of equal anal cancer-related mortality in HIV-positive and HIV-negative patients with early-stage anal cancer.

To estimate survival probabilities in individuals with untreated anal cancer, the mean 5-year DSS in the RT arm of the UKCCCR trial was defined as the upper 95% CI interval. The mean was subjectively estimated to be 0.42, and the lower CI interval to be 0.32.

Anal screening test and clinical presentation parameters

Parameters associated with the process of clinical diagnosis, leading to potential treatment are described in the following sections.

Clinical presentation

To estimate clinical presentation probabilities in individuals with undiagnosed anal cancer, reference was made to Wong *et al.*,[95] who reported on their local experience between 1991 and 2001. In the absence of screening they found that of 50 presenting patients, only four presented with metastatic disease. This implies that most patients present prior to the distant spread of disease. The parameter values remains highly uncertain, although it is assumed that diagnosed HIV-positive patients are more likely to be diagnosed with anal cancer due to their higher contact rate with the health service.

Table 23 presents the ranges that were included in the final calibration analysis for the annual clinical presentation probabilities for HIV negative or undiagnosed HIV positive, and diagnosed HIV-positive individuals. Alternative probabilities were specified for HG-AIN, and for anal cancer. The values were sampled from uniform distributions.

Screening test characteristics

A recent published systematic review of six eligible screening studies (two studies with methodological issues were excluded) found the sensitivity of anal Pap smear evaluation compared with HRA-

TABLE 22 Summary table for survival postanal cancer studies

| Stage | UKCCR | | Doniec | Wong | Edelman | Place | Stadler | Oehler-Janne | | |
	CMT	RT						HIV–	Matched HIV–	HIV+
Country	UK	UK	Germany	Australia	USA	USA	USA	Switzerland		
No.	292		50	38	17	14	8	81	10	10
Age	63 (26–85)	65 (26–88)	64±15	62	38 (31–47)	42±9	44 (34–61)	62±13	45.2±7	44.5±10
T1	0.13	0.13	0.20	0.33	0.38	0.21	–	0.15	0.2	0.2
T2	0.32	0.37	0.57	0.29	0.38	0.36	–	0.43	0.6	0.6
T3	0.40	0.39	0.20	0.27	0.25	0.43	–	0.31	0.2	0.2
T4	0.15	0.11	0.03	0.10	0.00	0.00	–	0.11	0	0
Node positive	0.23	0.18	0.30	0.18	0.31	0.43	–	0.605	0.1	0.1
Metastatic	0.03	0.02	0.00	0.08	0.12	0	–	–	0	0
HIV positive	–	–	–	0.17	1	1	1	0	0	1
HAART	N/A	N/A	N/A	–	–	0	1	N/A	N/A	1
5-year OS	0.49	0.4	0.74	0.63	0.33	0.2	0.43[a]	0.69[a]	0.69[a]	0.7[a]
5-year DSS	0.64	0.52	0.82	0.67[a]	–	–	0.43[b]	0.87[a]	1[a]	0.82[a]

DSS, disease-specific survival (individuals who die of causes other than anal cancer are censored); N/A, not applicable; OS, overall survival.
a These 5-year survival estimates were derived from non-5-year estimates assuming an exponential decay.
b If two observed deaths assumed to be due to anal cancer, as implied in text.

TABLE 23 *Annual clinical presentation rates*

AIN and HIV status	Range (%)
HIV negative, HG-AIN	1–3
HIV positive, HG-AIN	5–10
HIV negative, anal cancer	3–8
HIV positive, anal cancer	10–15

directed biopsies to be between 69% and 93%, with specificity being between 32% and 59%.[36] The ranges reported by the published review are similar to those found by the current review reported in the section on screening.

Variation in the results of the screening studies may be due to differences in the extent to which screen results were histologically confirmed, positive test definitions (i.e. whether an ASCUS result is defined as a positive screen), as well as the characteristics of the included individuals (e.g. Palefsky *et al.*[28] and Cranston *et al.*[34] reported different test characteristics in HIV-positive and HIV-negative MSM). These potential sources of variation precluded the application of meta-analytical methods to estimate screening test characteristics, and so the parameter values are informed by the presented ranges, with adjustment for differential rates in HIV-positive and HIV-negative MSM.

Table 24 presents analyses of test characteristics based on screening data for HIV-positive and HIV-negative MSM under alternative assumptions.[28] The results show that anal cytology is predicted to be a highly specific test in HIV-negative MSM, although sensitivity is low. Sensitivity is improved in HIV-positive MSM, particularly when ASCUS is defined as a positive test.

The studies include very few cases of HG-AIN and so the assumption of differential test characteristics based on lesion type is not included in the model. The model does differentiate between test characteristics in HIV-negative and positive MSM, and assumes that an ASCUS test result would be considered a positive test.

Table 25 presents the screening test parameter values, which were based on the reported aggregate ranges,[36] subjectively adjusted for the differences between HIV-positive and HIV-negative patients (based on the rates presented in *Table 23*). The presented data were represented as triangular distributions in the screening model.

The second category of screening parameters describes the likelihood that individuals eligible for screening will attend for screening. Cranston *et al.*[34] reported that around 10% of 125 MSM who were invited to take part in a screening study refused. However, as Knight[50] suggests, the more limiting factor is likely to be the identification of MSM to whom screening can be offered.

Men who have sex with men indicate that their preferred sources of safer sex support are predominantly friends, the gay press and sexual peers rather than formal HIV services.[96] A corresponding literature review concerning *MSM in Public Sex Environments* distinguishes between MSMs who identify as being either gay men or bisexual men, and MSM who do not identify as either.[97] The authors found that MSM who do not identify as gay or bisexual have not been reached in significant numbers.

Without direct quantitative estimates of the effectiveness of the identification of MSM from the literature, it was assumed that screening would be offered to 40–60% of HIV negative or undiagnosed HIV-positive MSM, and 80–90% of diagnosed HIV-positive MSM. It is further assumed that 5–20% of all MSMs offered screening will refuse.

Costs

Cost inputs to the anal cancer screening model include the cost of screening, costs of diagnosis of precancerous AIN lesions, costs of diagnosis of anal cancer, and costs of treating diagnosed anal cancer. The estimation of these parameters is described in the following sections.

Costs of screening for anal cancer

Goldie *et al.*[82] present estimates of the cost of anal cytology screening in the USA, using Medicare average allowed charges. In the earlier paper, screening costs are based solely on the cost of an anal Papanicolaou smear (cost US$26), whereas the later paper includes also the cost of a 'brief office visit' at an apparent additional cost of US$50.

In preference to using US costs, we have based our screening cost estimates on detailed costs estimated for the provision of cervical cancer screening in the UK.[98] The estimated cost per screen in this report was estimated to be £22.99 (range £20.52–28.17).

TABLE 24 *Screening test characteristics for the detection of ASILs*

	Normal	ASIL	Sensitivity	Specificity
Palefsky, HIV-negative MSM (assuming lesions seen, but not biopsied, were ASILs)				
Normal	204	21		
ASCUS	13	4	0.30 (0.15 to 0.5)[a]	0.92 (0.88 to 0.95)[a]
ASIL	4	5	0.17 (0.06 to 0.35)[b]	0.98 (0.95 to 0.995)[b]
Palefsky, HIV-negative MSM (assuming lesions seen, but not biopsied, were not ASILs)				
Normal	215	10		
ASCUS	13	4	0.47 (0.25 to 0.705)[a]	0.93 (0.88 to 0.955)[a]
ASIL	4	5	0.26 (0.1 to 0.51)[b]	0.98 (0.95 to 0.995)[b]
Palefsky, HIV-positive MSM (assuming lesions seen, but not biopsied, were ASILs)				
Normal	163	43		
ASCUS	59	33	0.67 (0.58 to 0.75)[a]	0.59 (0.53 to 0.65)[a]
ASIL	53	55	0.42 (0.335 to 0.51)[b]	0.81 (0.75 to 0.85)[b]
Palefsky, HIV-positive MSM (assuming lesions seen, but not biopsied, were not ASILs)				
Normal	175	31		
ASCUS	69	23	0.69 (0.59 to 0.78)[a]	0.57 (0.51 to 0.63)[a]
ASIL	62	46	0.46 (0.36 to 0.56)[b]	0.80 (0.75 to 0.84)[b]

a Rate assuming that ASCUS is a defined as a positive screen result.
b Rate assuming that ASCUS is a defined as a negative screen result.
95% CIs are shown in parentheses.

TABLE 25 *Screening test characteristics used in the anal cancer screening model*

HIV status	Sensitivity (range)	Specificity (range)
HIV negative	0.6 (0.45 to 0.75)	0.5 (0.3 to 0.7)
HIV positive	0.85 (0.65 to 0.95)	0.3 (0.15 to 0.45)

Costs of diagnosis and treatment of precancerous AIN lesions

Goldie *et al.*[82] applied Medicare average allowed charges clinical care algorithms, developed by the University of California at San Francisco Faculty Practice, to estimate the cost of diagnosis and treatment of precancerous lesions. Low-grade ASIL required a diagnostic anoscopy and biopsy of any abnormal lesion but no treatment. High-grade ASIL required referral to a surgeon, one preoperative office visit with anoscopy, electrocautery or excisional biopsy through a colposcope with anaesthesia in an outpatient surgical setting, postoperative oral analgesia for 2 weeks, one postoperative visit at 30 days, and subsequent follow-up every 6 months with anoscopy.

UK-relevant unit costs were attached to the resource use described above for the diagnosis, treatment and follow-up of LG-AIN and HG-AIN. In the absence of unit costs for procedures specific to anal cancer, unit costs reported for similar procedures for the diagnosis and treatment cervical cancer were applied. The resulting cost estimates are presented in *Table 26*.

The AIN diagnosis cost is applied to all individuals at the point at which they are either clinically diagnosed with AIN or they are subject to a false-positive screening test. It is assumed that patients diagnosed with LG-AIN will receive two follow-up anascopies per year while they remain in the LG-AIN state.

High-grade AIN treatment and follow-up costs are differentially applied to HIV-positive and

HIV-negative patients, based on the finding in the treatment review that HIV-positive patients have a substantially higher rate of recurrence of HG-AIN. All individuals with diagnosed HG-AIN are assumed to have repeat anascopy and biopsy every 6 months. As reported in the modelling review of treatment strategies, HIV-negative and positive patients were assumed to experience recurrences every 10 and 2 years, respectively.

Costs of treating diagnosed anal cancer

Ideally, the anal cancer model would specify stage-specific treatment costs for anal cancer, and model progression of disease to death (from anal cancer or other causes). This would allow differentiation between the (presumably) lower costs incurred by screen-detected cases who are more likely to be diagnosed with an earlier stage of disease than clinically presenting patients.

Unfortunately, as discussed in the anal cancer treatment section, limited data were available to describe the progression of anal cancer. The screening model simply describes the duration of DSS for treated and untreated individuals with anal cancer. This means that only the mean cost of treating anal cancer can be applied to the model. Goldie *et al.*[81] seemingly estimated the lifetime costs of treating anal cancer, based on the costs of initial treatment, continuing care and terminal care for colorectal cancer, which were similar to costs reported for a discharge diagnosis of anal cancer from the Healthcare Cost and Utilization Project.[99]

No UK relevant anal cancer treatment costs were identified, although a recent relevant study of screening for colorectal cancer provided UK-specific lifetime cost estimates of treatment for colorectal cancer by stage at diagnosis.[100] The uprated lifetime costs associated with cancer diagnosed at Dukes stage A (£8895) and at Dukes stage B (£13,334) were assumed to represent the costs of screen-detected and clinically presenting

anal cancers, respectively. No ranges were presented around the published cost estimates and so 95% CIs ranging from 75% to 125% of the estimated mean costs were assumed (represented as log-normal distributions). The sensitivity analysis assessed the impact of assuming equal lifetime costs for screen detected and clinically presenting anal cancers.

Costs of treating diagnosed HIV infection

Relevant UK-based costs of treating HIV infection by CD4 count were reported by Miners *et al.*,[101] which were derived from the National Prospective Monitoring System HIV Health Economics Consortium (NPMS HHC) study. These costs were uprated to 2007 values, and are reported in *Table 27*.

Utility values

In their study of screening for HIV-positive MSM, Goldie *et al.*[82] estimated a constant utility weight of 0.56 for individuals with AIDS and AIDS-related cancer. These estimates were derived from a rating scale valuation undertaken by patients (sample not given), and the subsequent Torrance transformation of rating scale valuations.

