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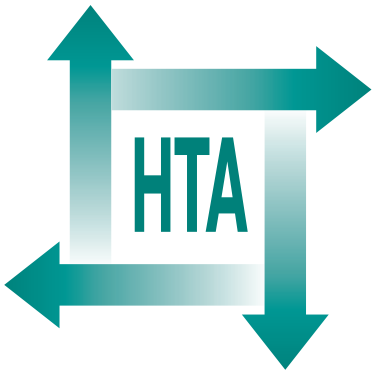

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The cost-effectiveness of screening for oral cancer in primary care

PM Speight,[1*] S Palmer,[2] DR Moles,[3] MC Downer,[3,4] DH Smith,[5] M Henriksson[2,6] and F Augustovski[2,7]

[1] School of Clinical Dentistry, University of Sheffield, UK
[2] Centre for Health Economics, University of York, UK
[3] Eastman Dental Institute, University College London, UK
[4] Oral Health and Development, University of Manchester, UK
[5] Center for Health Research, Kaiser Permanente, Portland, Oregon, USA
[6] Center for Medical Technology Assessment, Linköping University, Sweden
[7] Institute for Clinical Effectiveness and Health Policy, Buenos Aires, Argentina

* Corresponding author

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The research reported in this monograph was commissioned by the HTA Programme as project number 99/46/02. The contractual start date was in September 2001. The draft report began editorial review in April 2004 and was accepted for publication in July 2005. As the funder, by devising a commissioning brief, the HTA Programme specified the research question and study design. The authors have been wholly responsible for all data collection, analysis and interpretation, and for writing up their work. The HTA editors and publisher have tried to ensure the accuracy of the authors' report and would like to thank the referees for their constructive comments on the draft document. However, they do not accept liability for damages or losses arising from material published in this report.

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Abstract

The cost-effectiveness of screening for oral cancer in primary care

PM Speight,[1*] S Palmer,[2] DR Moles,[3] MC Downer,[3,4] DH Smith,[5] M Henriksson[2,6] and F Augustovski[2,7]

[1] School of Clinical Dentistry, University of Sheffield, UK
[2] Centre for Health Economics, University of York, UK
[3] Eastman Dental Institute, University College London, UK
[4] Oral Health and Development, University of Manchester, UK
[5] Center for Health Research, Kaiser Permanente, Portland, Oregon, USA
[6] Center for Medical Technology Assessment, Linköping University, Sweden
[7] Institute for Clinical Effectiveness and Health Policy, Buenos Aires, Argentina
* Corresponding author

Objectives: To use a decision-analytic model to determine the incremental costs and outcomes of alternative oral cancer screening programmes conducted in a primary care environment.
Design: The cost-effectiveness of oral cancer screening programmes in a number of primary care environments was simulated using a decision analysis model. Primary data on actual resource use and costs were collected by case note review in two hospitals. Additional data needed to inform the model were obtained from published costs, from systematic reviews and by expert opinion using the Trial Roulette approach. The value of future research was determined using expected value of perfect information (EVPI) for the decision to screen and for each of the model inputs.
Setting: Hypothetical screening programmes conducted in a number of primary care settings. Eight strategies were compared: (A) no screen; (B) invitational screen – general medical practice; (C) invitational screen – general dental practice; (D) opportunistic screen – general medical practice; (E) opportunistic screen – general dental practice; (F) opportunistic high-risk screen – general medical practice; (G) opportunistic high-risk screen – general dental practice; and (H) invitational screen – specialist.
Participants: A hypothetical population over the age of 40 years was studied.
Main outcome measures: The main measures were mean lifetime costs and quality-adjusted life-years (QALYs) of each alternative screening scenario and incremental cost-effectiveness ratios (ICERs) to determine the additional costs and benefits of each strategy over another.
Results: No screening (strategy A) was always the cheapest option. Strategies B, C, E and H were never cost-effective and were ruled out by dominance or extended dominance. Of the remaining strategies, the ICER for the whole population (age 49–79 years) ranged from £15,790 to £25,961 per QALY. Modelling a 20% reduction in disease progression always gave the lowest ICERs. Cost-effectiveness acceptability curves showed that there is considerable uncertainty in the optimal decision identified by the ICER, depending on both the maximum amount that the NHS may be prepared to pay and the impact that treatment has on the annual malignancy transformation rate. Overall, however, high-risk opportunistic screening by a general dental or medical practitioner (strategies F and G) may be cost-effective. EVPIs were high for all parameters with population values ranging from £8 million to £462 million. However, the values were significantly higher in males than females but also varied depending on malignant transformation rate, effects of treatment and willingness to pay. Partial EVPIs showed the highest values for malignant transformation rate, disease progression, self-referral and costs of cancer treatment.
Conclusions: Opportunistic high-risk screening, particularly in general dental practice, may be cost-effective. This screening may more effectively be targeted to younger age groups, particularly 40–60 year olds. However, there is considerable uncertainty in the parameters used in the model, particularly malignant transformation rate, disease progression, patterns of self-referral and costs. Further study is needed on malignant transformation rates of oral potentially malignant lesions and to determine the

outcome of treatment of oral potentially malignant lesions. Evidence has been published to suggest that intervention has no greater benefit than 'watch and wait'. Hence a properly planned randomised controlled trial may be justified. Research is also needed into the rates of progression of oral cancer and on referral pathways from primary to secondary care and their effects on delay and stage of presentation.

Contents

List of abbreviations

CEAC	cost-effectiveness acceptability curve
CI	confidence interval
ELS	equivalent life saved
EVPI	expected value of perfect information
GDP	general dental practitioner
ICD	International Classification of Diseases
ICER	incremental cost-effectiveness ratio
MTR	malignant transformation rate
NPV	negative predictive value
OR	odds ratio
PPV	positive predictive value
PSA	probability sensitivity analysis
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
ROC	receiver operating characteristic
SCC	squamous cell carcinoma
SD	standard deviation
SE	standard estimate of the mean
Sn	sensitivity
Sp	specificity
SROC	summary receiver operating characteristic
TCR	Thames Cancer Registry
VOI	value of information

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 at the end of the table.

Executive summary

Objectives

The objectives were to use a decision-analytic model to determine the incremental costs and outcomes of alternative oral cancer screening programmes conducted in a primary care environment. The following specific questions were addressed:

- What are the actual costs of screening for oral cancer and precancer in primary care settings?
- What are the actual costs of management of oral precancerous lesions and oral cancer, including costs of recurrent disease, long-term rehabilitation and palliation?
- What screening programmes in primary care may be cost-effective in terms of survival (life years gained) and overall gains in quality-adjusted life-years (QALYs)?
- What are the future research priorities? Specifically, what is the expected value of perfect information (EVPI) for the decision to adopt a screening programme and for each of the model inputs?

Design

The cost-effectiveness of oral cancer screening programmes in a number of primary care environments was simulated using a decision analysis model. Primary data on actual resource use and costs were collected by case note review in two hospitals. Additional data needed to inform the model were obtained from published costs, from systematic reviews and by expert opinion using the Trial Roulette approach. The value of future research was determined using EVPI for the decision to screen and for each of the model inputs.

Setting

Hypothetical screening programmes conducted in a number of primary care settings. Eight strategies were compared:

A no screen
B invitational screen – general medical practice
C invitational screen – general dental practice
D opportunistic screen – general medical practice
E opportunistic screen – general dental practice
F opportunistic high-risk screen – general medical practice
G opportunistic high-risk screen – general dental practice
H invitational screen – specialist.

Participants

A hypothetical population over the age of 40 years was studied.

Main outcome measures

The main measures were mean lifetime costs and QALYs of each alternative screening scenario and incremental cost-effectiveness ratios (ICERs) to determine the additional costs and benefits of each strategy over another.

Results

Cost-effectiveness

No screening (strategy A) was always the cheapest option. Strategies B, C, E and H were never cost-effective and were ruled out by dominance or extended dominance. Of the remaining strategies, the ICER for the whole population (age 49–79 years) ranged from £15,790 to £25,961 per QALY. Modelling a 20% reduction in disease progression always gave the lowest ICERs. Cost-effectiveness acceptability curves showed that there is considerable uncertainty in the optimal decision identified by the ICER, depending on both the maximum amount that the NHS may be prepared to pay and the impact that treatment has on the annual malignancy transformation rate. Overall, however, high-risk opportunistic screening by a general dental or medical practitioner (strategies F and G) may be cost-effective.

Expected value of perfect information analysis

EVPIs were high for all parameters with population values ranging from £8 million to

£462 million. However, the values were significantly higher in males than females but also varied depending on malignant transformation rate, effects of treatment and willingness to pay. Partial EVPIs showed the highest values for malignant transformation rate, disease progression, self-referral and costs of cancer treatment.

Discussion

Set against a benchmark figure of £20,000–30,000 per QALY, the results indicate that opportunistic screening for oral cancer may be cost-effective. In particular, opportunistic high-risk screening by general dental practitioners, who are already trained to examine the mouth, with an ICER of £18,919 may be a practical proposition. These data, however, assume that interventive treatment of precancerous lesions will prevent disease progression and reduce the malignant transformation rate. Literature reviews revealed that there is little evidence that this is the case. EVPI analysis showed considerable uncertainty around the parameters used in the model, but identified that potential future research would be of most value directed at more precise determination of malignant transformation rates.

Conclusions

Opportunistic high-risk screening, particularly in general dental practice, may be cost-effective. Screening may more effectively be targeted to younger age groups, particularly those aged between 40–60 years. However, there is considerable uncertainty in the parameters used in the model, particularly malignant transformation rate, disease progression, patterns of self-referral and costs.

Recommendations for further research

Studies are needed to determine the malignant transformation rates and the outcome of treatment of oral potentially malignant lesions. Evidence has been published to suggest that intervention has no greater benefit than 'watch and wait'. Hence a properly planned randomised controlled trial may be justified.

Studies are also needed to determine the rates of progression of oral cancers as well as on referral pathways from primary to secondary care and their effects on delay and stage of presentation.

The decision model should be run on data obtained from sources with less heterogeneity or uncertainty in the data.

Chapter 1
Introduction

Background

Oral cancer is defined as malignant neoplasms of the lip, tongue, gum, mouth, tonsil and pharynx [International Classification of Diseases (ICD) 10: C00–C14, excluding C07, C08 (salivary glands) and C11 (nasopharynx)].[1] In the UK in 1999 there were over 4000 new cases of oral cancer.[1] In England there were 3360 new cases with about 1350 deaths.[2] Overall, about 60% of patients die of intraoral lesions (excluding lip) within 5 years.[1,3] There has been no improvement in survival for decades and recent studies show that the incidence is increasing.[3] More than 60% of patients present with large lesions (>2 cm), which have a significantly worse prognosis. Management of these cases is often by a costly multidisciplinary approach involving surgery and/or radiotherapy followed by reconstruction, rehabilitation and counselling. Treatment results in considerable physical and psychological morbidity and may not prolong life. The only way to improve this situation in the absence of effective primary prevention is by improved detection of lesions while they are small (early). This may be achieved by increasing awareness among the population so that affected individuals may present earlier, or by screening or case finding for the detection of small, otherwise asymptomatic, cancers and precancers (secondary prevention).

The potential benefits of health education, particularly relating to cessation of tobacco use, have been advocated for some time,[4] and over the last few decades there has been a decrease in tobacco usage which has resulted in a reduced incidence of lung cancer.[5] However, over the same time period there has been no decrease in the incidence of oral cancer – indeed, there has been an increase in incidence among males in exactly the same age groups as show the decrease in lung cancer (40–64-year-olds),[3] suggesting that rising alcohol consumption may be a major factor responsible for the increased incidence of oral cancer.[6] We have shown that there is a positive correlation between mortality from liver cirrhosis and oral cancer over the same period and in the same age groups.[6] These data suggest that tobacco use may not be the most important aetiological factor in oral cancer and present considerable problems for those arguing for tobacco cessation programmes as the principle preventive measure against oral cancer.

Health education programmes aimed at motivating patients to present earlier have also been largely unsuccessful. Delay in diagnosis and presentation with late-stage disease may be due to patient delay or professional delay. Although both may contribute, there is no evidence that improved education regarding signs and symptoms results in shortened patient delay. Guggenheimer and colleagues[7] and Kowalski and colleagues[8] showed that the risk of being diagnosed with advanced disease did not necessarily depend on patient or professional delay. This suggests that symptomatology is independent of tumour stage and that it is a matter of chance as to when symptoms become evident – even if patients present as soon as they become aware of a lesion, it may be too late. Similarly, Kaufman and colleagues[9] showed that late-stage disease had a shorter interval between onset of symptoms and diagnosis and yet these lesions may still have a long detectable preclinical phase.[7] From these data, Kowalski and colleagues[8] concluded that screening or case-finding among high-risk groups is potentially the most effective method for early detection.