In the study of HIV-negative men, Goldie *et al.*[81] applied a quality adjustment weight of 0.60 (range 0.17 to 0.79) for individuals with anal cancer, which was based on utility weights reported for gastrointestinal cancer.

TABLE 27 *Annual per-patient cost of HIV treatment, uprated from 1999/2000 values*

CD4 count	Mean (£) (95% CI)
>200	9655 (8630 to 10,938)
<200	10,598 (9362 to 11,810)

TABLE 26 *Diagnosis and treatment costs for precancerous AIN*

Resource	Mean cost (£) (range)	Cost source[a]
AIN diagnosis (anascopy and biopsy)	403 (310 to 503)	Colposcopy, biopsy of cervix uteri
Follow-up (anascopy)	215 (165 to 250)	Colposcopy
Treatment of detected HG-AIN lesions	1041 (722 to 1308)	Lower genital tract minor procedures
a All unit costs were obtained from the *NHS Reference Costs 2005/06*.		

TABLE 28 *Literature sourced utility weights for HIV-positive individuals*

Study	Country	Instrument	Sample	HIV health state	Value
Mauskopf[103]	USA	QWB Scale	139 HIV patients	CD4 100–199	0.66
				CD4 200–349	0.69
				CD4 350–500	0.72
				CD4 > 500	0.72
Trueman[104]	Canada	Standard gamble	249 HIV patients	CD4 < 200	0.79
				CD4 200–500	0.82
Goldie[81]	USA	QWB Scale	139 HIV patients	CD4 < 200	0.8
				CD4 200–500	0.88
				CD4 > 500	0.94
Goldie[105]	USA	Rating scale	HIV patients	CD4 < 200	0.84
				CD4 > 200	0.94

QWB Scale, Quality of Well-being Scale.

TABLE 29 *Utility weight parameter values*

Health state	Utility weight (range)
HIV negative, no anal cancer	1
HG-AIN (utility multiplier)[a]	0.98 (0.95 to 0.99)
Anal cancer	0.58 (0.5 to 0.7)
HIV positive, CD4 > 500	0.94 (0.9 to 0.98)
HIV positive, CD4 200–500	0.87 (0.84 to 0.9)
HIV positive, CD4 < 200	0.80 (0.76 to 0.84)

a   HIV-negative or HIV-positive health-state utility weights are multiplied by the HG-AIN utility value.

The utility weights applied by Goldie *et al.*[81] for anal cancer are comparable with utility estimates for metastatic disease in other cancers (e.g. breast cancer[102]), and so applying these weights to all cancer patients may overestimate the utility effects of anal cancer. However, in the absence of alternative data sources, a same approach to representing the utility effects of anal cancer in HIV-positive and HIV-negative men was used in the current study.

The utility decrements were applied to both diagnosed and undiagnosed individuals. This application accounts for the likelihood that undiagnosed patients may have slightly higher utility than diagnosed patients, but that later diagnosed patients may have lower utility during their treatment period due to less later treatment being less effective in reducing symptoms (or increased symptoms due to more aggressive treatment).

Estimates of the utility impact of HIV infection were sourced from a number of studies that reported patient-based elicitation of utility values, as presented in *Table 28*. The weights reported by Mauskopf *et al.*[103] are lower than the other three studies, which all present similar weights by CD4 count category. To maintain comparability, the utility weights reported by Goldie *et al.*[81] were used in the current model.

Goldie *et al.*[81] used the same process to estimate a utility value for patients receiving treatment for HG-AIN lesions of 0.98. In the current study, a utility multiplier was specified for the HG-AIN state, which was applied to relevant HIV-negative and HIV-positive states in cycles where patients received treatment for HG-AIN. The final parameter values for the utility parameters are presented in *Table 29*, which were represented as triangular distributions in the model.

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Chapter 6
Anal cancer screening model calibration

Calibration of the anal cancer model was undertaken due to the extreme uncertainty in a number of the input parameters, but also to represent the joint parameter uncertainty. Parameters that were particularly uncertain include transition probabilities from HG-AIN to anal cancer, and clinical presentation rates for MSM (by HIV status) with precancerous and cancerous AIN lesions. Joint parameter uncertainty refers to the uncertainty around feasible combinations of values for different parameters, for example, combing values from the upper intervals of both the 'transition to anal cancer' and 'clinical presentation rate' parameters may predict unfeasible anal cancer incidence rates.

The general calibration process involves sampling 5000 sets of input parameters from the probability distributions defined for each parameter in Chapter 5, running the model for each set and comparing the predicted model outputs with observed output values.

Calibration outputs

The anal cancer screening model was calibrated to age-specific estimates of the incidence of anal cancer in the year 2003 as reported by the Cancer Registries,[2] which should reflect the impact of HAART on incidence rates in HIV-positive individuals. Some adjustments were made to the

presented incidence estimates to account for the completeness of the registry data.

Forman[106] investigated the completeness of incident cases of skin cancer in Yorkshire recorded by the regional cancer registry in 1994. Patients diagnosed with skin cancer were identified from four independent information sources (pathology laboratories, outpatient clinics, general practices and the NHS Trust's Information Services for information on patients who received inpatient care), which were then cross-checked against the regional cancer register. In total, the cancer registry registered 83.5% of all patients with skin cancer identified across the region.

Silcocks and Waterhouse[107] applied the Flow method to patients diagnosed with cancer in 1996. For all cancers, completeness was 87.2% by 1 year and 92.3% by 5 years. Completeness was greater, and increased more quickly, for rapidly fatal cancers, with 1- and 5-year values of 96.4% and 97.3% (lung), and 95.3% and 96.5% (stomach) compared with 77.3% and 89.1% (female breast) and 76.9% and 88.8% (prostate). Colorectal cancers were an intermediate case (86.3% and 91.8%).

Based on the findings of the above two studies, and the fact that anal cancer appears to be a relatively slow progressing cancer, it was assumed that the cancer registry estimates for anal cancer had 77% completeness. The estimated numbers of cancers

TABLE 30 *Age-specific incidence of anal cancer estimates used to inform model calibration*

Age group	Population at risk[a]	Observed	Adjusted[b]
15–24	3,019,907	1.64	2.13
25–34	3,460,727	1.97	2.56
35–44	3,635,349	20.46	26.60
45–54	3,219,359	45.08	58.60
55–64	2,553,926	79.37	103.19
65–74	1,921,442	69.75	90.67
75–84	1,096,245	57.64	74.94
85+	265,042	8.76	11.39

a Based on 2001 Census estimates for England.
b Adjusted for non-completeness of cancer registry data by uprating observed cases by 30%.

in each age group were, therefore, multiplied by 1.3 (1/0.77) to account for the missing cases.

The reported age-specific incidence rates were represented by beta distributions informed by the adjusted number of observed cases and the respective populations at risk, as presented in *Table 30*.

To estimate anal cancer incidence rates in the MSM population, it was necessary to define RRs of anal cancer for HIV-positive and HIV-negative MSM (compared with non-MSM). Age-specific anal cancer incidence rates in the non-MSM, and HIV-negative and HIV-positive MSM populations were then fitted to the observed aggregate anal cancer incidence rates for iteratively sampled RRs for each group, and the sizes of the respective groups.

Lampinen *et al.*[33] reference RRs of anal cancer among HIV-negative and HIV-positive MSM of 35 and 70, respectively. They also state that recent studies suggest that incidence rates among HIV-positive MSM may have further doubled, owing to increased survival since 1996 among men receiving potent antiretroviral treatment. A UK cohort study of 8640 HIV-positive individuals found the incidence of invasive anal cancer (diagnosed in 26 patients) to be 92 (95% CI 52 to 149) per 100,000 patient-years of follow-up in the post-HAART era (1996–2003),[23] a mean RR of 176 compared with the general population.

Based on these studies, the calibration process assumed a mean RR for HIV-negative MSM of 35 (with a subjectively defined 95% CI 25 to 45). The RR for HIV-positive men was taken directly from the UK study (mean 176, 95% CI 99 to 285). Random values for these parameters were sampled from log-normal distributions.

Frisch *et al.*[13] estimated RRs for the incidence of invasive anal cancers in AIDS patients by age. They found elevated risks, particularly among patients under the age of 30 years, as shown in *Table 31*. Age-specific RRs for HIV-negative and HIV-positive MSMs were fitted to the respective sampled aggregate values, and the age-specific RRs (i.e. the age-specific RRs were fitted such that the relationship between the age-specific RRs was as estimated by Frisch, and the weighted aggregate RR equalled the sampled aggregate RR).

Age-specific estimates of the size of the MSM HIV-positive population were sampled from Poisson distributions informed by the data provided by the

TABLE 31 *Relative risks, by age at onset of AIDS, of anal cancers[a]*

Age group (years)	RR
< 30	163
30–39	40
40–49	39
> 50	23
a Adapted from Hemmincki and Dong.[14]	

HPA, which were used to estimate the incidence of HIV in the MSM population (as described in Chapter 5, HIV incidence and progression in MSM). The sizes of the HIV-negative MSM populations were estimated by subtracting the sampled HIV-positive MSM population sizes from age-specific estimates of the MSM populations (as described in Chapter 5, HIV incidence and progression in MSM). The size of the non-MSM population at risk was estimated by subtracting the estimated numbers of MSM from age-specific estimates of the male population, informed by UK life tables.

For a sampled set of RRs and age-specific population sizes (non-MSM, HIV-positive MSM and HIV-negative MSM), a calibration outputs model defined the relationship between the anal cancer incidence rates in the different populations. The model then fitted the incidence rate in the non-MSM populations so that the weighted incidence rates matched the sampled aggregate incidence rates. This process was repeated for 5000 iterations in order to represent the correlated uncertainty around the age-specific incidence rates in HIV-negative and positive MSMs. The resulting estimates are presented in *Table 32*.

The model was also calibrated against the observed estimates of the prevalence of HIV-positive MSMs, as provided by the HPA and described in the HIV modelling section.

The calibration model

A separate model was developed to estimate model outputs for the year 2003 in the format of the calibration outputs described in the previous section. The calibration model commences in the year 1990, and runs separate analyses for individuals at the mid-point age of the six relevant age groups (15–25, 26–35, 36–45, 46–55, 56–65

TABLE 32 *Estimated aggregate incidence of anal cancer in MSM, and in MSM by HIV status*

	95% CI		
	Mean	Lower	Upper
Observed (estimated)			
Aggregate	37.4	22.7	57.6
HIV positive	9.1	4.0	23.0
HIV negative	28.3	15.9	48.8
Predicted			
Aggregate	40.8	27.0	54.8
HIV positive	11.3	7.6	15.5
HIV negative	29.5	18.8	40.9

and 66–75) from either the year in which they became 15 years old (i.e. 1998 for individuals aged 20 in the year 2003) or from 1990 at the age they were at the start of 1990 (e.g. 16 years for 30-year-olds in 2003).

Age groups aged over 15 years in 1990 were distributed between the 'HIV negative, no anal lesions' and the 'HIV negative, undiagnosed HG-AIN' states in the year 1990. The probability of having HG-AIN was informed by a simple submodel that estimated the progression of HIV-negative MSM from normal to HG-AIN (either directly or via LG-AIN) from an assumed incident MSM age of 26 years (using the transition probabilities for HIV-negative MSM described in Chapter 1, Incidence rate by age and gender).

Thus, the calibration model makes the following assumptions:

1. No MSMs who were HIV positive prior to 1990 remain alive in 2003.
2. Transition probabilities have remained constant between 1990 and 2003 (i.e. probabilities vary by age but not by calendar year)

It is recognised that neither of the above assumptions are likely to be true, although they bias the model in opposite directions. Assumption 1 decreases estimated cases of anal cancer, while the introduction of HAART in the mid-1990s is likely to have increased the incidence of anal cancer, so assuming that HAART influenced transition probabilities in the early 1990s will compensate the impact of assumption 1 to some degree.

For each of 2000 sets of input parameter values, the calibration model collected the age-specific incident rates of anal cancer in HIV-negative, and HIV-positive MSMs in 2003.