The Oral Health Strategy for England (1994) stated that dentists can play an important role in the early detection of oral cancer. A specific target, endorsed by the British Dental Association,[10] was that the rising incidence of oral cancer should be arrested by 2005. In 2002, the Chief Dental Officer for England published *NHS Dentistry: Options for Change*,[11] which sets out proposals for a modernised service. These include a standard oral health assessment which explicitly includes a prevention element which encompasses "lifestyle advice such as smoking cessation, oral health education, oral cancer screening". In 1993, a UK Working Group on Screening for Oral Cancer and Precancer made a series of detailed recommendations relating to research priorities for evaluating screening methods.[12] Since that time, a number of studies have been conducted into the validity of screening, the training of personnel in screening and evaluation of

screening programmes.[13–15] It was shown that dentists can detect relevant lesions with a sensitivity (0.74) and specificity (0.99) similar to those obtained in other screening programmes.[13,14] In an invitational programme, however, compliance for an oral examination was <25%, which, in association with the low prevalence of the disease in the general population, led to the conclusion that population screening for oral cancer may not be cost-beneficial.[15]

An alternative solution would be to screen opportunistically a subset of the population in which the prevalence of lesions would be at its highest. Using data from over 2000 individuals examined in two pilot screening programmes,[13,14] a machine learning model (neural network) was constructed which correctly predicted the presence of oral cancer or precancer in eight out of 10 positive cases.[16] The sensitivity was 0.80 and specificity 0.77 compared with 0.74 and 0.99, respectively, for dental screeners. Although the network had a false-positive rate of 23%, this is acceptable for a system designed as a 'prescreen filter' whereby those identified will be subjected to a detailed mucosal examination. In this respect, the neural network identified 25% of the population as being at high risk and among this group the prevalence of lesions (cancer or precancer) was 9% compared with 2.7% in the population as a whole.

This suggests that screening only those deemed to be at high risk may be effective in reducing mortality from oral cancer, but little is known about the practicalities, costs or cost-effectiveness of applying such a system in a primary care environment. It would seem that general dental practice should be an ideal place to initiate a programme of screening for high-risk groups since dentists are already trained to examine the mouth and it would be a simple matter to examine for mucosal lesions opportunistically when a patient presents for some other, unrelated, purpose.

There has been doubt that a population of average dental attenders would be relevant for oral cancer screening, on the assumption that high-risk individuals are, in general, less likely to attend the dentist and that the prevalence of disease among attenders would be low. However, data from a recent study suggests that this is not the case. In a pilot screening programme conducted in 18 general dental practices, oral mucosal examinations of 2265 subjects showed that 94 (4.0%) had a relevant lesion.[17] This proportion of 'positives' was similar to those in previous studies in hospital, medical practice and industrial settings[13,18] and suggests that dental attenders may be representative of the population as a whole. Similarly, the prevalence of carcinomas in this study (2/2277) was very close to the estimated prevalence of 1 in 1000 for a UK population. These findings are encouraging and support the view that opportunistic screening in general dental practice may be a feasible and effective approach.[12] However, there are no data at all on the costs or cost-effectiveness of such a strategy.

Rationale for choosing a simulation modelling approach rather than a randomised controlled trial

The ideal approach to the assessment of costs and outcomes of healthcare technologies is within the context of a clinical trial, and a randomised controlled trial (RCT) is generally considered to be the gold standard. However, under certain circumstances, other approaches may be used to generate equally valid cost-effectiveness data.[19] These include observational studies and analytical or modelling studies, which synthesise data collected from multiple sources and the literature. This latter approach is particularly appropriate where there are large gaps in knowledge or where a disease is of low prevalence, making a clinical trial costly or of uncertain value. Modelling approaches have been used to inform decision-makers about the feasibility of progressing to clinical trials for screening for colorectal cancer[20] and ovarian cancer.[21,22] In these studies, simulation modelling was used to determine cost-effectiveness and optimal screening protocols to be tested in an RCT.

To determine the effectiveness of oral cancer screening and of targeting high-risk groups, a crude simulation model of oral cancer screening was constructed, using decision analysis.[23–25] The model simulated the effects of screening a hypothetical population of 100,000 before and after application of machine learning to identify individuals at high risk. After screening the whole population with an assumed attendance of 50%, there was a gain of 56 quality-adjusted life-years (QALYs), equivalent to three lives saved. Using the neural network to target only those identified as high risk resulted in targeting 25% of the population, and screening of these resulted in a gain equivalent to eight lives saved.[25]

In this report, we present a more advanced simulation modelling approach to address specifically the question, 'What is the cost-effectiveness of screening for oral cancer in primary dental/medical care?'. There are compelling reasons why this is more appropriate than undertaking an RCT of oral cancer screening at the present time.

Although oral cancer is a serious public health problem, with high morbidity and mortality, and substantial costs to the NHS, it is a disease of relatively low prevalence. This means that large numbers of people would have to be examined if an RCT were to be used to evaluate an oral cancer screening programme. The knowledge base for the potential screening of oral cancer is fragmented. No single screening strategy has emerged from the literature as being superior to others and therefore worthy of full-scale evaluation to the exclusion of other potential strategies.[12,26]

Using an RCT approach, it would be necessary to evaluate any and all likely strategies, which would be prohibitively difficult and costly, or to choose one or two strategies and undertake the RCT with the knowledge that suitable alternative programmes have not been included in the evaluation. This approach would risk failing to identify the most effective programme and might lead to a false impression of the effectiveness or otherwise of oral cancer screening in general. Also, because there are few data regarding the likely costs of oral screening, any power calculations for an RCT are likely to be highly uncertain with an increased probability of incurring a Type II error.

Simulation modelling in these circumstances is therefore superior for a number of reasons:

- The simulation approach allows greater flexibility in both the number and scope of strategies that can be evaluated.
- Expected value of perfect information (EVPI) analysis can indicate which approaches show the greatest potential benefit and value for money. Appropriate methodologies may then be submitted selectively to a full-scale RCT evaluation in an environment that is both ethical and financially responsible.
- The model will indicate whether there is likely to be any benefit at all in adopting oral cancer screening.
- The cost of producing a computer simulation model is a fraction of the cost of an RCT.
- The simulation model provides a generic tool that could be applied to multiple screening scenarios in any setting.

Main alternative strategies for oral cancer screening

Invitational (population-based) screening programmes

Population screening involves specifically inviting people to attend for a screen. Invitations are usually issued by letter to a targeted population, usually based on general medical practice patient lists. General medical practitioners (GPs) are required to invite patients for health screens at specific mandatory intervals,[27] including cervical and breast cancer screening, but this does not include a screen for oral lesions and general dental practitioners (GDPs) are not, at present, under any similar obligation.

There is no national population-based screening programme for oral cancer in the UK. A study that aimed at determining the feasibility of invitational screening took place in a North London inner city medical practice. A total of 4348 registered patients, over the age of 40 years, were sent an invitation by post, including a fixed appointment at the medical practice, but also alternative options. Only 985 (23%) accepted the screening invitation after two mailings. Among those who were screened, 12 were referred with suspicious lesions and only eight attended the referral appointment.[15] In Tokoname, Japan, a demonstration project was begun in 1986, involving the annual screening of 60-year-old residents by postal invitation. Of 5187 people invited between 1986 and 1993, 802 attended and 38 screened positive for oral cancer or precancer.[28]

Opportunistic screening (case-finding)

This method involves offering patients a screen when they attend a clinic for some other, unrelated reason. Screening of the oral soft tissues forms part of a general oral examination by a GDP and represents an opportunity to detect asymptomatic lesions (both cancer and precancer). The extent to which this is actually carried out is unknown, although in one postal survey 84% of dentists claimed to include a regular mucosal examination on all patients.[29] GDPs receive the bulk of their income on a 'fee for item of service', but the current fee scale does not include provision to pay dentists specifically for a mucosal screen or for recording the results of such an examination. Opportunistic screening in general medical practice has not been attempted. GPs do not receive training in oral mucosal examination and the related costs of training have not been determined and may prove to be inhibitory to

such a programme. Although, in medical practices, auxiliaries and practice nurses carry out many routine screening procedures, this may not, at present, be possible for oral cancer screening because, under the definitions within the Dentists Act, auxiliaries may not be allowed to carry out such an examination.

Targeted 'high-risk group' screening

Since oral cancer is relatively uncommon, and most cases are known to occur in people over the age of 40 years who smoke and drink (especially males), it may be advantageous to implement secondary prevention programmes which screen a selected subset of the population who can be identified as being at increased risk of the disease.[12,30] These people may be identified opportunistically as they access primary care services (either medical or dental). The use of artificial intelligence systems (neural networks) to identify these high-risk groups is currently being evaluated.[16,25]

Workplace programmes

The workplace presents an environment in which screening or health promotion programmes may take place. Oral cancer workplace screening has been attempted in the UK,[13,31] and in Japan.[32] In a UK study, all the employees of a London commercial organisation over the age of 40 years were invited to attend for oral screening and 53% complied.[13] This is approximately the same proportion of people who would be expected to visit a dentist for a routine check-up and represents no improvement over practice-based opportunistic screening. Other schemes have reported similar levels of uptake. Workplace programmes are only likely to be feasible in companies that employ sufficiently large numbers on a minimum number of sites.

Aims and objectives of the study

The purpose of this project was to construct a decision-analytic model which can be used to determine the incremental costs and outcomes of alternative oral cancer screening programmes conducted in a primary care environment.

Specific objectives were to determine:

- the actual costs of screening for oral cancer, and precancer in primary care settings
- the actual costs of management of oral precancerous lesions and oral cancer, including costs of recurrent disease, rehabilitation and palliation
- the incremental cost-effectiveness of screening in terms of survival (life-years gained) and overall gains in QALYs
- the EVPI for the decision to adopt a screening programme and for each of the model inputs.

Chapter 2

Systematic review 1: test performance in screening for oral cancer and precancer

Introduction

The principal objective of this systematic review was to establish a range of values for test performance in the clinical screening of apparently healthy individuals for oral cancer and precancer. These values would provide one element of the input data for the model designed to simulate population screening for these disorders. Test performance, expressed in terms of sensitivity and specificity, is an important interim measure of effectiveness of a screening programme. Meta-analysis was proposed in order to obtain pooled values for these measures. Secondary objectives were to document the main sources of clinical heterogeneity among included studies and to identify any significant differences in test performance between groups of studies with disparate research designs, population demography and other characteristics. Such differences could suggest a possible need for sensitivity analyses.

Methods

General

The review was designed to be of low recall and high precision. It was based essentially on a detailed scrutiny of 47 publications of *prima facie* relevance[13–16,18,24,25,28,32–70] gained from a search of the literature. The review was conducted in accordance with guidelines promulgated by the NHS Centre for Reviews and Dissemination.[71] Attention was paid in particular to guidance on the evaluation of screening and diagnostic tests.

Advisory group

An advisory group was formed, consisting of core members of the research team, other advisers connected with the study and a research assistant who undertook the searches. These individuals were affiliated to several different institutions and represented a range of appropriate expertise. Four consultative meetings were held during 2001–2 and members communicated extensively by email in the intervening periods. The essential tasks of the advisory group were to decide the scope of the review and specific questions to be addressed; to approve and finalise the protocol; to monitor progress in identifying studies and deciding their suitability for inclusion (assessment of validity); to discuss the proposals for analysis of the material and completion of the review; and to agree the final report.

Identification of research

The following databases were searched: MEDLINE, EMBASE, CANCERLIT, CINAHL, AMED, BNI, HMIC, DARE T System and the Cochrane Library. The search was confined to English language papers published from 1980 to January 2002 inclusive. The strategy comprised the following facets: Population (P): oral cancers/precancers; Interventions (I): screening; and Outcomes (O): diagnostic test performance. The last item was based on a diagnostic efficacy filter developed for the NHS Cancer Guidance Project with some added terms. An example of the Boolean-structured search procedure, as applied on MEDLINE, is shown in Appendix 1. In the initial MEDLINE scoping search, P+I+O generated 343 hits. For those papers subsequently selected for full text screening, the bibliographic reference lists were handsearched for other relevant citations. No attempt was made to obtain grey literature, although one additional study which came to light[72] was examined.

Selection of studies

Titles, and abstracts where available, of all studies generated in the search were scrutinised by one reviewer (MCD) for their relevance to the objectives of the review. Citations that were *prima facie* of no relevance, for example laboratory studies and papers providing no original research data, were excluded from further consideration in this phase. A list of these papers (available on request) was retained. Full texts of all the remaining papers were then obtained for detailed examination.

Study quality assessment

Full text screening of all studies retained in the initial selection phase was undertaken independently by two reviewers (MCD, DRM). In

order to meet the inclusion criteria: (1) the investigation reported had to be a prospective clinical field study, (2) the criteria for a positive screen had to be defined, (3) there had to be a defined gold standard, e.g. verification through clinical examination by an expert, (4) the gold standard had to be applied to at least a proportion of assumed healthy individuals screened as negative, (5) it had to be possible to derive a full 2×2 contingency table from the data provided in order to calculate sensitivity (Sn) and specificity (Sp) values and related statistics and (6) the paper had to consist of the most current primary report of the investigation in question, thus eliminating any duplicated data. An example of the blank proforma used by the reviewers is illustrated in Appendix 2.