To account for slight bias due to the use of the mid-point age of each age group, the mean MSM rate was estimated as the mean proportion of each age group (in 2003) that were MSM during the preceding 13 years. In each age group, the mean MSM rate is compared with the proportion of MSM in the mid-point age for the age group, as those were the ages on which the calibration model is based. The ratio of the mean MSM rate to the MSM rate in the mid-point age for each age group was used to adjust the calibration estimates by multiplying the respective model outputs by this ratio.

Calibration data analysis

A two-stage calibration process was adopted. The first stage applied a threshold in which the predicted aggregate incidence rate of anal cancer was compared with the 95% CI for the aggregate incidence rate as estimated using the Cancer Registry data (described in Chapter 5, Anal cancer screening model structure).

The corresponding predicted estimates of the aggregate incidence of anal cancer in MSM, and in MSM by HIV status are presented in *Table 32*. The calibration threshold analysis found that 1719 of the 2000 input parameter sets estimated aggregate incidence rates within the 95% CIs. The comparison of the observed and predicted incidence rates (and 95% CIs) shows a close relationship.

The second stage of the calibration analysis involved estimating the sum of differences between the 1719 predicted output parameter values and the anal cancer incidence rate 95% CIs, by age group and HIV status. *Table 33* presents the observed and predicted ranges for each incidence category. The results show that extremely small numbers are expected in the early age groups, such that the differences between the observed and predicted incidence in these groups had minimal impact on the cost-effectiveness results. The overlap between the predicted and observed incidence in the other age categories is encouraging.

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TABLE 33 *Ranges for observed and predicted age- and HIV status-specific anal cancer incidence*

	Age range (years)					
	15–24	**25–34**	**35–44**	**45–54**	**55–64**	**65–74**
HIV positive						
Observed						
Lower	0.018	0.087	3.100	3.667	1.869	0.382
Upper	0.495	1.783	9.495	10.265	5.591	1.162
Predicted						
Lower	0.002	0.643	1.431	4.142	0.299	0.006
Upper	0.015	2.083	4.364	15.997	1.773	0.061
HIV negative						
Observed						
Lower	0.096	0.174	2.394	6.943	7.430	0.922
Upper	2.210	3.067	6.036	13.996	14.223	1.865
Predicted						
Lower	0.069	2.344	2.051	6.587	5.248	0.550
Upper	0.438	7.645	7.010	22.330	17.108	1.785

The following stages informed the assignment of sampling probabilities to each of the eligible input parameters:

1. Sum of differences between each age- and HIV status-specific incidence estimate and the bounds of the respective observed 95% CIs were calculated for each iteration.
2. Proportions of the sum of differences contributed by each input parameter set were estimated.
3. Reciprocals of the proportions of the sum of differences contributed by each iteration were estimated (no iterations had a sum of differences of zero).
4. Reciprocals were divided by the sum of the reciprocals to estimate the probability that each of the 1719 parameter sets was the most relevant set.

Anal cancer screening model analysis

Following the calibration process, and the identification and ranking of eligible input parameter sets, the model was analysed to estimate the costs and QALYs associated with 10 alternative screening programmes as well as a no screening option. The 10 programmes included five programmes for HIV-positive MSM only, and five programmes for all MSM. Screening intervals of 1, 2, 3, 4 and 5 years were analysed for both eligible populations.

The starting states for each age group (i.e. the distribution of each population across model's states in 2003) were informed by the calibration model that recorded the finishing states of each population for each input parameter set at the end of the calibration period (i.e. the year 2003). The model analysed each age group to a maximum age of 100 years and then combined the discounted (at 3.5% per annum) costs and effects for each age group on the basis of the respective proportions of the total person-years represented within the full model time horizon.

The reference case analysis involved the random sampling of 2000 sets of input parameter sets based on the ranking probabilities estimated as part of the calibration process. Additional analyses were undertaken in which the following assumptions were tested:

- no utility effects associated with false-positives or treatment for HG-AIN
- increasing the regression rates for individuals with LG-AIN lesions returning to having no AIN lesion.

Chapter 7

Screening for anal cancer in MSM: cost-effectiveness results

The section presents the results of the cost-effectiveness model built to analyse the cost-effectiveness of 10 alternative screening programmes for anal cancer compared with a no-screening option. The following discussion section provides a discussion and interpretation of the results in the context of decisions regarding the implementation of an anal cancer screening programme by the NHS.

Reference case cost-effectiveness results

The mean results from the reference case analysis of the model are presented in *Table 34*, which show that screening is actually more costly and less effective than providing no screening, i.e. no screening dominates screening for either HIV-positive MSM alone or all MSM. The reduced

number of QALYs gained is due to the utility decrements associated with false-positive screening results, and the treatment effects of HG-AIN.

Calculations were undertaken to inform the cost-effectiveness acceptability frontier, which describes the probability that the screening option with the highest expected net benefits is the most cost-effective option. These estimates show that no screening has the highest expected net benefits and is 100% certain (given the reference case model, inputs and assumptions) to be the most cost-effective option, to a value of a QALY of £50,000.

Sensitivity analyses

In addition to the probabilistic sensitivity analysis reported above, additional sensitivity analyses

TABLE 34 *Mean results from the reference case analysis*

| Model | Costs (£) | | | | | | QALYs: aggregate | ICER compared with no screening |
	Aggregate	Screening	False-positives	AIN and monitoring	Cancer	HIV		
No screening								
	32,250	0.00	0.00	2554	69.04	29,627	18.0197	
HIV positive								
Annual	32,800	3.71	3.02	3021	66.13	29,707	18.0136	Dominated
2 yearly	32,830	3.93	3.22	3046	65.17	29,711	18.0133	
3 yearly	32,899	4.50	4.12	3106	62.57	29,722	18.0125	
4 yearly	32,999	5.53	6.51	3192	60.56	29,734	18.0112	
5 yearly	33,094	7.28	12.35	3280	47.51	29,747	18.0099	
All MSM								
Annual	37,201	71.13	36.93	5057	85.07	31,951	18.0041	Dominated
2 yearly	37,425	76.46	38.96	5190	85.61	32,034	18.0034	
3 yearly	38,148	92.35	48.25	5540	85.57	32,382	18.0014	
4 yearly	39,841	112.28	77.11	6238	86.78	33,327	17.9992	
5 yearly	41,764	168.82	144.85	6972	70.99	34,408	17.9980	

were undertaken around the most uncertain input parameters. The estimates of anal cancer incidence used to calibrate the model were not excessively uncertain, and conservative assumptions had been implemented, for example a low completeness rate was assumed for the cancer registry data, and high estimates of the RRs for HIV-positive and HIV-negative MSM developing anal cancer were specified. Thus, anal cancer incidence in high-risk groups was not a key parameter for investigation.

Additional sensitivity analyses tested the impact of assuming that the effects of investigation following false-positive screen results and treatment for HG-AIN incurred no utility decrements. The mean results of this analysis are presented in *Table 35*, which show that the screening programmes for diagnosed HIV-positive individuals are now shown to be more effective than no screening, although the minimum incremental cost per QALY gained (ICQ) is almost £66,000. The ICQs for screening for all MSM drop to £50,000, but remain well above accepted cost-effectiveness thresholds. The related cost-effectiveness acceptability frontier is presented in *Figure 7*. This shows that no screening retains a very high probability of being the most cost-effective option, with the highest mean net benefits to a QALY value of £50,000.

Another uncertain parameter was the rate of regression of LG-AIN, which had been informed by the two main cohort studies of MSM and anal cancer.[57,61,70,89] However, Goldie *et al.*[81] had estimated higher regression rates, which may impact on cost-effectiveness by increasing the likelihood of progression from HG-AIN to anal cancer. The calibration model was re-run incorporating revised annual probabilities of regression from LG-AIN to no AIN (30% in HIV-negative MSM, 15% in HIV-positive MSM with CD4 count > 500, 10% with CD4 count 200–500, and 5% with CD4 count < 200), which were fitted to observed anal cancer incidence rates by altering the transition probability between HG-AIN and anal cancer. Recalibrating the model required increasing the HG-AIN to anal cancer rates by 22%.

Table 36 presents the mean results from the combining increased AIN regression rates with no utility decrements from screening, which show that the minimum ICQ from implementing any of the screening programmes for MSM is reduced to £44,656. Screening all MSM is shown to be more effective than screening HIV-positive MSM due to gains from the early detection of undiagnosed HIV-positive MSM as a result of screening for anal cancer.

TABLE 35 *Mean results from analyses assuming no utility decrement from false-positive screen results or treatment for HG-AIN*

| Screening option | Costs (£) | | | | | | QALYs: aggregate | ICER compared to no screening (£) |
| | Aggregate | Screening | False-positives | Treatment | | | | |
				AIN and monitoring	Cancer	HIV		
No screening								
	32,250	0.00	0.00	2554	69.04	29,627	18.1294	
HIV positive								
Annual	32,799	1.86	3.02	3021	66.13	29,707	18.1364	77,984
2 yearly	32,828	1.97	3.22	3046	65.17	29,711	18.1368	77,502
3 yearly	32,896	2.25	4.12	3106	62.57	29,722	18.1378	76,946
4 yearly	32,997	2.77	6.51	3192	60.56	29,734	18.1389	78,421
5 yearly	33,091	3.64	12.35	3280	47.51	29,747	18.1401	78,628
All MSM								
Annual	37,165	35.57	36.93	5057	85.07	31,951	18.2259	50,907
2 yearly	37,387	38.23	38.96	5190	85.61	32,034	18.2316	50,280
3 yearly	38,102	46.18	48.25	5540	85.57	32,382	18.2457	50,299
4 yearly	39,784	56.14	77.11	6238	86.78	33,327	18.2754	51,585
5 yearly	41,680	84.41	144.85	6972	70.99	34,408	18.3080	52,787

TABLE 36 *Mean results from analyses assuming increased annual regression rates from LG-AIN to no AIN,ª and no utility decrement from false-positive screen results or treatment for HG-AIN*

| Screening option | Costs (£) | | | Treatment | | | QALYs: aggregate | ICER compared to no screening (£) |
	Aggregate	Screening	False-positives	AIN and monitoring	Cancer	HIV		
No screening								
	31,339	0.00	0.00	2079	69.98	29,190	18.1174	
HIV positive								
Annual	31,890	2.21	8.70	2528	67.21	29,284	18.1257	66,407
2 yearly	31,926	2.38	9.70	2557	66.22	29,290	18.1263	66,173
3 yearly	32,000	2.81	12.60	2617	63.57	29,303	18.1274	65,923
4 yearly	32,108	3.61	19.56	2705	61.53	29,318	18.1288	67,457
5 yearly	32,221	5.19	37.71	2796	48.15	29,334	18.1303	68,675
All MSM								
Annual	35,079	45.97	79.35	3969	85.15	30,899	18.1917	50,328
2 yearly	35,336	51.34	87.34	4103	85.83	31,008	18.2069	44,656
3 yearly	35,957	64.56	110.57	4394	85.90	31,302	18.2205	44,810
4 yearly	37,335	86.70	174.65	4937	87.34	32,050	18.2472	46,182
5 yearly	39,143	149.23	334.40	5557	71.45	33,032	18.2799	48,040

a 30% in HIV-negative MSM, 15% in HIV-positive MSM with CD4 count > 500, 10% with CD4 count 200–500, and 5% with CD4 count < 200.
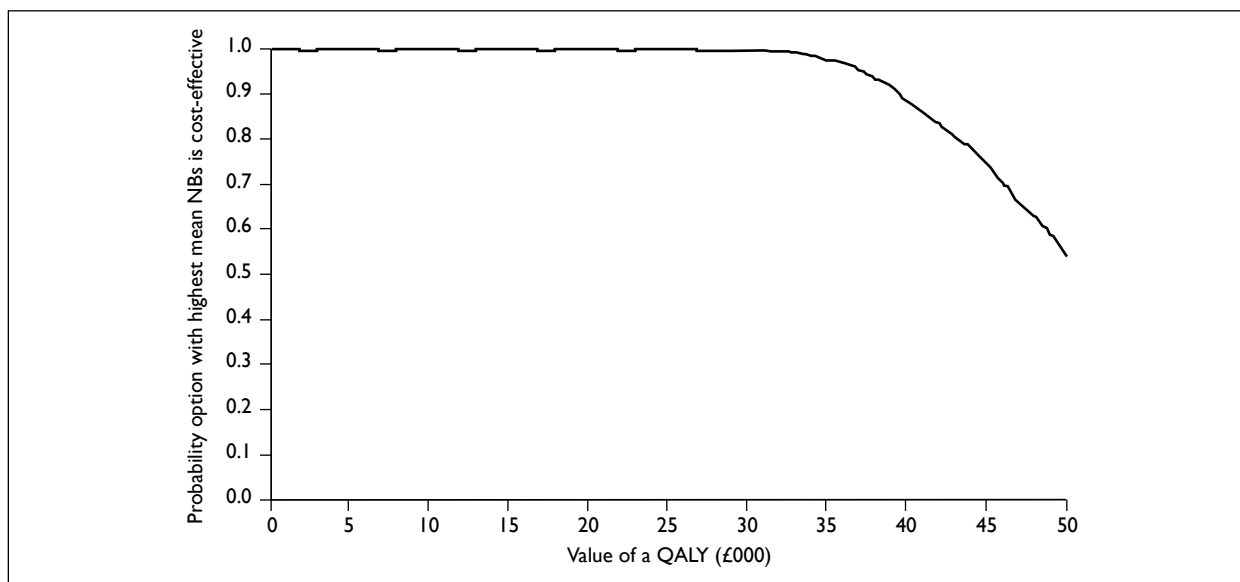
FIGURE 7 *Cost-effectiveness acceptability frontier assuming no utility decrement from false-positive screen results or treatment for high-grade anal intraepithelial neoplasia. NB, net benefit.*
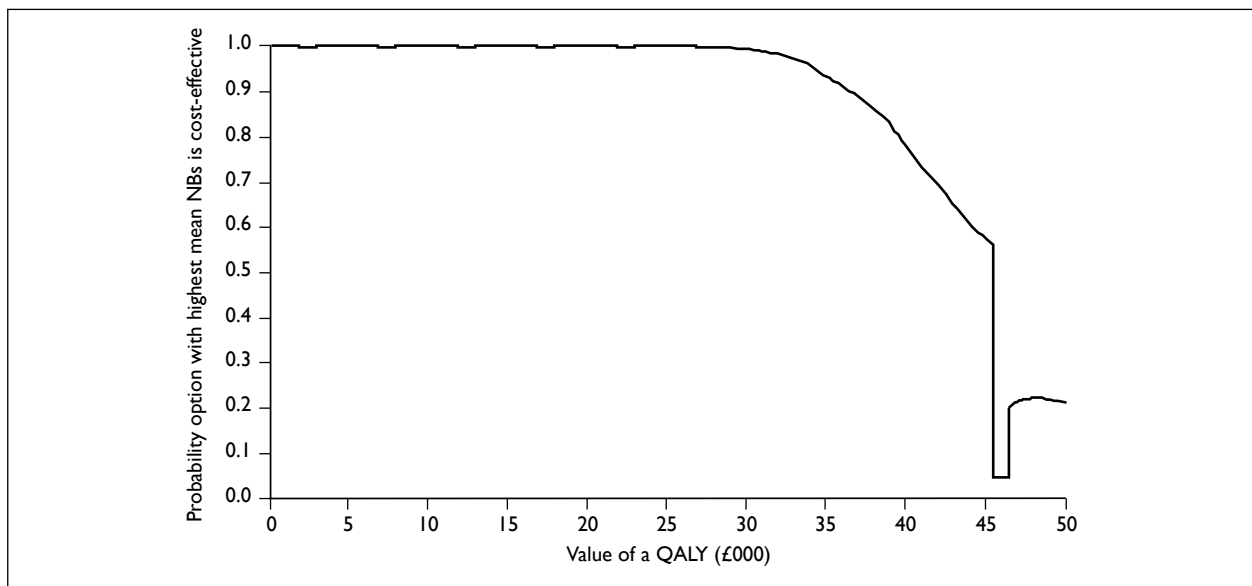
FIGURE 8 *Cost-effectiveness acceptability frontier assuming increased anal intraepithelial neoplasia (AIN) regression and no utility decrement from false-positive screen results or treatment for high-grade AIN. NB, net benefit.*

The cost-effectiveness acceptability frontier (*Figure 8*) shows that no screening has the highest mean net benefits to a value of a QALY of £45,000 with the probability of no screening being the most cost-effective option remaining above 50%.

At higher QALY values, screening programmes for all MSM have higher expected net benefits, although no screening retains a probability of cost-effectiveness of over 50% to a QALY value of £50,000.

Chapter 8

HIV-positive women: anal cancer screening analysis

The anal cancer screening model developed to evaluate screening options for MSM was adapted to evaluate screening programmes for high-risk women. Initial analyses focused on HIV-positive women, as cross-sectional data has shown that 26% of 251 HIV-positive women had AIN, compared with 8% of the high-risk HIV-negative women.[15] If screening is shown to be cost-effective in HIV-positive women then screening of other high-risk groups will then be explored.

Model population and calibration

A key aspect of the female HIV-positive screening model was that incidence of AIN in HIV-negative women is negligible, and assumed to be zero. As in the MSM model, the women's model includes HIV-negative individuals in order to describe the incidence of HIV-positive women over time, but all incident HIV-positive women enter the 'CD4 count > 500' state without AIN.

Fewer data were available from the literature to populate parameters for the HIV-positive women screening model, for example no longitudinal data describing AIN progression in HIV-positive women were identified. Indeed, the only female-specific data included estimates of age-specific HIV incidence, and the data required to estimate the calibration output parameters (age-specific anal cancer incidence). All other parameters were informed by data collected to populate the MSM screening model, although a separate calibration process was undertaken for the female screening model.

Unlike men, incidence rates of HIV infection in women have varied significantly over time, with low rates in the early 1990s (around 500 per year), rising to a peak in 2003 (3251) and then falling back to 2283 in 2007.[108] Thus, separate HIV incidence rates were defined for the years 1992–2000 and 2002–7 for the calibration model, while the latter incidence rates were used in the main analysis model.

The model was calibrated to age-specific numbers of anal cancers occurring in HIV-positive women (the calibration outputs), which were estimated using the following data:

- age-specific estimates of anal cancer incidence in women in 2005 (uprated to allow for under registration)[2]
- relative risk of anal cancer in HIV-positive women (6.8, 95% CI 2.7 to 14)[13]
- age-related RRs of anal cancer in HIV-positive women (e.g. RR of anal cancer in HIV women aged under 30 years, 30–39 years, etc.), informed by a study of HIV-associated anogenital cancers by age at onset of AIDS[13]
- prevalence of diagnosed HIV women in 2005 (converted to age-specific numbers assuming a similar proportional split to HIV-positive males)[109]
- prevalence of undiagnosed HIV women, based on observation that 33.7% of all HIV-positive individuals in the UK were undiagnosed in 2004 (assumed to have the same age distribution as diagnosed HIV women).[110]

Age-specific anal cancer incidence in HIV-positive women in 2005 was estimated using an adjusted version of the calibration outputs model described for MSM in Chapter 6. The model estimated the incidence rates in the HIV-positive female populations by sampling a set of parameter values describing the aggregate age-specific incidence of anal cancer in women, the aggregate RR of anal cancer in HIV-positive women, age-related RRs of anal cancer, and the size of the HIV-positive female population. For a sampled set of values, the model defined the relationship between the incidence rates for the HIV-positive and HIV-negative populations using the sampled RRs. The model then fitted the incidence rate in the HIV-negative population so that the weighted age-specific anal cancer incidence rates (based on the sampled sizes of the respective populations) matched the sampled aggregate incidence rate. This process was repeated for 2000 iterations in order to represent the correlated uncertainty around the age-specific incidence rates in HIV-negative and HIV-positive

women. The resulting estimates are presented in *Table 37*.

Table 37 shows that the calibration results obtained from applying the same AIN incidence and progression parameter values, as fitted for the MSM model, overestimated the rate of anal cancer in HIV-positive women. To the clinical authors' knowledge, there is no known biological reason that AIN would progress differently in HIV-positive men and HIV-positive women, but

one might expect AIN incidence to be lower in HIV-positive women than in HIV-positive MSM. Therefore, the model was recalibrated, keeping the same AIN progression parameters as estimated for the MSM model, but lowering AIN incidence until a good fit was achieved with the estimated anal cancer incidence rates (in HIV-positive women). This was achieved when HIV-positive MSM AIN incidence rates were reduced by 67%, and all 2000 iterations estimated rates within the 95% CI for the observed rates. Estimated AIN incidence rates

TABLE 37 *Estimated aggregate incidence of anal cancer in HIV-positive women*

| | 95% CI | |
Mean	Lower	Upper
Observed (estimated)		
1.1	0.3	3.9
Predicted (applying calibrated disease progression parameters from the MSM analysis)		
2.03	1.16	3.28
Predicted (applying calibrated disease progression parameters from the MSM analysis, but decreasing AIN incidence rates by 67%)		
1.10	0.61	1.77

TABLE 38 *Calibrated AIN incidence rates in HIV-negative/-positive MSM and HIV-positive women*

| | AIN incidence | Mean | 95% CI | |
			Lower	Upper
HIV-negative MSM				
	Low grade	0.074	0.048	0.106
	High grade	0.019	0.011	0.031
HIV-positive MSM				
> 500 CD4 count	Low grade	0.165	0.051	0.314
	High grade	0.028	0.009	0.057
200–500 CD4 count	Low grade	0.246	0.151	0.346
	High grade	0.043	0.025	0.063
< 200 CD4 count	Low grade	0.681	0.401	0.885
	High grade	0.118	0.065	0.177
HIV-positive women				
> 500 CD4 count	Low grade	0.054	0.017	0.104
	High grade	0.009	0.003	0.019
200–500 CD4 count	Low grade	0.081	0.050	0.114
	High grade	0.014	0.008	0.021
< 200 CD4 count	Low grade	0.226	0.133	0.292
	High grade	0.039	0.021	0.058

across the eligible populations are compared in
Table 38.

The second stage of the calibration analysis
involved estimating the sum of differences between
the 2000 predicted output parameter values
and the anal cancer incidence rate (95% CIs) by
age group. *Table 39* presents the observed and
predicted ranges for each incidence category. The
results show that the ranges for the observed and
expected data are an extremely good fit, which is
encouraging.

Anal cancer screening model analysis

The model was analysed to estimate the costs
and QALYs associated with programmes for HIV-
positive women with screening intervals of 1, 2,
3, 4 and 5 years. The starting states for each age
group (i.e. the distribution of each population
across model's states in 2003) were informed by
the calibration model that recorded the finishing
states of each population for each input parameter
set at the end of the calibration period (i.e. the year
2003). The model analysed each age group to a
maximum age of 100 years, and then combined the
discounted costs and effects (at 3.5% per annum)
for each age group on the basis of the respective
proportions of the total person-years represented
within the full model time horizon.

The reference case analysis involved the random
sampling of 2000 sets of input parameter sets,
based on the ranking probabilities estimated
as part of the calibration process. Additional
analyses were undertaken in which the following
assumptions were tested:

- no utility effects associated with false-positives
  or treatment for HG-AIN
- increasing the regression rates for individuals
  with LG-AIN lesions and returning to having
  no AIN lesion.

Results

The mean results from the reference case analysis
of the model are presented in *Table 40*. As for
MSM, screening HIV-positive women is more costly
and less effective than providing no screening, i.e.
no screening dominates screening. The reduced
number of QALYs gained is due to the utility
decrements associated with false-positive screening
results, and the treatment effects of HG-AIN.

Calculations were undertaken to inform the cost-
effectiveness acceptability frontier, which describes
the probability that the screening option with the
highest expected net benefits is the most cost-
effective option. These estimates show that no
screening has the highest expected net benefits
and is 100% certain (given the reference case
model, inputs and assumptions) to be the most
cost-effective option, to a value of a QALY of
£50,000.