The quality assessments having been carried out and the reviewers having made their initial selections of studies meeting the criteria for inclusion, a kappa value was calculated to compare agreement. Following this, the reviewers conferred and a final agreed list of studies was produced. A data extraction sheet recording the demographic characteristics of the population targeted in the programme described in the paper, together with essential details of the study design and a summary of the data extracted, was compiled for each selected study. An example of a completed data extraction sheet proforma is shown in Appendix 3. The full collection of completed forms is available on request.

Data synthesis

Global estimates for Sn and Sp were obtained from the selected studies using the summary receiver operating characteristic (SROC) curve meta-analytical technique[73] utilising a standard random effects meta-analysis within the STATA software package.[74] The method and its rationale, applied to this type of data have been described in greater detail elsewhere.[75] In a secondary analysis, the selected studies were dichotomised into two groups, on the basis of the extent of their clinical heterogeneity. A random effects meta-analysis regression was then performed to ascertain if there was any significant difference in the discriminatory ability of the screening test between the two groups of studies.

Results

Searches and quality assessment

The search of nine databases produced 481 hits. From these, 47 research reports[13–16,18,24,25,28,32–70] were retrieved for full text screening in order to assess their quality and validity. Applying the inclusion criteria to these reports, the first reviewer selected six studies[13,14,28,53,54,68] and the second reviewer eight,[13,14,28,53,54,65,68,70] for meta-analysis. The six studies selected by the first reviewer were common to both selections. For agreement between reviewers, kappa = 0.83. After conferring, seven papers[13,14,28,53,54,65,68] describing eight studies were finally included and data extraction sheets for these were prepared. A list of studies excluded at this stage and reasons for their exclusion is presented in *Table 1*. Outcome measures of test performance derived from the eight studies selected are presented in *Table 2* (four studies from developing countries are marked). Sn values ranged from 0.60 to 0.97. Sp values were at least 0.94, except for the two Sri Lankan studies,[65,68] where the groups of basic health workers undertaking screening returned false-positive rates of 25 and 19%, respectively.

Meta-analysis

Figure 1 shows the receiver operating characteristic (ROC) curve for the eight studies included in *Table 2*. The Forest plot (*Figure 2*) shows the results of the random effects meta-analysis of their discriminatory ability. The SROC curve for the studies is shown in *Figure 3*. The weighted pooled value of their Sn was 0.848. From the equation for the SROC curve, the corresponding value of Sp at this level of Sn was 0.965 [95% confidence interval (CI) 0.930 to 0.982]. When Sp was held at 0.965, the 95% CI for the corresponding value of Sn (0.848) was 0.730 to 0.919.

Heterogeneity

Although meeting the assessment criteria of quality and yielding the data essential for meta-analysis, the limited number of studies included nevertheless showed considerable clinical heterogeneity. The studies are listed column-wise in *Table 3* by first author with the most salient qualitative factors contributing to heterogeneity, taken from the data extraction sheets, cross-tabulated. Inspection shows that there were substantial differences in the target populations and their demographic characteristics, study designs, specified target lesions, categories and numbers of personnel undertaking screening and providing the gold standard clinical examinations, and the amount of training received by the screeners. It is obvious that the main differences lay between the pilot and substantive studies conducted in the industrialised countries (England and Japan), which utilised dentists as screeners[13,14,28] and the much larger house-to-

TABLE 1 *Studies excluded and reasons for exclusion*

First author	Is a prospective field study reported?	Are criteria for a positive screen defined?	Is there a defined gold standard?	Is at least a proportion of negatives verified?	Can a 2 × 2 contingency table be derived from data?	Is this the most current primary report of study?
Banoczy (1991)[33]		×	×	×	×	
Barra (1990)[34]			×	×	×	
Burzynski (1997)[35]		×	×	×	×	
Clayman (1995)[36]			×	×	×	
Dombi (2001)[37]			×	×	×	
Downer (1997)[24]	×					×
Downer (1998)[25]	×					
Eckert (1982)[38]			×	×	×	
Eckert (2000)[39]				×		
Epstein (1997)[40]				×		
Field (1995)[41]			×	×	×	
Garrote (1995)[42]			×	×	×	
Gupta (1991)[43]	×	×	×	×	×	×
Hawkins (1999)[44]	×	×	×	×	×	
Horowitz (1996)[45]	×	×	×	×	×	
Ikeda (1995)[46]				×	×	
Ikeda (1991)[32]		×	×	×	×	
Jovanovic (1992)[47]		×	×	×	×	
Jullien (1996)[18]	×					
Jullien (1995)[15]		×	×	×	×	
Lynch (1985)[48]				×	×	
Martin (1998)[49]				×	×	

First author	Is a prospective field study reported?	Are criteria for a positive screen defined?	Is there a defined gold standard?	Is at least a proportion of negatives verified?	Can a 2 × 2 contingency table be derived from data?	Is this the most current primary report of study?
Mashberg (1980)[50]				×		
Mashberg (1981)[51]				×		
Mashberg (1988)[52]				×	×	
Nagao (2000)[56]				×	×	
Nagao (2000)[55]			×	×	×	
Onofre (2001)[57]				×	×	
Prout (1987)[58]	×	×	×	×	×	
Rosenberg (1989)[59]	×	×	×	×	×	
Sankaranarayanan (2000)[60]				×	×	
Seoane (1997)[62]	×				×	×
Seoane (1997)[61]	×				×	
Silverman (1984)[63]				×		
Speight (1995)[16]	×					
Warnakulasuriya (1984)[64]				×	×	×
Warnakulasuriya (1996)[66]				×	×	
Warnakulasuriya (1988)[67]		×	×	×	×	
Wesley (1992)[69]	×	×			×	
Westman (1994)[70]		×			×	

A negative response is denoted by ×.

house case-finding programmes from the Indian subcontinent (marked) which used specifically trained basic health workers.[53,54,65,68] These two disparate groups of studies were dichotomised and a random effects meta-analysis regression carried out to ascertain if there were significant differences in discriminatory ability between them. An obtained value of $p = 0.99$ indicated no evidence to suggest any difference; however, the small number of studies ($n = 8$) should be borne in mind.

Discussion

Excluded studies

Although the initial selection of papers for full text screening was carried out by a single reviewer, selection bias was unlikely owing to the very specific inclusion requirements. Reports were excluded if one or more of the six criteria specified in the selection exercise were not satisfied (*Table 1*). Eight studies were excluded on the basis of one reason only, five of

TABLE 2 *Summary of quantitative data extraction for meta-analysis*

Parameter	Downer (1995)[13]	Ikeda (1995)[28]	Jullien (1995)[14a]	Jullien (1995)[14b]	Mathew (1997)[53c]	Mehta (1986)[54c]	Warnakulasuriya (1991)[65c]	Warnakulasuriya (1990)[68c]
Number screened and verified (*n*)	309	154	985	1042	2069	1921	3543	1872
Lesion prevalence in verified sample	5.50	9.74	2.23	3.07	10.25	1.41	50.72	21.63
Sn	0.71	0.60	0.64	0.81	0.94	0.59	0.97	0.95
Sp	0.99	0.94	0.99	0.99	0.98	0.98	0.75	0.81
PPV	0.86	0.50	0.64	0.68	0.87	0.31	0.80	0.58
NPV	0.98	0.96	0.99	0.99	0.99	0.99	0.96	0.98
Likelihood ratio (positive)	71.00	10.00	64.00	81.00	47.00	29.50	3.88	5.00
Likelihood ratio (negative)	0.29	0.43	0.36	0.19	0.06	0.42	0.04	0.06

NPV, negative predictive value; PPV, positive predictive value.
[a] GP patients.
[b] Hospital patients.
[c] Study conducted in a developing country.

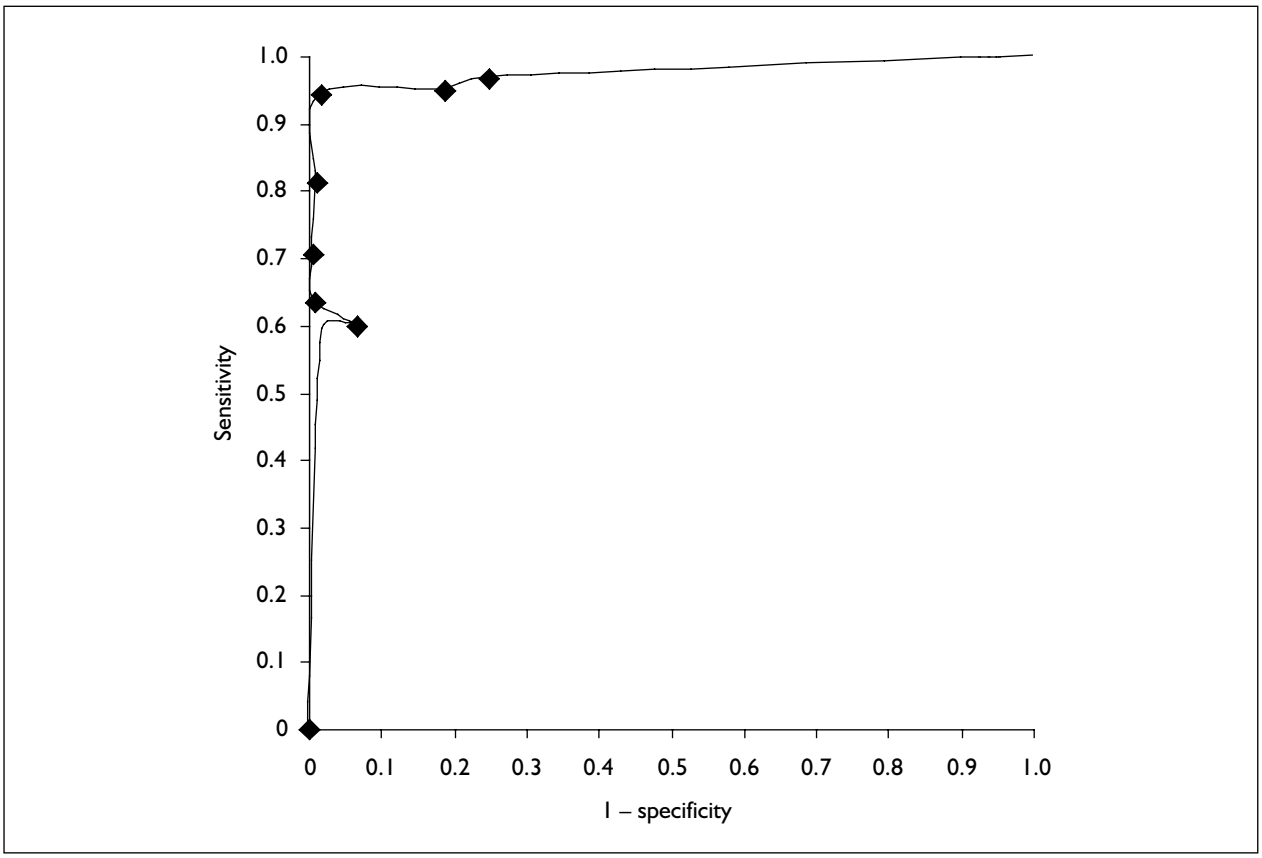

FIGURE 1 *ROC for eight studies included in meta-analysis*

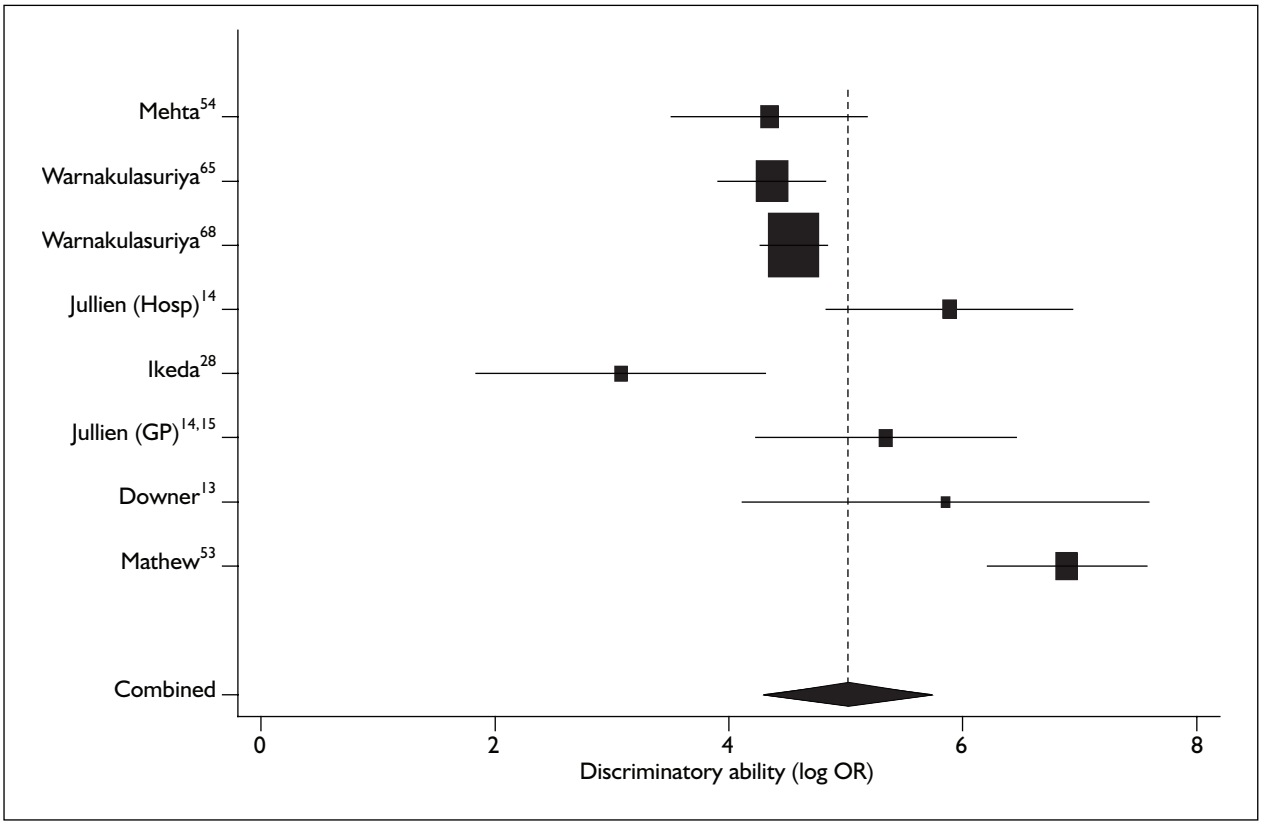

FIGURE 2 *Forest plot of eight studies included in meta-analysis*

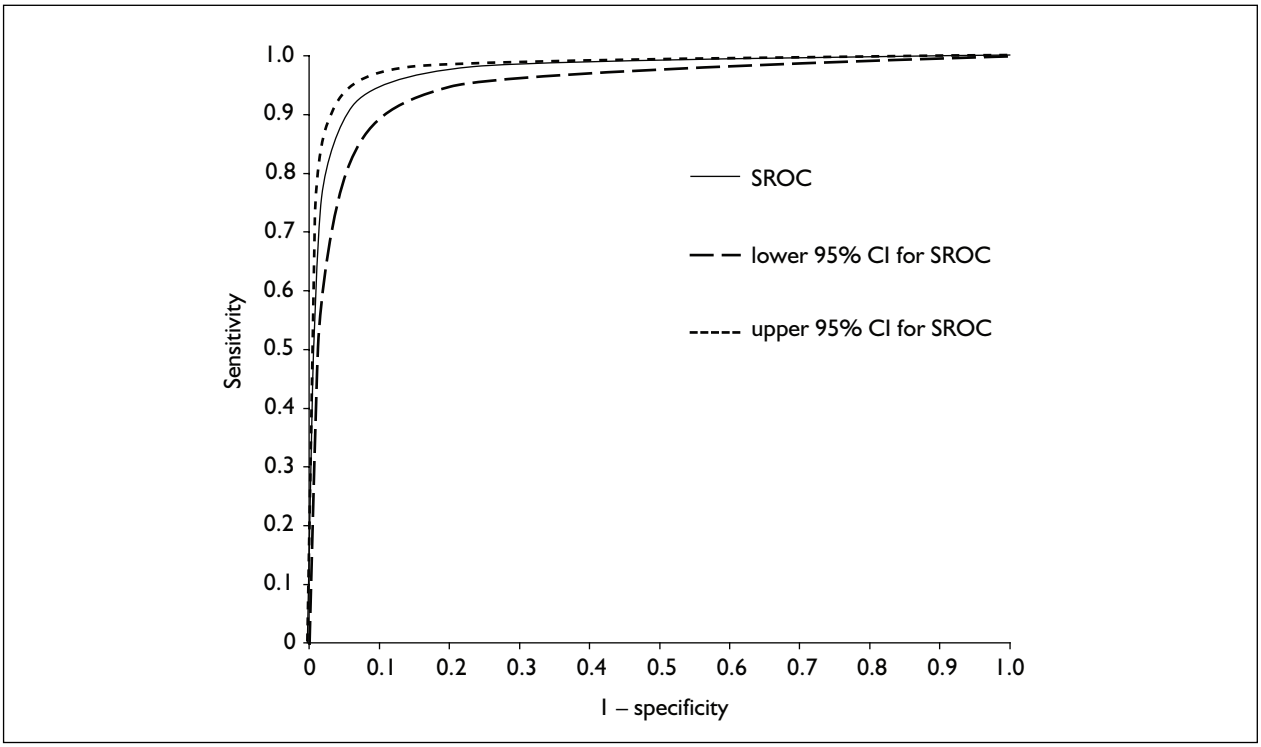

FIGURE 3 *Summary ROC for eight studies included in meta-analysis*

these[39,40,50,51,63] were concerned with the evaluation of toluidine blue, and not population screening and three[16,18,25] did not report original data. Without the essential information forming the basis of these criteria, a study would not have the necessary data to enter the meta-analysis of discriminatory ability – the basic quantitative outcome measure of test performance in screening, which the review sought to establish as its primary objective.

During planning, the question of whether assessments of performance in the clinical detection of oral cancer and precancer using toluidine blue dye, also known as tolonium chloride, as an aid should be admitted. The strongest argument against this was that the purpose of using toluidine blue is to disclose whether a suspicious mucosal lesion is likely to be squamous cell carcinoma (SCC). It is therefore an aid to oral cancer diagnosis and not an appropriate tool for use in population screening programmes of apparently healthy individuals. Even in clinical diagnosis it is not regarded as a substitute for histological confirmation of the status of a lesion by biopsy. Ultimately, it was decided that the two terms should be included in the search and nine studies involving the agent were revealed.[39,40,49–51,57,59,63,66] These were all subsequently selected for quality assessment in full text screening. However, the clinical studies were invariably carried out with individuals who already had an oral mucosal lesion, suspicious or otherwise, or a history of oral cancer, rather than on assumed healthy individuals. The fundamental purpose of screening is to sort out apparently well persons who probably have disease from those who probably do not;[76] it is not intended to be diagnostic. In none of the nine studies was the gold standard (in this case biopsy) applied to apparently healthy individuals, so that apart from meeting, or failing to meet, the remaining inclusion criteria, all nine studies were rendered ineligible for this reason alone (*Table 1*). It should also be stressed that confirmatory biopsy, although representing a 'hard' gold standard, could never be an appropriate reference criterion for a population screening study since it would be impracticable, and arguably unethical, to biopsy mucosal tissue, free from any signs of a lesion, in apparently healthy individuals.

Systematic reviews of toluidine blue as a diagnostic aid

The nine toluidine blue studies cited above contained one from 1989 reporting an early meta-analysis by Rosenberg and Cretin.[59] Three of the remaining eight studies were included in this.[50,51,63] Apart from one additional paper by Mashberg,[77] the other reports in Rosenberg and

TABLE 3 *Main sources of clinical heterogeneity among studies analysed. Studies conducted in developing countries are marked with an asterisk*

Qualitative variable	Downer (1995)[13]	Ikeda (1998)[28]	Jullien (1995)[14]	Jullien (1995)[14]	Mathew (1997)[53a]	Mehta (1986)[54a]	Warnakulasuriya (1991)[65a]	Warnakulasuriya (1990)[68a]
Target population	Company HQ staff	Eligible adults	GP practice patients	Hospital visitors	An adult population	High risk adults	Rural adults	Rural adults
Country	England	Japan	England	England	India	India	Sri Lanka	Sri Lanka
Age (years) and gender	40+, M/F	60, M/F	40+, M/F	40+, M/F	35–64, M/F	35+, M/F	20+, M/F	20+, M/F
Ethnicity	British	Japanese	Mainly British	Mainly British	Indian	Indian	Sri Lankan	Sri Lankan
Target lesions[b]	CELPYFK	CELPD	CELPYFK	CELPYFK	CELF	CLF	CELPYFK	CELPYFK
Type of programme	Pilot	Definitive	Pilot	Pilot	Definitive	Definitive	Definitive	Pilot
Recruitment procedure	Invitation	Invitation	Invitation	Opportunist	Case-finding	Case-finding	Case-finding	Case-finding
Category of screener (number))	GDP (2)	GDP (4)	Hospital and general dentist (24)	Hospital and general dentist (24)	Health worker (14)	Health worker (14)	Primary health worker (36)	Primary health worker (34)
Specifically trained	No	Yes	No	No	Yes	Yes	Yes	Yes
Gold standard	Oral medicine specialist	Specialist oral surgeon	Oral medicine specialist	Oral medicine specialist	Physicians (3)	University-based dentists	Project dentist	Project dentist
Screening setting	Dental surgery	Health centre	Health centre dental clinic	Hospital examination room	Subjects' homes	Subjects' homes	Subjects' homes	Subjects' homes
Reference examination setting	Dental surgery	Health centre	Health centre dental clinic	Hospital examination room	Subjects' homes	Subjects' homes	Referral centre/homes	Referral centre
Examiner blinding	Yes	Yes	Yes	Yes	Yes	Yes	Unreported	Unreported

[a] Studies conducted in developing countries.
[b] C, carcinoma; D, chronic candidosis; E, erythroplakia; F, submucous fibrosis; K, actinic keratosis; L, leukoplakia; P, lichen planus; Y, lupus erythematosus.

Cretin's review were either published before 1980 or were from non-English language journals. In their discussion, the authors noted that toluidine blue had not been accepted as an oral cancer screening device in the USA because of the "fair number of false-positive results, usually caused by adherence of the dye to areas of inflammation or trauma".

A further, recent systematic review by Gray and colleagues[72] of the effectiveness of toluidine blue as an adjunct to oral cancer screening was also examined. Seven of the nine studies generated in the current searches appeared among Gray and colleagues' literature citations[40,49–51,59,63,66] and four of these[40,50,63,66] were ultimately included in their review. Apart from the paper by Mashberg[77] referred to above, the remaining 10 reports analysed by these workers were again either from before 1980 or from non-English language journals. There were 14 published studies that met their inclusion criteria, albeit Gray and colleagues noted the poor quality of 10 of these. Only one, by Warnakulasuriya and Johnson,[66] was rated as 'good'. All 14 studies were conducted in secondary care settings on high-risk population groups. Although there were sufficient data from the papers to compute Sn and Sp values, the authors did not attempt to conduct a meta-analysis. There was an inherent difficulty applying to all the papers as to whether 'equivocal' staining should be treated as positive or negative for SCC. Reported Sn varied from 1.00[40,66] to as low as 0.40[78] and Sp ranged from 0.31[63] to 0.92.[50] The only study undertaken in a primary care setting[31] was considered too small to detect any significant effect of the use of toluidine blue as an adjunct to oral cancer screening in general dental practice. Gray and colleagues' conclusions, which appeared to be fully supported by their findings, stated that currently there was no evidence to suggest that toluidine blue was a cost-effective method of picking up oral cancers in a primary care setting. Given the large number of people who would have false-positive rates for a first positive test and even a double positive test, the harm of using it in terms of anxiety could well outweigh the benefits in terms of additional cancers detected. They noted in addition that in December 2000 there were no known studies or clinical trials in progress on toluidine blue as a screening test for oral cancer in a general practice setting. They also recommended against further research in this area.

Statistical considerations

Studies evaluating screening programmes may differ in their thresholds for calling a test result positive. Among the studies included in the current meta-analysis, this could have arisen from variation in the target lesions specified or through systematic variation resulting from specific training of the screeners, or lack of it. Since the Sn and Sp of a screening test are inter-related, changes to the threshold for a positive diagnosis will affect both measures. Hence if investigators consider it essential to detect as many positive cases as possible, the Sn of a screening test could theoretically be improved, but only at the cost of reducing Sp. This variation in positive threshold can be usefully summarised with an ROC curve. This is achieved by plotting the Sn of a test against 1 – Sp.

A method for combining the results of several studies must account for both the discriminatory ability of each study and the variation in diagnostic threshold. It is inappropriate to pool, directly, the results of each investigation since the differing prevalence of positive lesions across studies acts as a confounding factor when diagnostic thresholds differ. This is particularly likely to be a problem if there is a wide range of prevalence of disease across different studies (e.g. if trying to combine studies from different populations such as the UK and India). It is also inappropriate to calculate Sn and Sp separately within each study and to attempt to derive a weighted average of each measure (e.g. with weights being based on study size). This avoids the problem of confounding, but may still lead to an underestimate of the true accuracy if there is variation in the diagnostic thresholds used by different investigators.[73]

Since Sn and Sp are inter-related and since both diagnostic thresholds and disease prevalence may vary, the correct approach to combining the results of several studies is to use meta-analysis to produce an SROC previously referred to. If the odds ratio (OR) is constant across different thresholds, this will lead to a symmetrical SROC curve. Hence, if positive and negative screening results change the odds equally, then the diagnostic threshold is not skewed (biased) towards either diagnosis. To gain a global estimate of Sn and Sp it is necessary to derive a weighted estimate for one measure and then calculate the corresponding value (and CI) for the other measure using the results of the meta-analysis.

Heterogeneity

Meta-regression was conducted to identify any significant differences in discriminatory ability between the programmes conducted in the two

industrialised countries, England and Japan, and in the two developing countries of the Indian subcontinent. In the latter, trained health workers rather than dentists were employed as screeners, reflecting the prevailing economic circumstances in those regions. No evidence of a difference in discriminatory ability was found.