Sensitivity analyses

Additional sensitivity analyses tested the impact of
assuming that the effects of investigation following
false-positive screen results and treatment for HG-
AIN incurred no utility decrements. The mean
results of this analysis are presented in *Table 41*,
which show that the screening programmes for
diagnosed HIV-positive women are now shown
to be more effective than no screening, although

TABLE 39 *Ranges for observed and predicted age-specific anal cancer incidence in HIV-positive women*

	Age range (years)					
	15–24	**25–34**	**35–44**	**45–54**	**55–64**	**65–74**
Observed						
Lower	0	0.046	0.146	0.154	0.058	0.009
Upper	0.019	0.446	0.834	0.832	0.303	0.045
Predicted						
Lower	0.000	0.018	0.163	0.249	0.061	0.009
Upper	0.003	0.120	0.896	1.454	0.340	0.058

TABLE 40 *Mean results from the reference case analysis for HIV-positive women*

Model	Costs (£)			Treatment			QALYs: aggregate	ICER compared with no screening
	Aggregate	Screening	False-positives	AIN, plus monitoring	Cancer	HIV		
No screening								
	234	0.00	0.00	5	0.09	228	20.49186	
HIV positive								
5 yearly	238	0.05	0.21	8	0.08	229	20.49181	Dominated
4 yearly	238	0.06	0.24	9	0.08	229	20.49181	Dominated
3 yearly	239	0.07	0.31	9	0.08	229	20.49180	Dominated
2 yearly	240	0.09	0.49	10	0.07	229	20.49179	Dominated
Annual	241	0.15	0.95	10	0.06	229	20.49178	Dominated

TABLE 41 *Mean results from analyses assuming no AIN-related utility decrement and 50% reduction in screening costs*

Screening option	Costs (£)			Treatment			QALYs: aggregate	ICER compared with no screening (£)
	Aggregate	Screening	False-positives	AIN, plus monitoring	Cancer	HIV		
No screening								
	234	0.00	0.00	5	0.09	228	20.49200	
HIV positive								
5 yearly	238	0.02	0.21	8	0.08	229	20.49205	88,247
4 yearly	238	0.03	0.24	9	0.08	229	20.49205	88,403
3 yearly	239	0.03	0.31	9	0.08	229	20.49206	89,837
2 yearly	240	0.05	0.49	10	0.07	229	20.49207	94,372
Annual	241	0.08	0.95	10	0.06	229	20.49207	102,878

the minimum ICQ is £88,247. Data to inform the related cost-effectiveness acceptability frontier shows that no screening retains a 100% probability of being the most cost-effective option, with the highest expected net benefits to a QALY value of £50,000. Increasing regression rates from LG-AIN had little further effect on the ICQs for screening HIV-positive women.

Chapter 9

Discussion

The discussion of the findings of this report on the cost-effectiveness of screening anal cancer in high-risk groups is presented in two parts. The first section concerns the findings of the systematic review of all aspects of screening for anal cancer. The second section describes the outputs, interpretations, and limitations of the presented model-based cost-effectiveness analysis of screening for anal cancer.

The systematic review

Limited information is available from published research about the potential impact of anal cancer screening of high-risk groups. The limitations are from the study designs used, as well as the quality of reporting of the studies.

The main role of the screening studies[27,28,30,31,34,35] included in the report is in assessing whether the screening test performance is adequate to justify the establishment of an anal cancer screening programme. Not all the studies gave completeness of the information.

In their systematic review of anal Pap smear screening for HIV-infected patients, Chiao *et al.*[36] reported that the data published highlight limitations to current anal Pap smear screening-related research, with no randomised or cohort studies existing to determine if there are improved survival or outcomes for those who have been screened.

The NSC[1] has produced a modified version of the World Health Organization (WHO) screening criteria to take into account the more rigorous standards of evidence, as well as to increase the weight given to the potential negative effects of screening. The document states that all the criteria should be satisfied before a screening programme is introduced.

The NSC[1] criteria (where applicable) are outlined below, and are commented on with reference to anal cancer screening.

The condition

- The condition should be an important health problem.

As mentioned in the background section, anal cancer in the general population is a rare disease. However, in high-risk groups it is more prevalent, but identifying and accessing these high-risk groups could be problematic.

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

The natural history of anal cancer is not well understood.

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

If primary prevention is taken as identification of risk factors then some risk factors are known. HIV and receptive anal intercourse are two of the risk factors identified with anal cancer. It is possible that some prevention of anal cancer could be achieved by the modification of risk factors, but high-risk groups would need to be notified of their risk of anal cancer.

The test

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

All types of screening included in this report appear to meet the above criterion.

- The test should be acceptable to the population.

Anal cancer screening may be undertaken by using anal cytology or anal pap smears. Self-collected anal cytology specimens has been evaluated in

two studies[33,34] and self-collected specimens seem to be comparable with clinician collect specimens. However, neither study reported on how acceptable the population thought the test was.

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 later treatment.

The treatment and outlook for anal cancer will depend, to a large extent, on its stage. Treatment options such as RT and combined RT plus chemotherapy are available.

The screening programme

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

No such RCTs were identified.

• 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.

No evidence has been identified by this review that answers this question.

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

The screening process does not appear to present any physical harm; however, any psychological effects of anal cytology screening or pap smears have not been evaluated in the studies included in this review.

• 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).

See following section.

Other criteria from the NSC[1] are not discussed further as they do not have a direct relevance to this review.

The cost-effectiveness model

Parameter uncertainty

The reference case cost-effectiveness model found that screening for anal cancer is very unlikely to be cost-effective. A key determinant of this finding was the low observed incidence of anal cancer in the UK population. Estimated anal cancer incidence in the MSM population (by HIV status) was not conservative, incorporating upper ranges of the RRs of anal cancer in HIV-negative and HIV-positive MSM compared with the general population of 45 and 272, respectively. The analysis also used a low estimate of completeness in the observation of cases of anal cancer by the Cancer registries (assuming 30% of cases were not recorded). The assumed low completeness rate may occur due to the higher likelihood of comorbidities in HIV-positive patients, although based on the available evidence, the analysis allowed for high estimates of anal cancer incidence.

The dominance of the no screening option for HIV-positive women was driven by the estimated RR of HIV-positive women developing anal cancer compared with the general population (mean 6.8, 95% CI 2.7 to 14). This is compared to an estimated RR of 176 for HIV-positive MSM.

Confidence in the results of the anal cancer screening model would be further increased, however, with an audit of the accuracy of the cancer registries' identification of cases of anal cancer. A linked activity that would also help justify the observed results would be an audit of the proportion of cancer cases that occurred in HIV-positive men and women, and/or MSM.

Sensitivity analyses showed that the reference case results were most sensitive to alternative assumptions around the utility effects of false-positive results and treatment of HG-AIN. It is unlikely that a false-positive screening result, and in particular, treatment of HG-AIN, have no utility effects, but direct estimation of these effects would further increase the confidence in the results of the cost-effectiveness model.

Alternative estimates of the probability of regression from LG-AIN altered the reference

case results, although not as significantly. The reference case regression rates were informed by published data from two cohort studies of AIN incidence and progression in MSM. These data were not presented in the best format to inform regression rates, and so assumptions were required to estimate the regression parameters. A next step might be to request access to the primary data from these studies to enable analyses more appropriate to populating the anal cancer screening model reported in this study.

A value of information (VoI) analysis could have been undertaken, but this study provides an example of the possible limitations of VoI analyses. It is clear that the reference case model would attach a zero value to the collection of further information (as all iterations to a QALY value of £50,000 showed no screening to be cost-effective), whereas the sensitivity analyses around utility decrements and AIN regression would only show a positive VoI at high values of a QALY (i.e. over £40,000). Thus, a VoI analysis was not conducted.

Structural uncertainty

In the HIV-positive screening programmes, costs associated with treating HIV infection are increased slightly, as would be expected due to the small increase in survival of HIV-positive individuals due to the detection of some additional cases of anal cancer. In the screening programmes for all MSM, HIV treatment costs increase more substantially. This is a consequence of the assumptions in the model around the detection of HIV infection as a result of detecting AIN lesions. The model assumed that individuals with undiagnosed HIV infection, in whom an AIN lesion was detected, would receive a diagnostic test for HIV infection and subsequently receive treatment for HIV. Treatment for HIV infection also leads to improved outcomes, which is a potential by-product of the anal cancer screening programme.

The issue of screening for anal cancer leading to the detection of additional HIV-positive MSM is a moot point, as undiagnosed HIV infected individuals may be more or less likely to attend a screening programme. It is unknown whether undiagnosed HIV-positive individuals are undiagnosed because they avoid contact with the health service and, therefore, would be unlikely to attend an anal cancer screening programme, or whether they are hesitant to directly ask for

an HIV test but would view the opportunity to be screened for anal cancer as an indirect (and possibly preferred) approach to ascertaining their HIV status. The model assumes undiagnosed HIV-positive MSM are equally likely to be screened as HIV-negative MSM, although all of the screening attendance parameters are subject to significant uncertainty.

To identify and screen individuals at high risk of anal cancer would be a difficult task. A specific mode of operation for a screening programme was not defined due to the unique issues around identifying and inviting different categories of MSM to a screening programme. Based on published qualitative data, it was assumed that screening would be offered to 40–60% of HIV-negative or undiagnosed HIV-positive MSM, and 80–90% of diagnosed HIV-positive MSM. Quantitative data informed an estimate that 5–20% of all MSMs offered screening will refuse. If further research on the natural history of anal cancer identifies screening as potentially cost-effective then pilot screening studies could usefully inform screening attendance and acceptance parameters.

The anal cancer screening model was complicated, jointly modelling HIV and AIN progression. Due to previous experience in the development of complex screening models with limited data, every effort was made to apply the model as a cohort-based model rather than as an individual sampling model (ISM). To apply the probabilistic calibration methods described in this report, ISMs require model running times several orders of magnitude higher than cohort models.

The main limiting assumptions of the applied cohort model included the use of non-time-dependent transition probabilities. This meant that the probability of individuals with, for example, HG-AIN, progressing to anal cancer was not described as a function of the time with HG-AIN. However, the model did incorporate a proxy for time-dependent progression by assuming that transition probability increased with age.

The model did not represent the impact of repeat episodes; for example, it did not differentiate between individuals with no evidence of AIN who had previously regressed from LG-AIN and those who had never had AIN. It also did not separately categorise patients by the numbers of recurrences experienced following treatment for HG-AIN.

Our decision was to include the costs associated with antiretroviral treatment for those individuals who are HIV positive. We did this specifically as screening would lead to the identification of HIV-positive MSMs, with associated treatment costs, and the lifetime costs of care for HIV-positive individuals will be determined, in part, by life expectancy. These are legitimate factors to consider in assessing the overall costs and benefits of introducing a screening programme in these high-risk groups.

Finally, the model adopted a simplistic representation of the postdiagnosis phase of the disease, primarily due to data inadequacies. The model represented only a single anal cancer state that did not allow for the explicit differentiation between stages of presentation for screen-detected and clinically presenting cases of anal cancer. The reference cases analysis incorporated a cost differentiation proxy by assuming greater lifetime treatment costs for clinically presenting cancers. The impact on survival was handled by assuming a high annual mortality rate in undiagnosed cancers, based on the lowest survival rates in relevant clinical trials.

The influence of the above model limitations is difficult to predict, although it is likely that they have only a minor impact on the cost-effectiveness results given the extent to which no screening has been shown to generate the highest net benefits.

Other possible limitations of the analysis include the lack of relevant data to inform anal cancer natural history transition probabilities from a UK MSM population. The San Francisco study states that 'results should be interpreted with caution since they were performed in highly sexually active populations with a mean age of over 40 years'[57] (p. 501), although no data on sexual activity levels were presented. The Seattle study showed that the study population had provided a mean of between four and five sexual partners in the past year; over 50% had experienced over 51 lifetime sexual partners; 15% (HIV negative) and 29% (HIV positive) had receptive anal intercourse more than three times per month. The Seattle study also presented data describing the RR of HG-AIN for men engaging in receptive anal intercourse more than three times per month. The RR of 2.2 (95% CI 0.9 to 5.5) indicates that this may well be a significant risk factor.

No data to inform the level of sexual activity in MSM living in the UK were identified and so the USA-based transition probabilities were not adjusted. If UK MSM are less sexually active, transition probabilities to HG-AIN may be reduced. This would mean that fewer MSM would develop HG-AIN (the screening programme would detect fewer positive cases) and that the calibrated rates of progression from HG-AIN to anal cancer would increase (detected cases would have been more likely to progress to cancer).

Chapter 10
Conclusions

From the review sections of this report, it is clear that many of the criteria for assessing the need for a population screening programme[1] have not been met for anal cancer. There is limited knowledge about the epidemiology and natural history of the disease, along with a paucity of good-quality evidence concerning the effectiveness of screening for anal cancer. The absence of such data, combined with the possible reluctance of high-risk groups to attend an anal cancer screening programme, makes introduction of population-based screening for anal cancer difficult.