In addition to the main sources of heterogeneity (*Table 3*), other features of the studies should be noted. For example, there were major differences in the size of the target populations covered in the programmes, in the numbers screened and in the numbers and proportions of screened cases verified. In the Japanese study of Ikeda and colleagues,[28] of 5187 eligible individuals, 802 were screened, following invitation, in the years covered in the report (1986–93). However, only 154 test results (those from 1993) were verified against the gold standard examiner. In the study of Mathew and colleagues[53] in Kerala, India, 32,000 individuals had been recruited. Of the 9000 examined by May 1996, 2069 test results had been verified by physicians. In the study of Mehta and colleagues,[54] also in Kerala, 39,331 individuals out of an estimated high-risk population of 117,281 were screened. Of these, 1921 cases were verified. In the two Sri Lankan studies,[65,68] the target population covered in what was described as the pilot[68] was 87,277, of whom 29,295 were screened and 1872 verified. In the second (reproducibility) study,[65] 72,867 individuals were targeted and 57,124 screened. Of these, 3543 cases were verified. The last four studies, conducted in areas of high oral cancer incidence and mortality, were clearly of a different order of size from the remainder. An unexpected feature of the study by Mehta and colleagues[54] was the low prevalence of target lesions (1.41%) among the cases verified in their high-risk target population. This may reflect the fact that the verifications were conducted on clusters of cases at nodal points in the field rather than at referral centres.

On a final point, there was a lack of independence between certain groups of studies in the meta-analysis, which may also have had some bearing on the findings. The two Sri Lankan studies[65,68] were conducted by the same principal investigator using a similar methodology. The studies reported by Downer and colleagues[13] and Jullien and colleagues[14] carried out in London, of which two were invitational and one opportunistic, used the same core research team and the same examination methods and criteria, and shared a gold standard examiner.

Conclusions

The meta-analysis has produced a range of values, derived from relevant field studies, to provide data on test performance in clinical screening for oral cancer and precancer, an important interim measure of screening programme effectiveness.

A generally high level of discriminatory ability and consistency in test performance was apparent among the studies included, irrespective of their clinical heterogeneity.

No reports were found of the use of toluidine blue dye as an aid in population screening of apparently healthy individuals for oral cancer and precancer. Two reviews of this material which were examined suggested that its use in screening in primary care would not be beneficial and could not be recommended.

Chapter 3

Systematic review 2: measures of effectiveness in screening for oral cancer and precancer

Background

This chapter reports the results of a systematic review of measures of effectiveness of screening for oral cancer and precancer in a variety of settings. The outcome measures relate to available information on all the stages in the process of a screening programme from recruitment through to individual outcomes (survival) or population-based outcomes (incidence, stage-shift and mortality). Many programmes reported 'process' measures such as compliance with screening, but few reported long-term or population-based health outcomes such as mortality rates from oral cancer. There was considerable heterogeneity in the methods and personnel used in the various programmes and in the outcomes reported. No attempt was made to synthesise these data formally using methods such as meta-analysis. For the purpose of producing a computer simulation model, the aim was to provide a range of potential values that could be included in the modelling process, not to decide upon a single summary measure.

Details of the administrative and organisational aspects of the review (e.g. use of guidelines and the setting up of an advisory group) were as described in the previous chapter.

Objectives

The objectives were to produce ranges of values for all available 'process' and health outcome measures of effectiveness of oral cancer/precancer screening for inclusion in the computer simulation model.

Criteria for considering studies for this review

Types of studies

- Any study design reporting either a process or health outcome measure of effectiveness in oral cancer or precancer screening.

Types of participants

- Adults, irrespective of whether the study was based on whole populations or subgroups.

Types of interventions

- Any screening intervention irrespective of whether it was solely a visual examination, or a visual examination followed by a specialist examination (with or without verification by biopsy).
- Any setting.
- Any form of recruitment.

Types of outcome measures

The following outcomes were chosen to be of potential use (although not all were reported in the literature):

- Morbidity.
- Mortality.
- Survival.
- Stage shift.
- Compliance with invitation and/or follow-up.
- Recruitment.
- Case fatality.
- Number of referrals to secondary care per annum.
- Proportion of target population screened per year (population screening programmes).
- Yield of precancer.
- Yield of cancer.

Search strategy for identification of studies

The following databases were searched: MEDLINE, EMBASE, CANCERLIT, CINAHL, AMED, BNI, HMIC, DARE T System and the Cochrane Library. The search was confined to English language papers published from 1980 to January 2002 inclusive. For those papers subsequently selected for full text screening, the bibliographic reference lists were handsearched for other relevant citations. No attempt was made to obtain grey literature. A sample search strategy for MEDLINE is included as Appendix 4.

Methods of the review

The titles and abstracts identified by the electronic searches were screened by two reviewers (PMS, DRM) to exclude any studies that were clearly irrelevant. At this first stage, if it was unclear whether a study was relevant it was retained. Similarly, if either reviewer believed that a study was potentially relevant it was retained. Full text articles were obtained for all potentially relevant studies from the Eastman Library, British Dental Association Library, inter-library loans and the British Library. The full text articles were independently screened by the two reviewers (PMS, DRM) to ensure that they were concerned with oral cancer/precancer and fulfilled the following two criteria:

1. a report of an oral cancer screening programme/exercise
2. at least one effectiveness outcome reported.

Disagreements were resolved by discussion. It was not necessary to include a third reviewer to adjudicate at any stage.

Data on study characteristics and all available outcomes were abstracted and summarised in evidence tables. Where more than one article reported the same study, only the most contemporary (and complete) results were included to avoid duplication. Where several articles reported different aspects of the same programme, these were combined as appropriate and indicated as multiple articles in the evidence tables. Formal synthesis by meta-analysis was either inappropriate (owing to heterogeneity) or not desirable since it was not needed for the computer simulation process.

Results

The searches produced 1114 references. Of these, 92 articles were deemed potentially relevant and retrieved for full text screening. Two articles could not be obtained.[79,80] Of the remaining 90, agreement was reached for the inclusion of 28 studies.[13–15,28,32,34,38,41,46,48,53–56,60,64,65,67–70,81–87] The initial kappa score for agreement was reasonable ($\kappa = 0.60$).

The flow of articles through the screening and data abstraction process is summarised in *Figure 4*. The excluded studies along with their reasons for exclusion are listed in Appendix 5. The study characteristics for the included reports are summarised in *Table 4*. *Table 5* summarises the results from studies that reported measures of compliance and *Table 6* summarises yield, stage shift and survival.

Study characteristics

A wide range of screening initiatives were reported. Most programmes were based in industrialised countries,[13–15,28,32,34,38,41,46,55,56,69,70,81,84–87] and were generally of short duration, recruited relatively small numbers of participants and utilised health professionals to undertake the screening. The only long-term large-scale population-based studies in an industrialised country were from Japan.[28,32,46,55,56] All other population-based programmes were carried out in either the Indian subcontinent[53,54,60,64,65,67–69,83] or Cuba[82] and tended to rely on non-professional staff or specifically trained health workers/volunteers to screen large numbers of participants. Methods of recruitment varied from opportunistic to invitational, and targeted populations varied both in terms of age (from 20+ to 60+ years old) and other risk behaviours such as tobacco and alcohol consumption. In some instances, screening was the only intervention, whereas in others this was combined with a health education campaign. Programmes varied in reported length from 2 days to several years.

Compliance

Just under half of the studies reported compliance with invitation. The rates varied according to the recruitment method and target population. At best this was close to 100% compliance in the case of a group of participants who were invited to have an oral cancer screening along with a routine dental check.[41] At the other extreme, it was as low as 12% in a population-based screening programme for people aged over 60 years old.[32] For people who screened positive for potential oral cancer or precancer, the rates of compliance differed according to the geographic setting. Most industrialised countries reported very high levels of compliance of up to 100%. By comparison, the programmes that were carried out in the Indian subcontinent had compliance rates of the order of 50%. The lowest levels of compliance were reported in Cuba at 30%.[82]

Health outcomes

Five studies reported health outcomes.[53,60,69,82,85] Fernandez Garrote and colleagues reported true population health outcomes based on the national population cancer registry. There was an increase in the proportion of stage I cancers across the population as a whole; a decrease in stage II and

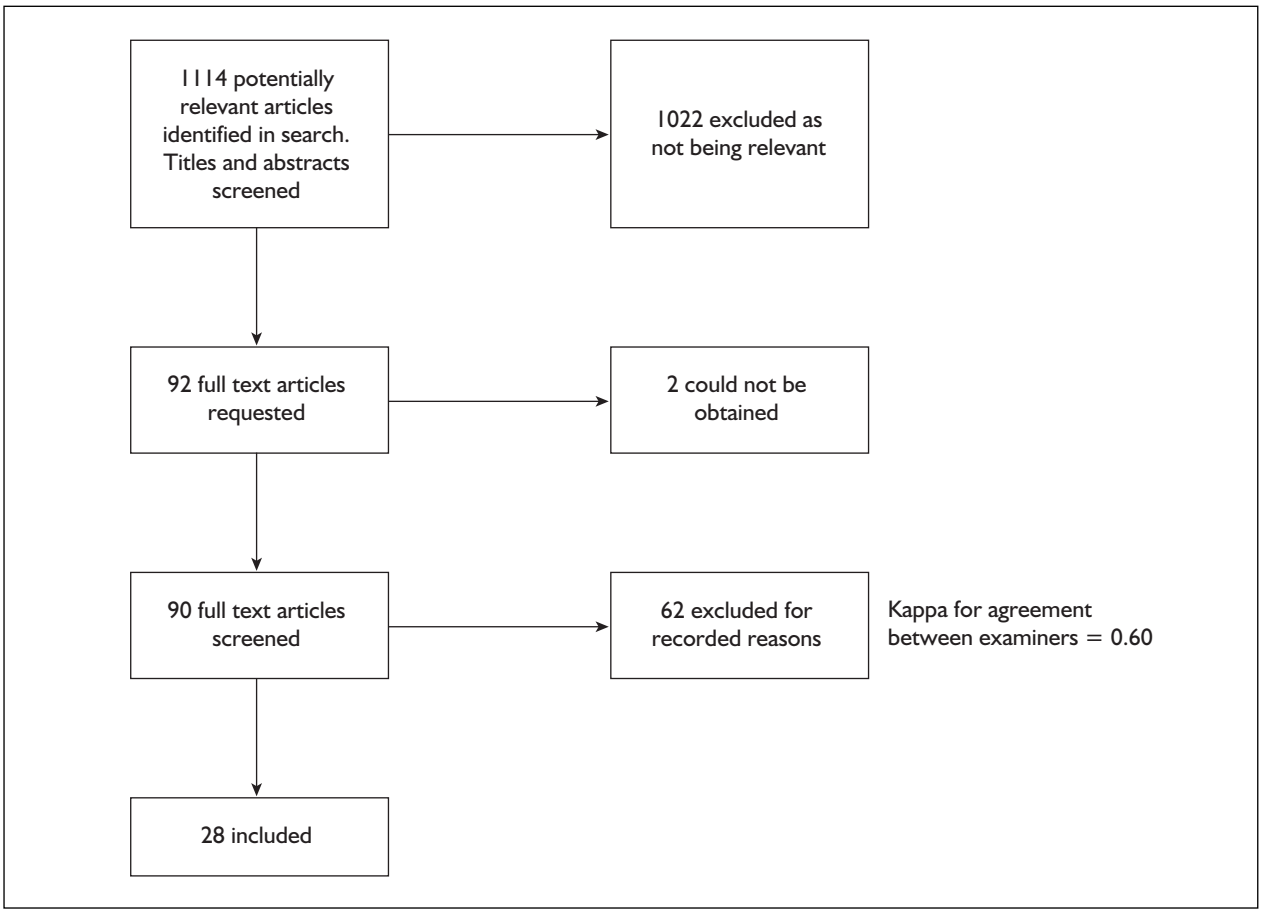

FIGURE 4 *Flow diagram for the review process*

TABLE 4 *Characteristics of included studies*

First author	Year of publication	Time frame of study	Population/target group	Intervention
Barra	1990	December 1988–May 1989	Attendees at a general medical practice with history of tobacco use and/or 4+ glasses of wine/day, north-eastern Italy	Invited to check-up by 1 of 2 ENT specialists at a cancer referral centre
Campisi	2001	?	Stratified random sample of men aged 40+ years, Italian island	Examination in local dental clinic
Downer	1995	'1 year'	Staff >40 years old at company headquarters, London	Screening by on-site dentists + validation by oral medicine specialist. Multiple publicity on-site to advertise programme
Eckert	1982	27 months 1979–1981	Not specified. Based in metropolitan Detroit	Screening by 147 dental hygienists. Based in regional service centres and outreach target sites
Field	1995	?	Patients registered at an industrial dental clinic, UK	Screening as part of routine recall. Letters of invitation to 1949 patients. Screened by 3 dentists

continued

TABLE 4 *Characteristics of included studies (cont'd)*

First author	Year of publication	Time frame of study	Population/target group	Intervention
Fernandez Garrote[82]	1995	1984–1990	All population aged ≥15 years, Cuba	Mostly opportunistic screening based on regional clinics
Ikeda[32]	1991	September 1986–June 1988	Factory and office workers from two companies in Aichi prefecture + population >60 years old from Tokoname city, Japan	All factory workers and city population >60 years old notified by post and requested to attend screenings. 4 dentists provided screening in medical clinics attached to workplaces and health centre in the city.
Ikeda[28,46]	1995	1986–1993	All residents of Tokaname city, Japan, who where aged 60 years during study period	Questionnaire sent to all residents aged 60 years, followed up by invitation for responders to attend screening. 1 day of screening each year in October/November in health centre. Screened patients also assessed by oral medicine specialist
Jullien[14]	1995	'1 year'	People aged 40+ years either outpatients at a London dental hospital or outpatients at an inner city medical practice	Opportunistic recruitment for screening at dental hospital and postal invitation for medical practice. Soft gold standard provided by oral medicine specialist
Jullien[15]	1995	?	Patients aged 40+ years registered at an inner city medical practice, London	Screening following 2 rounds of postal invitations
Lynch[48]	1985	'2 days'	Village residents in rural Thailand aged 20+ years	Community programme involving lay volunteers to raise awareness and recruit subjects for screening at community social centre (screening included other cancers in addition to oral)
Mathew[83]	1995	April–May 1988	Villagers with tobacco habits aged 30+ years old in Kerala, India	Distribution of mouth self-examination leaflets to households by 450 students, with people being invited to attend for screening if they suspected they had a positive lesion
Mathew[53]	1997	December 1995–May 1996	90,000 people aged 35–64 years old in 13 rural administrative regions (panchayats)	Community-based RCT. Visual inspection by trained health workers in 7 intervention panchayats (+ health education component – advising smokers to stop)
Mehta[54]	1986	December 1982–December 1983	'High-risk individuals' (35+ years old and tobacco habits) in Ernakulum district, Kerala, India	Examination by basic health worker + health education to discontinue tobacco habits
Nagao[55,56]	2000	1996–1998	Adults aged 40+ years old in Tokoname city, Japan	Annual letter of invitation to all 40+ years old (20–39 year olds also 'encouraged to attend') for general + oral health screen
Pearson[84]	2001	?	Bangladeshi medical care users aged 40+ years in inner city London	Opportunistic examination of people in GP waiting rooms

continued

TABLE 4 *Characteristics of included studies (cont'd)*

First author	Year of publication	Time frame of study	Population/target group	Intervention
Riley[85]	1994	1985–1989	SEER data from several US registries comparing stage at diagnosis between HMO and FFS patients	Descriptive: type of patient care received HMO vs FFS
Sankaranarayanan[60]	2000	October 1995–?	People aged 35+ years old resident in 13 panachayanths in Trivandrum district, Kerala, India. 59,894 in intervention group and 54,707 in control	Community-based RCT. Visual inspection by trained health workers. Aiming for 3 examinations at 3-yearly intervals in 7 intervention panachayanths (+health education component – advising smokers to stop)
Tye[86]	1986	?	People aged 60+ years (? setting)	?
Warnakulasuriya[64,67,68]	1984, 1988, 1990	'1 year'	2 studies reported in same publication: 1. Kadugannawa. Population: Kadugannawa area of Sri Lanka (87,277 adults 20+ years old) 2. Gampola. Population: Gampola area of Sri Lanka	1. Screening by 35 PHCW house to house visits. PHCW responsible for arranging referral. Letter sent to non-attenders at referral centre. Travel costs of patients reimbursed and PHCW paid for confirmed lesions 2. Opportunistic screening by doctors and dentists in hospital setting
Warnakulasuriya[65]	1991	'1 year'	72,867 adults aged 20+ years old in Galle, Sri Lanka	Screening by PHCW + health education – 'vigorous' health education programme included as attempt to improve compliance
Wesley[69]	1992	1990–?	Adults 20+ years old in Trivandrum area of India	Two intervention groups: 1. 6 cancer detection camps + publicity 2. youth volunteers trained and asked to visit all households in their area
Westman[87]	1992	?	US Veterans Affairs general medical patients	Opportunistic screening at GP appointments by primary care clinicians
Westman[70]	1994	?	Consecutive patients attending a Veterans Affairs medical centre in Durham, North Carolina, USA	Each patient examined opportunistically by two primary care clinicians and then a dentist (gold standard)

ENT, ears, nose and throat; FFS, fee for service; HMO, health maintenance organisation; PHCW, primary healthcare worker.

III cancers and no change in the proportion of stage IV cancers.[82] Mathew and colleagues reported 5-year survival in the patients identified by the screening programme but there was no suitable comparison group.[83] Riley and colleagues compared the stage distribution of cancers according to the method of payment to the healthcare provider, but this was not a comparison between differing screening interventions.[85]

Sankaranarayanan and colleagues reported a higher proportion of stage I and II cancers in the screening intervention group than the control. They also had a lower proportion of deaths after 3 years in the intervention group.[60] Wesley and colleagues reported different proportions of 'early' versus 'late' cancers in their two intervention groups favouring the cancer detection camps over the youth volunteers.[69]

TABLE 5 *Studies reporting compliance*

First author	Year of publication	No. invited	No. screened	No. referred for follow-up	Compliance with follow-up	Proportion of target population screened per year (population programmes only)
Barra[34]	1990	671	436			
Campisi[81]	2001	180	118			
Downer[13]	1995	553	292 (+17 from another site)			
Eckert[38]	1982		6,841	1,534	1,162	
Field[41]	1995	1,949	1,947	4	4	
Fernandez Garrote[82]	1995		12,990,677	30,244	8,703	11.9–26.8%
Ikeda[32]	1991		3,131 Compliance to invitation: 76.5 and 59.7% at 2 factories, 12.2% for city residents 60+ years old			
Ikeda[28,46]	1995	5,187	802	32	25	
Jullien[14]	1995		2,027			
Jullien[14]	1995	3,826	985			
Lynch[48]	1985		349	4	3	
Mathew[83]	1995		247			
Mathew[53]	1997		90,000			
Mehta[54]	1986		39,331	523	377	
Nagao[55,56]	2000ab	47,513	19,056	200	137	
Pearson[84]	2001	185	137			
Sankaranarayanan[60]	2000	59,894	49,179	3,585	1,877	
Tye[86]	1986				Compliance with referral/ advice 26%	
Warnakulasuriya[64,67,68]	1984, 1988, 1990	1. 87,277 2. ?	29,295 21,318	1,220 133	614 66	
Warnakulasuriya[65]	1991	72,867	57,124	3,559	2,193	
Wesley[69]	1992	1. ?	1,552			
		2. ?	3,571			
Westman[70]	1994	92	86			

Discussion

The studies exhibited considerable heterogeneity in target populations, methods and choice of outcomes reported. Whereas many studies reported 'process' measures such as the numbers of participants screened and their compliance at various stages, very few studies followed patients long enough to report health outcomes. Fewer still were able to report health outcomes on a population basis as opposed to solely for the screened subgroup. Those studies that did report health outcomes appeared to indicate that oral cancers were being detected at an earlier stage and that survival was possibly improved. However, these measures are all subject to the potential influences of both 'length bias' and 'lead time bias'. The unequivocal measure of the success of an oral cancer screening programme in this respect would be to see a reduction in population mortality. None of the studies identified in this review reported that measure. However,

TABLE 6 *Studies reporting yield, stage shift, mortality or survival*

First author	Year of publication	Yield 'precancer'	Yield cancer	Stage shift/mortality/survival
Barra[34]	1990	55	10	
Campisi[81]	2001	15 leukoplakia 5 actinic chelitis 1 smoker's palate	1	
Downer[13]	1995	17		
Eckert[38]	1982	15	18	
Field[41]	1995	3	1	
Fernandez Garrote[82]	1995	2,367 leukoplakia 852 other premalignant	705	Stage shift from National Cancer Registry Stage I increased from 24% in 1983 to 49% in 1989 Stage II decreased from 26% in 1983 to 15% in 1989 Stage III decreased from 30% in 1983 to 15% in 1989 Stage IV remained at 20% incidence and mortality was unchanged
Ikeda[32]	1991	77 leukoplakia		
Ikeda[28,40]	1995		2	
Jullien[14]	1995	51	3	
Lynch[48]	1985		4	
Mathew[83]	1995	52 leukoplakia 20 oral submucous fibrosis	7 (+ 8 with recurrent cancer)	Stage I, 5 out of 6 survived to 5 years (1 patient refused treatment and died within 2 years) Stage III, 0 out of 1 survived to 5 years
Nagao[55]	2000	37	2	
Pearson[84]	2001	34 leukoplakia 1 erythroplakia 1 submucous fibrosis		
Riley[85]	1994			Stage distribution (%) for buccal cavity and pharynx: HMO / FFS *in situ* 3.2 / 2.8 local 49.0 / 40.6 regional 42.3 / 49.0 distant 5.5 / 7.7 unstaged 6.9 / 6.7
Sankaranarayanan[60]	2000	1,310	36 directly from screening but 47 in total in intervention group	Stage distribution: Intervention (n = 47) / Control (n = 16) I 22 (46.8%) / 0 (0%) II 12 (25.5%) / 2 (12.5%) III 9 (19.2%) / 4 (25.0%) IV 4 (8.5%) / 10 (62.5%) Deaths after 3 years: 7 (14.9%) / 9 (56.3%)
Warnakulasuriya[64,67,68]	1984, 1988, 1990	1. 338 2. 29	3 9	
Warnakulasuriya[65]	1991	1,716	20	
Wesley[69]	1992	1. 108 2. 378	17 39	'Early' vs 'late' cancers 1. 4 vs 13 2. 28 vs 11
Westman[87]	1992	8		

subsequent to completing the literature searches, further interim results have been published by the Trivandrum group.[88] These latest results compare population-based mortality between the intervention and control arms of the trial, but are currently unable to demonstrate any significant difference between the groups.

Reviewers' conclusions

Although many 'process' measures were reported by the studies identified in the current review, there is no evidence in favour of or against the potential health benefits associated with an oral cancer screening programme. The outcomes identified will inform many of the potential screening scenarios to be modelled by the computer simulation. However, they are not sufficient on their own to provide all the necessary data. This highlights the necessity of including information from the 'expert panel' for those areas in which there are no suitable data available in the literature.

Overall, this review confirms that there are insufficient data available to determine the effectiveness of oral cancer screening programmes at present.

Chapter 4

Determination of resource use and costs of management of oral cancer and precancer

Introduction

The mainstay of management for oral cancer is a multidisciplinary approach including surgery and radiotherapy, which for all but minor disease is followed by prolonged rehabilitation involving speech therapy, dentistry and psychosocial counselling. Since most patients first present with advanced disease, it is intuitive that the cost burden to the NHS may be significant. Data on costs of elements of treatment are available in the UK, but these are mostly generic, for example the cost of an inpatient stay or of a course of radiotherapy. There have been no studies which have accurately itemised clinical events and resource use involved in the management of patients with oral cancer or precancer. There are insufficient data to calculate actual costs, which can be used in a cost-effectiveness analysis.

Aims and objectives

The aims of this study were to identify the resources used and to determine the costs of the detection and management of oral cancer in primary and secondary care.

Specific objectives were:

1. to determine the costs of oral cancer detection in primary dental care
2. to determine the resources used (cost-generating events) in the treatment of oral cancer and precancer in secondary care:
   (a) by case note review in a large teaching hospital
   (b) by case note review in a district general hospital
3. To utilise published data and national statistics to allocate unit costs to clinical events.

Methods

Cost of oral cancer detection in primary dental care

The resources used for detection of relevant mucosal lesions involve a systematic examination of the oral cavity following a predefined protocol.[12,14] To estimate the time taken, a questionnaire was sent to 16 GDPs who had recently been involved in a pilot oral cancer screening programme in their own dental practices.[17] Questions related to the time taken for a basic NHS examination and the extra time needed to carry out and record a thorough examination of the oral soft tissues. Expert opinion was also sought from a number of experienced GDPs and hospital specialists. The actual costs were determined from published fee scales for GDPs.[89] The costs allow only for the additional time the dentist would need to examine the soft tissues and record the information. No costs were allowed for additional consumables, since it was assumed that the mucosal examination would be carried out as a part of a routine dental examination.

Cost of oral cancer management in secondary care

Ethics

Determination of resource use and clinical events involved a case note review at two large hospitals: University College London Hospitals (Maxillofacial Unit) and Barnet and Chase Farm District General Hospital. (Department of Maxillofacial Surgery). Permission from the appropriate Local Research Ethics Committees was sought and the project was approved:

- Barnet, Enfield and Haringey LREC
  LREC no. 894 (10 August 2001)
- Eastman Dental Institute and Hospital, JREC
  01/E004 (1 June 2001).