The reported cost-effectiveness analyses of screening for anal cancer emphasise this conclusion. The results show little likelihood that screening any of the identified high-risk groups will generate health improvements at reasonable cost. These results could be further confirmed by updating some key parameters at little additional cost. The most efficient way to proceed would be audit the accuracy of the cancer registries identification of cases of anal cancer, as well as audit the proportion of cancer cases that occur in HIV-positive men and women, and/or MSM. If these data show the screening model has underestimated the impact of anal cancer in any of the populations evaluated, a utility study of the effects of treatment for HG-AIN may be justified.

The findings of this review and model are consistent with the available evidence. However, the advice not to initiate a large-scale screening programme weighs heavily on those clinicians who are only too aware of the increasing risk of anal cancer in their HIV-positive patients.[111] Concerned clinicians will be proactive in undertaking awareness raising with their patients and undertaking anal examination when they present in clinic.

Chapter 11

Recommendations

1. Based on the available evidence, an organised screening programme for anal cancer is unlikely to be cost-effective in any of the proposed eligible populations.
2. The existing cancer registries should be audited to further inform estimates of the incidence of anal cancer in high-risk groups.
3. Consideration of (1) the feasibility, (2) effectiveness and (3) the cost-effectiveness of routine testing of high-risk populations attending NHS services for other purposes would be valuable.
4. Further research into the likely adherence and compliance of high-risk populations with (1) opportunistic testing and (2) preventative treatment strategies is also required.
5. Research to further clarify the risk contribution of HPV infection, and, by extension, the potential value of HPV vaccination in HIV-negative and HIV-positive high-risk populations would also be justified.

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Appendix 1

Surveillance Epidemiology and End Results (SEER)

The Surveillance Epidemiology and End Results (SEER) programme of the National Cancer Institute (NCI) is an authoritative source of information on cancer incidence and survival in the USA. SEER currently collects and publishes cancer incidence and survival data from population-based cancer registries covering approximately 26% of the US population. SEER coverage includes 23% of African Americans, 40% of the Hispanic population, 42% of American Indians and Alaska Natives, 53% of Asians and 70% of Hawaiian/Pacific Islanders.

The SEER programme registries routinely collect data on patient demographics, primary tumour site, tumour morphology and stage at diagnosis, first course of treatment, and follow-up for vital status. The SEER programme is the only comprehensive source of population-based information in the USA that includes stage of cancer at the time of diagnosis and patient survival data.

See http://seer.cancer.gov/about/

Appendix 2

NSC criteria for appraising the viability, effectiveness and appropriateness of a screening programme

Ideally, all of the following criteria should be met before screening for a condition is initiated.

The condition

1. The condition should be an important health problem.
2. 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, disease marker, latent period or early symptomatic stage.
3. All of the cost-effective primary prevention interventions should have been implemented as far as practicable.
4. If the carriers of a mutation are identified as a result of screening the natural history of people with this status should be understood, including the psychological implications.

The test

5. There should be a simple, safe, precise and validated screening test.
6. The distribution of test values in the target population should be known, and a suitable cut-off level defined and agreed.
7. The test should be acceptable to the population.
8. 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.
9. When testing for mutations, if all possible mutations are not being tested then the criteria used to select the subset of mutations to be covered by screening should be clearly set out.

The treatment

10. 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.
11. There should be agreed evidence-based policies covering which individuals should be offered treatment and the appropriate treatment to be offered.
12. Clinical management of the condition and patient outcomes should be optimised in all health-care providers prior to participation in a screening programme.

The screening programme

13. There should be evidence from high-quality RCTs to show 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's 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.
14. 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.
15. The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment).
16. The opportunity cost of the screening programme (including testing, diagnosis and 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).
17. There should be a plan for managing and monitoring the screening programme, and an agreed set of quality assurance standards.

18. Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be available prior to the commencement of the screening programme.
19. All other options for managing the condition should have been considered (e.g. improving treatment, providing other services) to ensure that no further cost-effective intervention could be introduced or current interventions increased within the resources available.
20. 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.
21. 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.
22. If screening is for a mutation then the programme should be acceptable to people who are identified as carriers and to other family members.

Appendix 3
Search strategies

Epidemiology search strategy

Database: Ovid MEDLINE (1966 to January week 1 2006).

Search strategy
1. exp Anus Neoplasms/
2. anus neoplasm$.tw.
3. neoplasm$, anus.tw.
4. anal neoplasm$.tw.
5. neoplasm$, anal.tw.
6. anal cancer$.tw.
7. cancer$, anal.tw.
8. cancer of anus.tw.
9. anus cancer$.tw.
10. cancer of the anus.tw.
11. anal squamous carcinoma.tw.
12. circumanal gland neoplasm$.tw.
13. exp Anal Gland Neoplasms/
14. neoplasm$, anal gland.tw.
15. anal gland neoplasm$.tw.
16. neoplam$, circumanal gland.tw.
17. neoplasm$, perianal gland.tw.
18. perianal gland neoplasm$.tw.
19. or/1–18
20. exp Epidemiology/
21. exp Natural History/
22. epidemiolog$.ti.
23. inciden$.ti.
24. prevalen$.ti.
25. Incidence/
26. Prevalence/
27. or/20–26
28. 19 and 27

Search terms for the disease (anal cancer) (1–18) were combined with 'epidemiology' search terms (20–26).

Screening technologies search strategy

Database: Ovid MEDLINE (1966 to January week 1 2006).

Search strategy
1. anal cytologic screening.tw.
2. anoscopy.tw.
3. anal cytology.tw.
4. liquid based cytology.tw.
5. Mass Screening/
6. Occult Blood/
7. Sigmoidoscopy/
8. Colonoscopy/
9. mass screening.tw
10. occult blood.tw.
11. Diagnostic Tests, Routine/
12. diagnos$.tw.
13. diagnosis/
14. diagnostic us$.tw.
15. "reproducibility of results"/
16. Observer Variation/
17. di.fs.
18. sigmoidoscop$.ti,ab.
19. colonoscop$.ti,ab.
20. reproducibility of results.ti,ab.
21. observer variation$.ti,ab.
22. Diagnosis/
23. or/1–22
24. exp Anus Neoplasms/
25. anus neoplasm$.tw.
26. neoplasm$, anus.tw.
27. anal neoplasm$.tw.
28. neoplasm$, anal.tw.
29. anal cancer$.tw.
30. cancer$, anal.tw.
31. cancer of anus.tw.
32. anus cancer$.tw.
33. cancer of the anus.tw.
34. anal squamous carcinoma.tw.
35. circumanal gland neoplasm$.tw.
36. exp Anal Gland Neoplasms/
37. neoplasm$, anal gland.tw.
38. anal gland neoplasm$.tw.
39. neoplam$, circumanal gland.tw.
40. neoplasm$, perianal gland.tw.
41. perianal gland neoplasm$.tw.
42. exp Precancerous Conditions/
43. preneoplastic condition$.tw.
44. exp *Papillomavirus, Human/
45. human papillomavirus$.ti,ab.
46. infectious human wart virus$.ti,ab.
47. human wart virus, infectious.ti,ab.
48. papilloma virus, human.ti,ab.
49. anal cytological abnormalit$.ti,ab.
50. anal human papillomavirus disease$.ti,ab.
51. anal squamous intraepithelial neoplasia.ti,ab.
52. anal high grade squamous intraepithelial lesion$.ti,ab.

53. high-grade anal squamous intraepithelial lesion$.ti,ab.
54. or/24–53
55. exp Cohort Studies/
56. Prognosis/
57. exp Mortality/
58. exp morbidity/
59. morbidity.ti,ab.
60. mortality.ti,ab.
61. (natural adj history).ti,ab.
62. prognos$.ti,ab.
63. course.ti,ab.
64. predict$.ti,ab.
65. exp "Outcome Assessment (Health Care)"/
66. outcomes$1.ti,ab.
67. (inception adj cohort$1).ti,ab.
68. disease progression/
69. exp survival analysis/
70. or/55–69
71. 23 and 54 and 70

Search terms for specific diagnostic test and diagnosis terms (1–22) were combined with search terms for anal cancer (24–41) and premalignant indicators of disease (42–53) and search terms for morbidity and mortality (55–69) the primary outcome that diagnosis is trying to prevent.

Screening policies/programmes search strategy

Database: Ovid MEDLINE (2004 to November week 3 2006).

Search strategy
1. screening program$.ti,ab.
2. Mass Screening/
3. mass screening$.ti,ab.
4. cancer screening$.ti,ab.
5. screening programme$.ti,ab.
6. screening polic$.ti,ab.
7. screening$.ti,ab.
8. screening campaign$.ti,ab.
9. or/1–8
10. exp Anus Neoplasms/
11. anus neoplasm$.tw.
12. neoplasm$, anus.tw.
13. anal neoplasm$.tw.
14. neoplasm$, anal.tw.
15. anal cancer$.tw.
16. cancer$, anal.tw.
17. cancer of anus.tw.
18. anus cancer$.tw.
19. cancer of the anus.tw.
20. anal squamous carcinoma.tw.
21. circumanal gland neoplasm$.tw.

22. exp Anal Gland Neoplasms/
23. neoplasm$, anal gland.tw.
24. anal gland neoplasm$.tw.
25. neoplam$, circumanal gland.tw.
26. neoplasm$, perianal gland.tw.
27. perianal gland neoplasm$.tw.
28. or/10–27
29. 9 and 28

Search terms for screening policies and programmes (1–8) were combined with search terms for anal cancer (10–27).

The screening policies/programmes and screening technologies effectiveness searches was combined with methodological search filters designed to retrieve the highest levels of evidence.

Guidelines
1. guideline.pt.
2. Health Planning Guidelines/
3. practice guideline.pt.
4. or/1–3

Systematic reviews
1. meta-analysis/
2. exp review literature/
3. (meta-analy$ or meta analy$ or metaanaly$). tw.
4. meta analysis.pt.
5. review academic.pt.
6. review literature.pt.
7. (systematic$ adj3 (review$ or overview$)).tw.
8. or/1–7

RCTs
1. clinical trial.pt

The screening police/programmes and screening technologies search strategies were also combined with search terms for high-risk groups:

1. Sexual Behavior/
2. anal intercourse.ti,ab.
3. anal sex.ti,ab.
4. at-risk sexual behaviour$.ti,ab.
5. at-risk sexual behavior$.ti,ab.
6. Bisexuality/
7. bisexual$.ti,ab.
8. gay$.ti,ab.
9. hiv-negative.ti,ab.
10. human immunodeficiency virus-negative.ti,ab.
11. hiv-positive.ti,ab.
12. hiv-infected person$.ti,ab.
13. human immunodeficiency virus-positive.ti,ab.
14. exp HIV/

15. homosexual$.ti,ab.
16. exp Homosexuality/
17. male-male sex.ti,ab.
18. men who have sex with men.ti,ab.
19. unprotected anal intercourse.ti,ab.
20. or/1–19

Cost-effectiveness searches

To retrieve papers on cost-effectiveness and comparative costs of candidate technologies/programmes/policies, searches were conducted in MEDLINE, EMBASE, NHS Economic Evaluation Database (EED) and Office of Health Economics (OHE) Health Economic Evaluations Database (HEED). Search terms for screening technologies and programmes/policies given above were utilised. Search filters designed to retrieve economic evaluations, economic models and QoL literature were applied to the MEDLINE and EMBASE searches. An example of the MEDLINE (Ovid) search filter is provided below:

1. exp "Patient Acceptance of Health Care"/
2. exp "Costs and Cost Analysis"/
3. cost$.ti.
4. (cost$ adj2 (effective$ or util$ or benefit$ or minimi$)).ab.
5. (economic$ or pharmaco economic$ or pharmaco-economic$).tw.
6. Quality-Adjusted Life Years/
7. quality adjusted life.tw.
8. (qaly$ or qald$ or qale$ or qtime$).tw.
9. disability adjusted life.tw.
10. daly$.tw.
11. Health Status Indicators/
12. (sf36 or sf 36 or short form 36 or shortform 36 or sf thirtysix or sf thirty six or shortform thirtysix or shortform thirty six or short from thirtysix or short form thirty six).tw.
13. (sf6 or sf 6 or short form 6 or shortform 6 or sf six or sfsix or shortform six or short form six).tw.
14. (sf12 or sf 12 or short from 12 or shortform 12 or sf twelve or sftwelve or shortform twelve or short form twelve).tw.
15. (sf16 or sf 16 or short form 16 or shortform 16 or sf sixteen or sfsixteen or shortform sixteen or short form sixteen).tw.

16. (sf20 or sf 20 or short form 20 or shortform 20 or sf twenty or sftwenty or shortform twnety or short from twenty).tw.
17. (euroqol or euro qol or eq5d or eq 5d).tw.
18. (hql or hqol or h qol or hrqol or hr qol).tw.
19. (hye or hyes).tw.
20. health$ year$ equivalent$.tw.
21. health utilit$.tw.
22. (hui or hui1 or hui2 or hui3).tw.
23. disutil$.tw.
24. rosser.tw.
25. quality of wellbeing.tw.
26. qwb.tw.
27. willingness to pay.tw.
28. standard gamble$.tw.
29. time trade off.tw.
30. time tradeoff.tw.
31. tto.tw.
32. exp Models, Economic/
33. *Models, Theoretical/
34. *Models, Organizational/
35. economic model$.tw.
36. Markov Chains/
37. markov$.tw.
38. Monte Carlo Method/
39. monte carlo.tw.
40. exp Decision Theory/
41. (decision$ adj2 (tree$ or analy$ or model$)).tw.
42. or/1–41

Treatment search strategy

Searches on the high-risk groups search terms combined with the treatment search terms below were also conducted.

1. exp Therapeutics/
2. treatment$.ti,ab.
3. therap$.ti,ab.
4. exp Radiotherapy/
5. radiotherap$.ti,ab.
6. chemotherap$.ti,ab.
7. surger$.ti,ab.
8. or/1–7

Appendix 4

QUOROM trial flow chart

Potentially relevant citations identified through electronic searches and hand searching
n = 2102

Papers rejected at the title stage
n = 1403

Abstracts screened and inspected
n = 699

Papers rejected at the abstract stage
n = 493

Full copies retrieved and inspected
n = 206

Full papers excluded
n = 125

Publications meeting inclusion criteria
n = 81

Studies meeting inclusion criteria:

cost-effectiveness	*n* = 6
natural history	*n* = 1
prevalence	*n* = 13
diagnosis	*n* = 3
epidemiology	*n* = 5
screening	*n* = 11
treatment	*n* = 10
risk	*n* = 29
quality of life	*n* = 2
outcomes	*n* = 1

Appendix 5
Quality of screening studies

Study	Randomisation	Blinding	Patient dropouts/exclusions	Intention-to-treat analysis
de Ruiter 1994[27]	N/A	None reported	61 patients did not have an adequate anal smear, excluding them from comparison between anal cytology and histology	No
Palefsky *et al.* 1997[28]	N/A	Analyst (pathologist)	None reported	Yes
Mathews *et al.* 2004[29]	N/A	None reported	Repeat evaluable anal cytological results were available only for 642 patients, and concurrent anal cytological testing and HRA biopsy were performed in 154 patients who underwent HRA	No
Panther *et al.* 2004[30]	N/A	None reported	None reported	Yes
Fox *et al.* 2005[37]	N/A	Analyst (pathologist)	None reported	Yes
Arain *et al.* 2005[31]	N/A	None reported	127 patients did not have surgical biopsies and/or repeat smears within 6 months, leaving 71 patients who did so	No
Friedlander *et al.* 2003[32]	N/A	Analyst (cytotechnologist)	None reported	Yes
Lampinen *et al.* 2006[33]	Yes, each individual randomly assigned the order in which their paired swabs (self vs clinician) were to be collected using a sealed-envelope method	Analyst (cytopathologist)	None reported	Yes
Cranston *et al.* 2004[34]	None	None reported	Approximately 10% of those invited to participate refused; of those that agreed, 20% did not return the required materials in a timely fashion. Of the remaining 106 participants, four were excluded because of incomplete collected samples. 102 were included in the analysis	No
Varnai *et al.* 2006[35]	N/A	None reported	None reported	Yes

N/A, not applicable.

Appendix 6

Quality of treatment studies

Study	Randomisation	Blinding	Patient dropouts/exclusions	Intention-to-treat analysis
UKCCCR Anal Cancer Working Party 1996[40]	Yes, centre block randomisation	Not reported	RT group, five classed as ineligible due to inappropriate randomisation, and six deaths RT/chemotherapy group, three classed as ineligible due to inappropriate randomisation, and nine deaths	Yes
Cummings *et al.* 1984[41]	None	Analyst	None reported	Yes
Doniec *et al.* 2006[42]	N/A	Not reported	None reported	Yes
Edelman and Johnstone 2006[44]	N/A	Not reported	None reported	Yes
Place *et al.* 2001[45]	N/A	Not reported	None reported	Yes
Brown *et al.* 1999[43]	N/A	Not reported	Of the 46 identified patients, six excluded for HG-AIN, and six excluded from further analysis	No
N/A, not applicable.				

Appendix 7
Life course models

Life course model (with HIV)
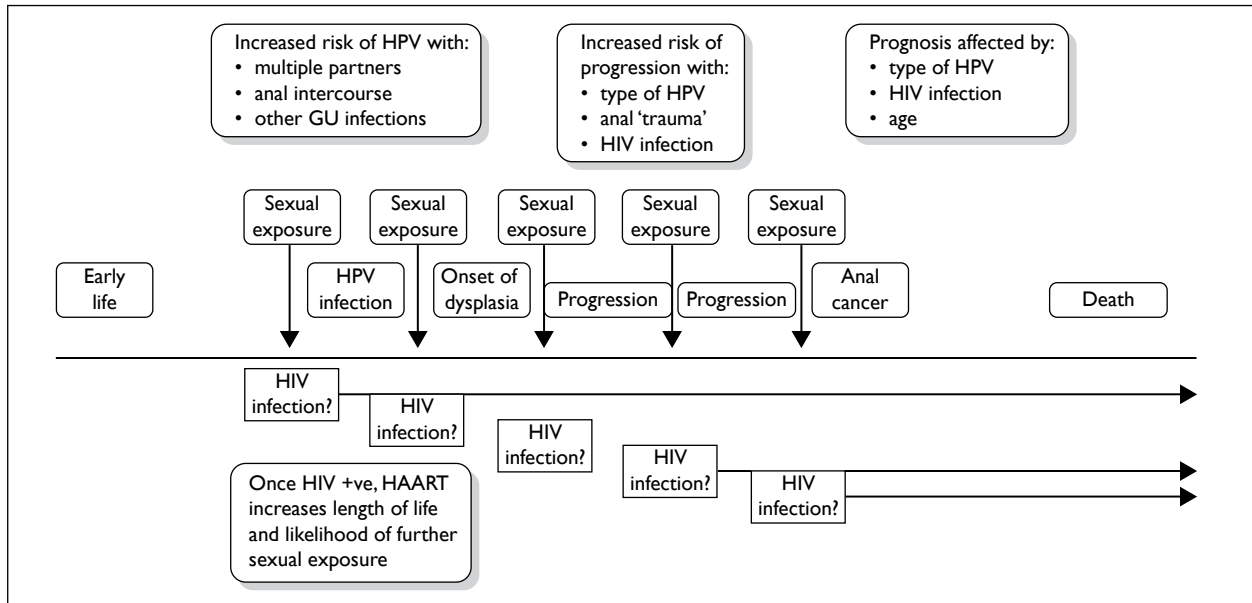
Life course model modified for HIV-negative women
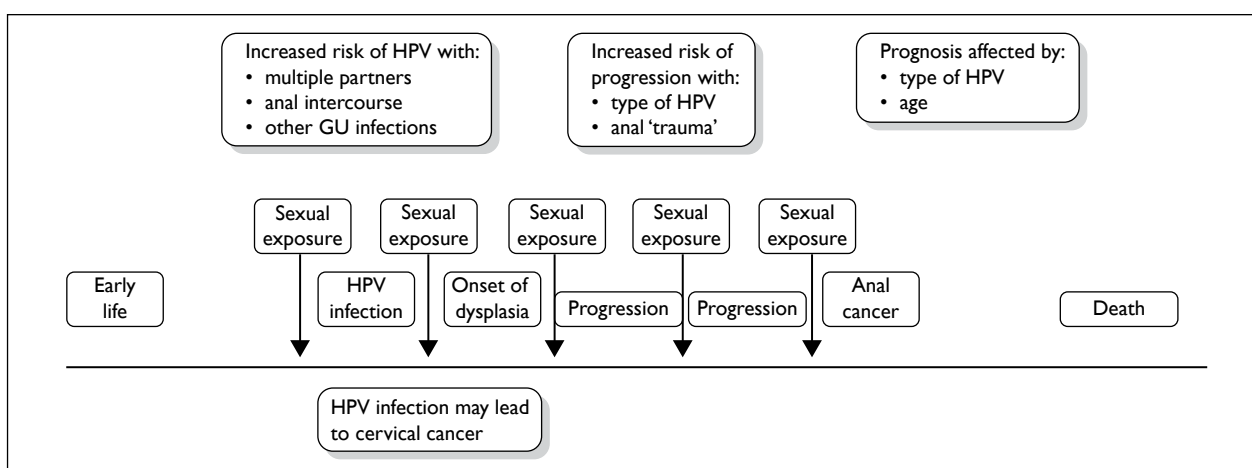
Appendix 8
Updated searches

We carried out the updated full searches in January 2010. After duplicates had been removed, 843 papers were identified. As with the original searches the titles and abstracts were read (where available) to identify any papers which fell into the categories of interest in a screening study, e.g. natural history, epidemiology, screening, diagnostics and treatment. We were particularly looking for any studies that added new and important data which would enhance our current knowledge of screening for anal cancer and in particular any new evidence in the condition in HIV-positive women.

We selected 92 papers for full review.

From these 11 were found to be opinion articles not reporting any data.

Fourteen papers from the title and abstract appeared to report on anal cancer but were actually reporting on other cancers.

Three were letters commenting on previous studies and ordered in error.

Treatment studies fell into two categories, those treating anal cancer and those treating anal warts, and made up the greatest number of studies at 13. These studies reported results very similar to those used in the model for the treatment of anal cancer. The treatment of warts was beyond the scope of the study.

Six studies described the possible impact of vaccination programmes on the future of the disease but these were mostly confined to the impact of cervical cancer.

Six studies described the risk factors in developing anal cancer but reported no new data to that already included in the review.

Nine studies reported on the epidemiology of anal cancer but did not report any new data that would change the parameters used in the model. These papers mostly confirmed that individuals with HIV were at risk of developing anal cancer.

A number of papers (8) reported on HIV-positive women and the increased risk for this group. The evidence reported supported the data used in the model. However, some authors predicted an upward trend in the number of affected individuals.

Four studies reported on the test. They were divided between acceptability, self-administered and new technology such as biomarkers which are at the early stages of development.

Five described screening programmes for anal cancer in non-UK health-care settings.

Two papers came from the economic searches. One of those was on the possible impact of a vaccination programme which included boys, which is currently not judged cost-effective. The second reported on the cost of non-HIV-associated cancers, including anal cancer, in the USA.

Eight reported on HIV and anal cancer in terms of antiretroviral therapies. The case for any link between HAART and the prevention of anal cancer was not made.

One study reported on guidelines for treating anal cancer.

One study reported a survey of current practice in treatment of anal warts in genitourinary clinics in the UK.

One study reported on screening MSM for anal cancer in a UK setting. This has been included in the updated review.

Health Technology Assessment reports published to date

Volume 1, 1997

No. 1
Home parenteral nutrition: a systematic review.
By Richards DM, Deeks JJ, Sheldon TA, Shaffer JL.

No. 2
Diagnosis, management and screening of early localised prostate cancer.
A review by Selley S, Donovan J, Faulkner A, Coast J, Gillatt D.

No. 3
The diagnosis, management, treatment and costs of prostate cancer in England and Wales.
A review by Chamberlain J, Melia J, Moss S, Brown J.

No. 4
Screening for fragile X syndrome.
A review by Murray J, Cuckle H, Taylor G, Hewison J.

No. 5
A review of near patient testing in primary care.
By Hobbs FDR, Delaney BC, Fitzmaurice DA, Wilson S, Hyde CJ, Thorpe GH, *et al.*

No. 6
Systematic review of outpatient services for chronic pain control.
By McQuay HJ, Moore RA, Eccleston C, Morley S, de C Williams AC.