Case note review to determine resource utilisation

From pathology department records and records of minimum datasets held in the maxillofacial surgery departments, five groups of patients were identified at each centre – patients treated for oral precancer and patients treated for oral cancer in each of the four TNM stages I–IV. Twenty subjects were identified in each group, making a target of 100 case notes per centre. Cases were selected which had been first diagnosed between 1998 and 2000 in an attempt to obtain a full 3-year

management cycle. Data were recorded on a standard proforma (Appendix 6) which recorded, *inter alia*, outpatient visits, inpatient stays, pathology, radiology and imaging costs, costs of radiotherapy and chemotherapy and costs of rehabilitation and speech therapy. Resources incurred from recurrent disease were also accounted for.

Calculation of costs

Costs of each event were determined from published statistics and NHS resources. These sources are explained and listed in Chapter 6.

Results

Cost of oral cancer detection in primary dental care

Four GDPs returned completed and valid questionnaires. The mean extra time required to carry out a mucosal examination was 2.63 minutes [range 1.5–5 minutes; standard deviation (SD) 1.38]. Expert opinion suggested that this was a reasonable time and was equivalent to the extra time allowed within the General Dental Services for an 'extended examination'. The published fee scales for 2003–4 show a standard fee for an examination and report of £6.85 and a fee of £10.25 for an extended examination. The difference of £3.40 was therefore used as the cost of an extended mucosal examination.

Cost of oral cancer management in secondary care

Description of the sample

A total of 147 case notes were successfully reviewed, 95 from the teaching hospital and 52 from the district general hospital. This reflected the poor quality and inaccessibility of the records and the lack of records for precancerous lesions in the district general hospital (only one case). The final resource use and cost analysis revealed no differences between the two centres so the data are therefore pooled and described together.

The mean age was 62.6 (SD 14.7) years with the bulk of the patients (71.5%) in the 50–79 year age group (*Table 7*). The disease categorisation and stage distribution are given in *Table 8*; there were 22 precancerous lesions and 125 oral cancers. The histological diagnosis of the precancerous lesions was moderate epithelial dysplasia in 15 (68%) cases and severe dysplasia in seven (32%). The cancers were all squamous cell carcinomas arising from the epithelium of the oral mucosa. Twenty-four (19.2%), 67 (53.6%) and 23 (18.4%) were well, moderately or poorly differentiated, respectively. Tumour grade was not recorded in 11 cases.

TABLE 7 *Distribution of age for entire sample*

Decade (years)	No.	%
20–29	5	3.4
30–39	6	4.1
40–49	14	9.5
50–59	35	23.8
60–69	32	21.8
70–79	38	25.9
80–89	17	11.6
Total	147	100.0

TABLE 8 *Distribution of disease and stage for entire sample*

Disease stage	No.	%
Precancer	22	15.0
Cancer stage I	40	27.2
Cancer stage II	29	19.7
Cancer stage III	15	10.2
Cancer stage IV	41	27.9
Total	147	100.0

TABLE 9 *Duration of follow-up for all patents*

Minimum follow-up (years)	No.	%
< 1	6	4.1
1	47	32.0
2	41	27.9
3	53	36.0
Total	147	100.0

The mean follow-up time was 2.61 (SD. 1.13) years. Data for a full 3-year cycle were only available for 53 (36%) cases (*Table 9*).

Resource use

Resource use for inpatient stays and outpatient attendances are summarised in *Tables 10–14*. Most of the resources were utilised in year one, with inpatient stays of up to 30 days for late-stage disease. The number of episodes of inpatient hospitalisation also increased by stage with means (SD) of 0.4 (0.73), 1.3 (1.0), 2.7 (3.0), 2.6 (2.0) and 3.1 (2.3) for precancer, stage I, stage II, stage III and stage IV disease in the first year, respectively.

TABLE 10 *Resource use – patients with precancer*

Year after diagnosis	Inpatient length of stay, mean (SD) (days)	Outpatient attendances, mean (SD)
1	1.86 (3.51)	6.68 (4.16)
2	0.07 (0.27)	3.79 (3.24)
3	0 (0)	4.11 (2.47)

TABLE 11 *Resource use – patients with stage I cancer*

Year after diagnosis	Inpatient length of stay, mean (SD) (days)	Outpatient attendances, mean (SD)
1	9.28 (11.34)	15.17 (6.94)
2	0.45 (2.13)	4.74 (3.36)
3	0.38 (1.39)	3.38 (3.20)

TABLE 12 *Resource use – patients with stage II cancer*

Year after diagnosis	Inpatient length of stay, mean (SD) (days)	Outpatient attendances, mean (SD)
1	19.72 (23.96)	15.38 (10.36)
2	0.24 (0.77)	7.0 (5.04)
3	0.33 (0.71)	6.67 (5.39)

TABLE 13 *Resource use – patients with stage III cancer*

Year after diagnosis	Inpatient length of stay, mean (SD) (days)	Outpatient attendances, mean (SD)
1	30.69 (27.35)	19.31 (10.81)
2	1.00 (1.61)	5.82 (6.95)
3	0.33 (0.82)	7.67 (10.52)

TABLE 14 *Resource use – patients with stage IV cancer*

Year after diagnosis	Inpatient length of stay, mean (SD) (days)	Outpatient attendances, mean (SD)
1	29.90 (25.69)	18.37 (10.81)
2	4.17 (11.99)	8.00 (8.66)
3	4.63 (19.47)	5.89 (8.46)

Costs

The actual annual costs of managing patients over a 3-year period are summarised in *Tables 15–19*. The total costs over the 3-year period were precancer £1869, stage I £4914, stage II £8535, stage III £11,883 and stage IV £13,513.

Discussion

This is the first study to determine systematically the volume of resource and the costs involved in managing oral cancer and precancer. Despite the low response rate, the responses from the GDPs were only used to check the robustness of the assumption related to one specific model input. As such, the overall response rate was not a significant limitation of the study. From an NHS perspective, all relevant costs were considered. However, from a societal perspective it was not possible, in this retrospective analysis, to determine any additive patient-related expenses or impact on productivity. Other studies have costed components of treatment or have estimated costs. Hopper and colleagues,[90] for example, calculated a cost of almost £17,000 for a single

TABLE 15 *Actual cost of management (£) – patients with precancer*

Year after diagnosis	Inpatient cost, mean (SD)	Outpatient cost, mean (SD)	Total cost, mean (SD)
1	509 (958)	614 (382)	1123 (1112)
2	20 (73)	348 (298)	368 (349)
3	0 (0)	378 (227)	378 (227)

TABLE 16 *Actual cost of management (£) – patients with stage I cancer*

Year after diagnosis	Inpatient cost, mean (SD)	Outpatient cost, mean (SD)	Total cost, mean (SD)
1	2533 (3096)	1415 (663)	3948 (3281)
2	119 (569)	433 (301)	552 (554)
3	105 (379)	309 (293)	414 (624)

TABLE 17 *Actual cost of management (£) – patients with stage II cancer*

Year after diagnosis	Inpatient cost, mean (SD)	Outpatient cost, mean (SD)	Total cost, mean (SD)
1	5585 (6859)	1547 (1074)	7132 (6684)
2	65 (210)	639 (494)	701 (633)
3	91 (193)	611 (491)	702 (613)

TABLE 18 *Actual cost of management (£) – patients with stage III cancer*

Year after diagnosis	Inpatient cost, mean (SD)	Outpatient cost, mean (SD)	Total cost, mean (SD)
1	8377 (7467)	1870 (1058)	10246 (7454)
2	302 (524)	545 (668)	848 (922)
3	91 (223)	698 (961)	789 (960)

TABLE 19 *Actual cost of management (£) – patients with stage IV cancer*

Year after diagnosis	Inpatient cost, mean (SD)	Outpatient cost, mean (SD)	Total cost, mean (SD)
1	8162 (7012)	1733 (1011)	9895 (7107)
2	1138 (3273)	713 (801)	1851 (3800)
3	1264 (5316)	503 (740)	1768 (5334)

episode of palliative surgery for advanced oral cancer. Another study estimated direct medical costs of US$3000 and US$23,000 (approximately £1800 and £13,800) for treatment of stage I and II+ oral cancer, respectively,[91] but the source of the costs is not stated. Both studies were estimates and neither accounted for indirect costs or costs of follow-up. A more comprehensive study from Greece, which involved a case note review, calculated the cost of treating the primary lesion in 95 patients.[92] The costs were: stage I US$3400, stage II US$5400, stage III US$9500 and stage IV US$10,520, equivalent to about £2040, £3240, £5700 and £6312, respectively.

Chapter 5

Systematic review 3: the cost-effectiveness of screening for oral cancer

Methods

A broad range of studies was considered for inclusion in the assessment of cost-effectiveness, including economic evaluations conducted alongside trials, modelling studies and analyses of administrative databases. Only full economic evaluations that compared two or more options and considered both costs and consequences (including cost-effectiveness, cost–utility and cost–benefit analyses) were included.

The following databases were searched for relevant published literature: Cochrane Controlled Trials Register (CCTR), EMBASE, Health Economic Evaluations Databases (HEED), MEDLINE, National Research Register (NRR), NHS Economic Evaluation Database (NHS EED), PsycINFO and Science Citation Index. Full details of the main search strategy for this review are presented in Appendix 7.

Two reviewers independently assessed all obtained titles and abstracts for inclusion. Any discrepancies were resolved by discussion. Data from the included studies were extracted into tables independently by the principal reviewer. The second reviewer checked these tables and any discrepancies were resolved by discussion. The quality of the cost-effectiveness studies was assessed according to a checklist updated from that developed by Drummond and colleagues.[93] This checklist reflects the criteria for economic evaluation detailed in the methodological guidance developed by the National Institute for Health and Clinical Excellence.[94] This information is tabulated and summarised within the text of the report.

Summary of studies included in the cost-effectiveness review

The systematic literature search identified only one study that met the criteria for inclusion in the cost-effectiveness review.[91] The following sections provide a detailed overview of the cost-effectiveness evidence from this source and an assessment of the quality and relevance of the data from the perspective of the UK NHS. The quality checklist for this study is reported in Appendix 8. An overall summary of the cost-effectiveness evidence is provided in *Table 20*.

Review of van der Meij and colleagues (2002).[91] Cost-effectiveness of screening for the possible development of cancer in patients with oral lichen planus

Overview

This study by van der Meij and colleagues evaluated the cost-effectiveness of screening a population of 100,000 for oral lichen planus over a period of 1 year compared with not screening.[91] Two alternative screening strategies were considered: (1) screening by an oral specialist (defined as oral and maxillofacial surgeons) and (2) screening by a dentist. The study was based on a deterministic, decision-analytic model. The main focus of the study was screening by an oral specialist, and as such the study did not make any direct statements concerning the relative cost-effectiveness of this strategy compared with screening by a dentist. However, it is possible to determine the relative cost-effectiveness of the alternative screening strategies from the information reported in the paper.

The decision model used in the study was based on a previous model reported by Downer and colleagues.[24] Their model only considered the effectiveness of alternative screening strategies and did not conduct a formal cost-effectiveness analysis and, as such, is not reviewed here. The model by van der Meij and colleagues adapted the model of Downer and colleagues to provide estimates of cost-effectiveness relevant to The Netherlands. The model is based on a simple decision-tree framework which estimates the proportion of patients assumed to be healthy and those with cancer. Healthy patients are assumed to have a 25-year life expectancy. Patients with cancer have a reduced life expectancy depending on the stage at

TABLE 20 *Summary of the existing cost-effectiveness evidence*

Authors	Van der Meij *et al.*[91]
Year of publication	2002
Type of economic evaluation	Cost-effectiveness analysis
Setting	The Netherlands
Currency used	US$
Year to which costs apply	Not stated
Perspective used	Health service
Time frame	Lifetime
Comparators	1. No screening 2. Screening by oral specialist (oral and maxillofacial surgeons) 3. Screening by dentists The screening strategies were based on a one-off screen
Source(s) of effectiveness data	A range of sources. No details provided on how estimates were identified
Source(s) of resource use data	Not stated
Source(s) of unit cost data	Not stated
Modelling approach used	Deterministic analysis
Summary of effectiveness results	The health gain from screening by an oral specialist was estimated to be 592 QALYs (equivalent to 23.68 lives saved), compared with no screening, in a population of 100,000 The health gain for screening by dentists was not reported. An estimate from one of the figures indicates that this is between 775 and 800 QALYs, compared with no screening
Summary of cost results	The additional cost of screening by an oral specialist, compared with no screening, was estimated to be ~$1,265,229 The additional cost of screening by a dentist was not reported. An estimate from one of the figures indicates that the additional cost of screening by a dentist is likely to be in the region of $400,000–425,000, compared with no screening
Summary of cost-effectiveness results	Results are presented in terms of the cost per ELS for screening by an oral specialist compared with no screening. This is estimated to be $53,430. Estimates of the cost per additional QALY are not reported. These can be calculated to be ~$2137 per additional QALY gained based on estimates reported in the paper An estimate of the cost-effectiveness of screening by dentists is not calculated. This is likely to be in the region of $12,900–13,300 per ELS and $500–550 per additional QALY gained, compared with no screening
Sensitivity analysis	Sensitivity analysis was conducted on four variables: (1) costs of cancer treatment, (2) the malignant transformation rate, (3) sensitivity and specificity of an oral examination and (4) proportion of cancers found in stage I Sensitivity analysis was only conducted on screening by oral specialist compared with no screening
Main conclusions	Screening for oral lichen planus appears to be cost-effective

which they are identified (18.75 years for stage I and 8.325 years for stage II+). Estimates of the cost of treatment are also considered. Owing to the structure of the model, no account is taken of the differential timing of particular events (e.g. the time at which patients are identified in each strategy) and hence discounting is not applied in the study.