No. 7
Neonatal screening for inborn errors of metabolism: cost, yield and outcome.
A review by Pollitt RJ, Green A, McCabe CJ, Booth A, Cooper NJ, Leonard JV, *et al.*

No. 8
Preschool vision screening.
A review by Snowdon SK, Stewart-Brown SL.

No. 9
Implications of socio-cultural contexts for the ethics of clinical trials.
A review by Ashcroft RE, Chadwick DW, Clark SRL, Edwards RHT, Frith L, Hutton JL.

No. 10
A critical review of the role of neonatal hearing screening in the detection of congenital hearing impairment.
By Davis A, Bamford J, Wilson I, Ramkalawan T, Forshaw M, Wright S.

No. 11
Newborn screening for inborn errors of metabolism: a systematic review.
By Seymour CA, Thomason MJ, Chalmers RA, Addison GM, Bain MD, Cockburn F, *et al.*

No. 12
Routine preoperative testing: a systematic review of the evidence.
By Munro J, Booth A, Nicholl J.

No. 13
Systematic review of the effectiveness of laxatives in the elderly.
By Petticrew M, Watt I, Sheldon T.

No. 14
When and how to assess fast-changing technologies: a comparative study of medical applications of four generic technologies.
A review by Mowatt G, Bower DJ, Brebner JA, Cairns JA, Grant AM, McKee L.

Volume 2, 1998

No. 1
Antenatal screening for Down's syndrome.
A review by Wald NJ, Kennard A, Hackshaw A, McGuire A.

No. 2
Screening for ovarian cancer: a systematic review.
By Bell R, Petticrew M, Luengo S, Sheldon TA.

No. 3
Consensus development methods, and their use in clinical guideline development.
A review by Murphy MK, Black NA, Lamping DL, McKee CM, Sanderson CFB, Askham J, *et al.*

No. 4
A cost–utility analysis of interferon beta for multiple sclerosis.
By Parkin D, McNamee P, Jacoby A, Miller P, Thomas S, Bates D.

No. 5
Effectiveness and efficiency of methods of dialysis therapy for end-stage renal disease: systematic reviews.
By MacLeod A, Grant A, Donaldson C, Khan I, Campbell M, Daly C, *et al.*

No. 6
Effectiveness of hip prostheses in primary total hip replacement: a critical review of evidence and an economic model.
By Faulkner A, Kennedy LG, Baxter K, Donovan J, Wilkinson M, Bevan G.

No. 7
Antimicrobial prophylaxis in colorectal surgery: a systematic review of randomised controlled trials.
By Song F, Glenny AM.

No. 8
Bone marrow and peripheral blood stem cell transplantation for malignancy.
A review by Johnson PWM, Simnett SJ, Sweetenham JW, Morgan GJ, Stewart LA.

No. 9
Screening for speech and language delay: a systematic review of the literature.
By Law J, Boyle J, Harris F, Harkness A, Nye C.

No. 10
Resource allocation for chronic stable angina: a systematic review of effectiveness, costs and cost-effectiveness of alternative interventions.
By Sculpher MJ, Petticrew M, Kelland JL, Elliott RA, Holdright DR, Buxton MJ.

No. 11
Detection, adherence and control of hypertension for the prevention of stroke: a systematic review.
By Ebrahim S.

No. 12
Postoperative analgesia and vomiting, with special reference to day-case surgery: a systematic review.
By McQuay HJ, Moore RA.

No. 13
Choosing between randomised and nonrandomised studies: a systematic review.
By Britton A, McKee M, Black N, McPherson K, Sanderson C, Bain C.

No. 14
Evaluating patient-based outcome measures for use in clinical trials.
A review by Fitzpatrick R, Davey C, Buxton MJ, Jones DR.

No. 15

Ethical issues in the design and conduct of randomised controlled trials.

A review by Edwards SJL, Lilford RJ, Braunholtz DA, Jackson JC, Hewison J, Thornton J.

No. 16

Qualitative research methods in health technology assessment: a review of the literature.

By Murphy E, Dingwall R, Greatbatch D, Parker S, Watson P.

No. 17

The costs and benefits of paramedic skills in pre-hospital trauma care.

By Nicholl J, Hughes S, Dixon S, Turner J, Yates D.

No. 18

Systematic review of endoscopic ultrasound in gastro-oesophageal cancer.

By Harris KM, Kelly S, Berry E, Hutton J, Roderick P, Cullingworth J, *et al.*

No. 19

Systematic reviews of trials and other studies.

By Sutton AJ, Abrams KR, Jones DR, Sheldon TA, Song F.

No. 20

Primary total hip replacement surgery: a systematic review of outcomes and modelling of cost-effectiveness associated with different prostheses.

A review by Fitzpatrick R, Shortall E, Sculpher M, Murray D, Morris R, Lodge M, *et al.*

Volume 3, 1999

No. 1

Informed decision making: an annotated bibliography and systematic review.

By Bekker H, Thornton JG, Airey CM, Connelly JB, Hewison J, Robinson MB, *et al.*

No. 2

Handling uncertainty when performing economic evaluation of healthcare interventions.

A review by Briggs AH, Gray AM.

No. 3

The role of expectancies in the placebo effect and their use in the delivery of health care: a systematic review.

By Crow R, Gage H, Hampson S, Hart J, Kimber A, Thomas H.

No. 4

A randomised controlled trial of different approaches to universal antenatal HIV testing: uptake and acceptability. Annex: Antenatal HIV testing – assessment of a routine voluntary approach.

By Simpson WM, Johnstone FD, Boyd FM, Goldberg DJ, Hart GJ, Gormley SM, *et al.*

No. 5

Methods for evaluating area-wide and organisation-based interventions in health and health care: a systematic review.

By Ukoumunne OC, Gulliford MC, Chinn S, Sterne JAC, Burney PGJ.

No. 6

Assessing the costs of healthcare technologies in clinical trials.

A review by Johnston K, Buxton MJ, Jones DR, Fitzpatrick R.

No. 7

Cooperatives and their primary care emergency centres: organisation and impact.

By Hallam L, Henthorne K.

No. 8

Screening for cystic fibrosis.

A review by Murray J, Cuckle H, Taylor G, Littlewood J, Hewison J.

No. 9

A review of the use of health status measures in economic evaluation.

By Brazier J, Deverill M, Green C, Harper R, Booth A.

No. 10

Methods for the analysis of quality-of-life and survival data in health technology assessment.

A review by Billingham LJ, Abrams KR, Jones DR.

No. 11

Antenatal and neonatal haemoglobinopathy screening in the UK: review and economic analysis.

By Zeuner D, Ades AE, Karnon J, Brown J, Dezateux C, Anionwu EN.

No. 12

Assessing the quality of reports of randomised trials: implications for the conduct of meta-analyses.

A review by Moher D, Cook DJ, Jadad AR, Tugwell P, Moher M, Jones A, *et al.*

No. 13

'Early warning systems' for identifying new healthcare technologies.

By Robert G, Stevens A, Gabbay J.

No. 14

A systematic review of the role of human papillomavirus testing within a cervical screening programme.

By Cuzick J, Sasieni P, Davies P, Adams J, Normand C, Frater A, *et al.*

No. 15

Near patient testing in diabetes clinics: appraising the costs and outcomes.

By Grieve R, Beech R, Vincent J, Mazurkiewicz J.

No. 16

Positron emission tomography: establishing priorities for health technology assessment.

A review by Robert G, Milne R.

No. 17 (Pt 1)

The debridement of chronic wounds: a systematic review.

By Bradley M, Cullum N, Sheldon T.

No. 17 (Pt 2)

Systematic reviews of wound care management: (2) Dressings and topical agents used in the healing of chronic wounds.

By Bradley M, Cullum N, Nelson EA, Petticrew M, Sheldon T, Torgerson D.

No. 18

A systematic literature review of spiral and electron beam computed tomography: with particular reference to clinical applications in hepatic lesions, pulmonary embolus and coronary artery disease.

By Berry E, Kelly S, Hutton J, Harris KM, Roderick P, Boyce JC, *et al.*

No. 19

What role for statins? A review and economic model.

By Ebrahim S, Davey Smith G, McCabe C, Payne N, Pickin M, Sheldon TA, *et al.*

No. 20

Factors that limit the quality, number and progress of randomised controlled trials.

A review by Prescott RJ, Counsell CE, Gillespie WJ, Grant AM, Russell IT, Kiauka S, *et al.*

No. 21

Antimicrobial prophylaxis in total hip replacement: a systematic review.

By Glenny AM, Song F.

No. 22

Health promoting schools and health promotion in schools: two systematic reviews.

By Lister-Sharp D, Chapman S, Stewart-Brown S, Sowden A.

No. 23

Economic evaluation of a primary care-based education programme for patients with osteoarthritis of the knee.

A review by Lord J, Victor C, Littlejohns P, Ross FM, Axford JS.

Volume 4, 2000

No. 1
The estimation of marginal time preference in a UK-wide sample (TEMPUS) project.

A review by Cairns JA, van der Pol MM.

No. 2
Geriatric rehabilitation following fractures in older people: a systematic review.

By Cameron I, Crotty M, Currie C, Finnegan T, Gillespie L, Gillespie W, *et al.*

No. 3
Screening for sickle cell disease and thalassaemia: a systematic review with supplementary research.

By Davies SC, Cronin E, Gill M, Greengross P, Hickman M, Normand C.

No. 4
Community provision of hearing aids and related audiology services.

A review by Reeves DJ, Alborz A, Hickson FS, Bamford JM.

No. 5
False-negative results in screening programmes: systematic review of impact and implications.

By Petticrew MP, Sowden AJ, Lister-Sharp D, Wright K.

No. 6
Costs and benefits of community postnatal support workers: a randomised controlled trial.

By Morrell CJ, Spiby H, Stewart P, Walters S, Morgan A.

No. 7
Implantable contraceptives (subdermal implants and hormonally impregnated intrauterine systems) versus other forms of reversible contraceptives: two systematic reviews to assess relative effectiveness, acceptability, tolerability and cost-effectiveness.

By French RS, Cowan FM, Mansour DJA, Morris S, Procter T, Hughes D, *et al.*

No. 8
An introduction to statistical methods for health technology assessment.

A review by White SJ, Ashby D, Brown PJ.

No. 9
Disease-modifying drugs for multiple sclerosis: a rapid and systematic review.

By Clegg A, Bryant J, Milne R.

No. 10
Publication and related biases.

A review by Song F, Eastwood AJ, Gilbody S, Duley L, Sutton AJ.

No. 11
Cost and outcome implications of the organisation of vascular services.

By Michaels J, Brazier J, Palfreyman S, Shackley P, Slack R.

No. 12
Monitoring blood glucose control in diabetes mellitus: a systematic review.

By Coster S, Gulliford MC, Seed PT, Powrie JK, Swaminathan R.

No. 13
The effectiveness of domiciliary health visiting: a systematic review of international studies and a selective review of the British literature.

By Elkan R, Kendrick D, Hewitt M, Robinson JJA, Tolley K, Blair M, *et al.*

No. 14
The determinants of screening uptake and interventions for increasing uptake: a systematic review.

By Jepson R, Clegg A, Forbes C, Lewis R, Sowden A, Kleijnen J.

No. 15
The effectiveness and cost-effectiveness of prophylactic removal of wisdom teeth.

A rapid review by Song F, O'Meara S, Wilson P, Golder S, Kleijnen J.

No. 16
Ultrasound screening in pregnancy: a systematic review of the clinical effectiveness, cost-effectiveness and women's views.

By Bricker L, Garcia J, Henderson J, Mugford M, Neilson J, Roberts T, *et al.*

No. 17
A rapid and systematic review of the effectiveness and cost-effectiveness of the taxanes used in the treatment of advanced breast and ovarian cancer.

By Lister-Sharp D, McDonagh MS, Khan KS, Kleijnen J.

No. 18
Liquid-based cytology in cervical screening: a rapid and systematic review.

By Payne N, Chilcott J, McGoogan E.

No. 19
Randomised controlled trial of non-directive counselling, cognitive–behaviour therapy and usual general practitioner care in the management of depression as well as mixed anxiety and depression in primary care.

By King M, Sibbald B, Ward E, Bower P, Lloyd M, Gabbay M, *et al.*

No. 20
Routine referral for radiography of patients presenting with low back pain: is patients' outcome influenced by GPs' referral for plain radiography?

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