Summary of effectiveness data

The prevalence of oral lichen planus was set at 1% and the annual malignant transformation rate (MTR) was assumed to be 0.2%. Neither of these estimates appears to have been derived from any formal searches or appropriate synthesis of relevant data. Although the authors present a summary of 17 studies on the possible malignant

transformation of oral lichen planus, no attempt appears to have been made to combine these estimates to derive a single estimate (and associated uncertainty) to be applied in the decision model. The authors report that the figure of 0.2% per annum approached the median of the 17 studies (0.26%).

The effectiveness of the alternative screening strategies was based on the likely attendance rates (50% at an oral specialist compared with 75% at a dentist), the test performance of oral specialists (Sn = 0.91, Sp = 0.92) and dentists (Sn = 0.8, Sp = 0.8) and the proportion of patients identified in each cancer stage in the alternative scenarios. Despite the importance of these parameters in the model, there does not appear to have been any attempt to derive these estimates using systematic methods. Estimates of the Sn and Sp were derived from a single study and no details were provided to determine the reliability of these estimates. The attendance rates appear to be based entirely on assumptions made by the authors. Furthermore, the proportion of patients identified at each cancer stage was ascertained using a simple stage-shift adjustment, reflecting an assumption concerning the proportion of patients identified in stage I and stage II–IV (referred to as stage II+). The proportion of oral lichen planus patients who developed oral cancer in year 1 was assumed to be 40% (stage I) and 60% (stage II+). In the screening strategies, all patients who tested positive were assumed to be detected at the earliest stage (i.e. stage I). Screened false negatives were assumed to have either stage I cancers (40%) or stage II+ cancers (60%). The authors provided no adequate justification for these estimates.

Health gain was expressed as QALYs and equivalent lives saved (ELSs). The health state utilities for oral cancer used to derive the QALY estimates were based on those reported by Downer and colleagues[23] of 0.88 for stage I and 0.68 for stage II+. The overall QALYs in the non-screened population were estimated to be 2,292,809. Total QALYs for the population screened by an oral specialist were 2,293,401. The health gain from screening by an oral specialist was thus reported to be 592 QALYs compared with not screening. The authors derived an estimate of the ELS by assuming a 25-year life expectancy (based on a healthy 55-year-old in The Netherlands), namely 592/25 = 23.68 lives saved. The equivalent health gain for screening by a dentist is provided only in graphical form. This appears to be within the range 775–800 QALYs compared with not screening. Using the same assumption of life expectancy as applied by the authors, screening by a dentist results in a gain of between 31 and 32 ELS.

Summary of resource utilisation and cost data

The costs included in the model comprised the cost of screening, biopsy costs and the cost of oral cancer treatment (stage I and stage II+). The costs of treatment (all costs in US$) of stage I and stage II+ were reported to be $3000 and $23,000 per case, respectively. These costs were stated as representing the direct medical costs of treatment. However, no information was provided on how these costs were derived, hence it is not possible to determine whether these are appropriate costs or not. No details were provided on the potential resource utilisation that comprised these cost estimates, so the relevance of these estimates to the UK NHS is unclear.

The total costs incurred in the 'no screening' strategy was estimated to be $3,000,000. The total costs of screening by an oral specialist were reported to be $4,265,229. Hence the extra costs of screening by an oral specialist compared with not screening were estimated to be $1,2665,229. The estimates of the additional costs of screening by a dentist were not reported in the paper. Estimates from one of the figures indicates that the extra costs of screening by a dentist, compared with not screening, is likely to be in the region of $400,000–425,000.

Summary of cost-effectiveness analysis

The cost-effectiveness of screening by an oral specialist was summarised by presenting the incremental cost per ELS (i.e. the ratio of the additional costs to the additional health gain for screening compared with not screening). The cost per ELS was estimated to be $53,430 (i.e. $1,265,229/23.68). This cost per ELS is based on an average life expectancy of 25 years. To facilitate a broader range of comparisons, it is also important to consider the cost per additional QALY. Although this estimate is not reported in the paper, it can be estimated to be ~$2,137 per QALY (i.e. $1,265,229/592).

A summary of the incremental cost per ELS/QALY was not presented for screening by a dentist. Since screening by a dentist is a relevant comparator to screening by an oral specialist (and also not screening), this strategy should be considered when determining the relative cost-effectiveness of screening for oral lichen planus. Owing to the limited data reported by the authors in relation to the costs and health gain of

screening by a general dentist, an accurate assessment is not possible. However, since screening by a dentist was both less expensive and had a higher health gain compared with screening by an oral specialist, it is possible to conclude that screening by a dentist would dominate a policy of screening by an oral specialist. In this instance, the incremental cost per ELS/QALY reported by the authors should actually be based on a comparison of screening by a dentist compared to not screening. This is likely to be in the region of $12,900–13,300 per ELS and $500–550 per additional QALY gained compared with not screening.

Conclusions

This study is the only published study found in the review process that could be considered a full economic evaluation. The results indicate that screening for oral lichen planus appears to be cost-effective. Indeed, the results presented by the authors fall well within the range considered as representing value for money in the NHS (see Chapter 6 for more details). Although a direct comparison of the alternative screening strategies is not formally undertaken in the paper, the results suggest that screening by a dentist is likely to dominate screening by an oral specialist (i.e. screening by an oral specialist is not cost-effective compared with screening by a dentist). Despite the authors' conclusions, the reliability of these results is difficult to assess. The study appears to be of limited quality and lacks transparency concerning the derivation of several key parameters.

From a UK NHS perspective, the study has a number of important limitations. First, this study has not directly compared the full range of possible strategies that would appear to be relevant to the NHS (including screening by other practitioners, e.g. GPs). Second, the estimates applied in the model do not appear to have been derived using any systematic methods. Estimates for a number of key parameters in the model appear to be based on assumptions made by the authors. In addition, the generalisability of the costs applied in the model to the UK NHS is not clear. No details on the derivation of the treatment costs for oral cancer are provided, hence it is not possible to determine whether these were appropriate or not. Finally, no account is made for the timing of various events in the model. The impact of discounting applied to the estimates of costs and health gain is potentially important and should be formally considered.

Owing to these limitations, it is not possible to make any reliable comparison of the relative cost-effectiveness of alternative screening strategies from this evidence.

The cost-effectiveness of alternative screening strategies for oral cancer has, therefore, not been adequately addressed in existing studies. The next chapter details the results of a new decision-analytic model that has been developed to address this issue more formally.

Chapter 6

Cost-effectiveness model

Introduction

In health technology assessment, there is an increasing role for decision analysis in synthesising data, identifying optimal treatment decisions under conditions of uncertainty and prioritising additional research.[95] The use of Bayesian decision theory to establish expected utilities for alternative treatment strategies has been accepted as a rational basis for decision-making for some time.[96,97] More recently, a Bayesian decision theoretic framework for the economic evaluation of healthcare programmes has been presented.[98–100] This framework suggests that the economic choice between mutually exclusive healthcare programmes should be distinguished from the conceptually separate question of whether more information should be acquired to inform this decision in the future.

Within this framework, the choice between programmes should be based on expected utility, and the only valid reason to consider the uncertainties surrounding the outcome of interest is to establish the value of acquiring additional information by conducting further research. Bayesian decision theory and value-of-information analysis provide an explicit and rigorous framework within which both the decision problems posed in health technology assessment can be addressed. These methods have a firm foundation in statistical decision theory[101,102] and have been successfully used in other areas of research, such as engineering and environmental risk analysis.[103] More recently these methods have been extended to priority setting in the evaluation of healthcare technologies.[98,99] In addition, they have been applied to a number of different health technologies, including a series of case studies for the NHS Health Technology Assessment Programme.[104]

The application of these methods requires two main tasks to be completed:

1. construction of a probabilistic decision-analytic model to represent the decision problem and to characterise the current decision uncertainty
2. establishing the value of additional information to inform this decision in the future.

The following section outlines the process and approach used to complete the first task, describing the structure of the model in detail and providing an overview of the key assumptions and data sources used to populate the model, and the methods used to conduct the probabilistic analysis. The final task related to establishing the value of additional information is covered in Chapter 7.

Methods

The objective was to compare the cost-effectiveness of no screening with a range of alternative screening strategies for oral cancer, based on a one-off prevalence screen, including invitational and opportunistic programmes undertaken in both primary medical and dental locations. An NHS perspective was adopted and costs were expressed in UK£ at a 2002–3 price base and health outcomes in terms of QALYs. Annual discount rates of 3.5% for costs and 3.5% for benefits were applied based on current UK guidance.[94]

For the main analysis, a lifetime time horizon was used, that is, the model considers the costs and outcomes of a hypothetical cohort over a period of 60 years. The model is made up of three parts: (1) a prognostic model to represent the disease progression and survival of those patients whose disease remains undetected; (2) a separate prognostic model for those patients whose disease is detected (either via the formal screening programme or as part of routine case finding); and (3) a screening model reflecting the diagnostic performance of the alternative screening strategies included.

The model is probabilistic in that input parameters are entered into the model as probability distributions to reflect second-order uncertainty, that is, uncertainty in mean costs and outcomes and in probabilities and utilities.[105] Monte Carlo simulation was used to propagate uncertainty in input parameters through the model in such a way that the results of the analysis could also be presented with their uncertainty. A brief overview of the probabilistic approach is provided below.

Overview of probabilistic sensitivity analysis (PSA)

Uncertainty is intrinsic to decisions concerning the cost-effectiveness of health technologies. This uncertainty will be associated with the data inputs, such as estimates of resource use, the probability of particular clinical events and the extent to which the analysis can be generalised to routine clinical practice. PSA requires distributions for the input parameters in the model to be specified. The distribution represents the uncertainty in the estimation of each parameter (e.g. a more diffuse distribution reflects a higher level of uncertainty). Consequently, the quality and quantity of information available can be reflected in the probability distributions assigned to each input parameter in the model.[95] The objective of PSA is to calculate the combined impact of the model's various uncertainties in order to determine a probability distribution for the possible model outcomes.

The parameters used in a decision model represent summary values related to the average experience across a population of potential patients. Therefore, the relevant uncertainty to be reflected in the parameter distribution is uncertainty related to the sampling distribution of the parameter, as opposed to the variability (or heterogeneity between individual subjects) in the values observed in a particular population.[106] Computer simulation can then be used to propagate these distributions through the model so that the cost-effectiveness estimates indicate the uncertainty surrounding the implementation/adoption decision rather than uncertainty surrounding a single input. The impact of patient heterogeneity (e.g. different age/sex characteristics) on this decision is explored in separate analyses. This approach ensures that uncertainty in the decision due to the imprecision in parameter inputs can be separated from uncertainty in whether an intervention is cost-effective for particular subgroups of the population. For this analysis, significant differences were identified in several key parameters between males and females and across specific age groups. Separate analyses were therefore conducted for both the general population (combining results for males and females) and for specific age and sex groupings.

Treatment strategies under comparison

A number of possible strategies were identified as being relevant to NHS practice, including invitational (population-based) screening programmes, opportunistic screening (case-finding), targeted 'high-risk group' screening, workplace programmes and mobile screening programmes. Following the review of available evidence identified as part of the systematic review and in consultation with clinical advisors, the following strategies were included in the model.

A. *No screening* – this is intended to reflect current practice, where lesions may be identified in routine care either via self-referral or through case finding during routine check-ups.

B. *Invitational screening (general medical practice)* – all patients registered with a GP are invited for a visual screen. Patients who comply with the invitation receive a visual examination by the GP and any suspicious lesions are referred to secondary care for a biopsy.

C. *Invitational screening (general dental practice)* – all patients registered with a GDP are invited for a visual screen. Patients who comply with the invitation receive a visual examination by the GDP and any suspicious lesions are referred to secondary care for a biopsy.

D. *Opportunistic screening (general medical practice)* – all patients who attend their GP during the first year receive a visual examination by the GP and any suspicious lesions are referred to secondary care for a biopsy.

E. *Opportunistic screening (general dental practice)* – all patients who attend their GDP during the first year receive a visual examination by the GDP and any suspicious lesions are referred to secondary care for a biopsy.

F. *Opportunistic 'high-risk' screening (general medical practice)* – all patients who attend their GP and are identified as being at high risk during the first year receive a visual examination by the GP and any suspicious lesions are referred to secondary care for a biopsy.

G. *Opportunistic 'high-risk' screening (general dental practice)* – all patients who attend their GDP and are identified as being at high-risk during the first year receive a visual examination by the GDP and any suspicious lesions are referred to secondary care for a biopsy.

H. *Invitational screening (secondary care)* – the entire population is invited for a visual screen. People who comply with the invitation receive a visual examination by a secondary care specialist and any suspicious lesions receive a biopsy.

Strategies F and G are based on an approach in which high-risk patients are identified with the aid of artificial intelligence. Owing to the relatively

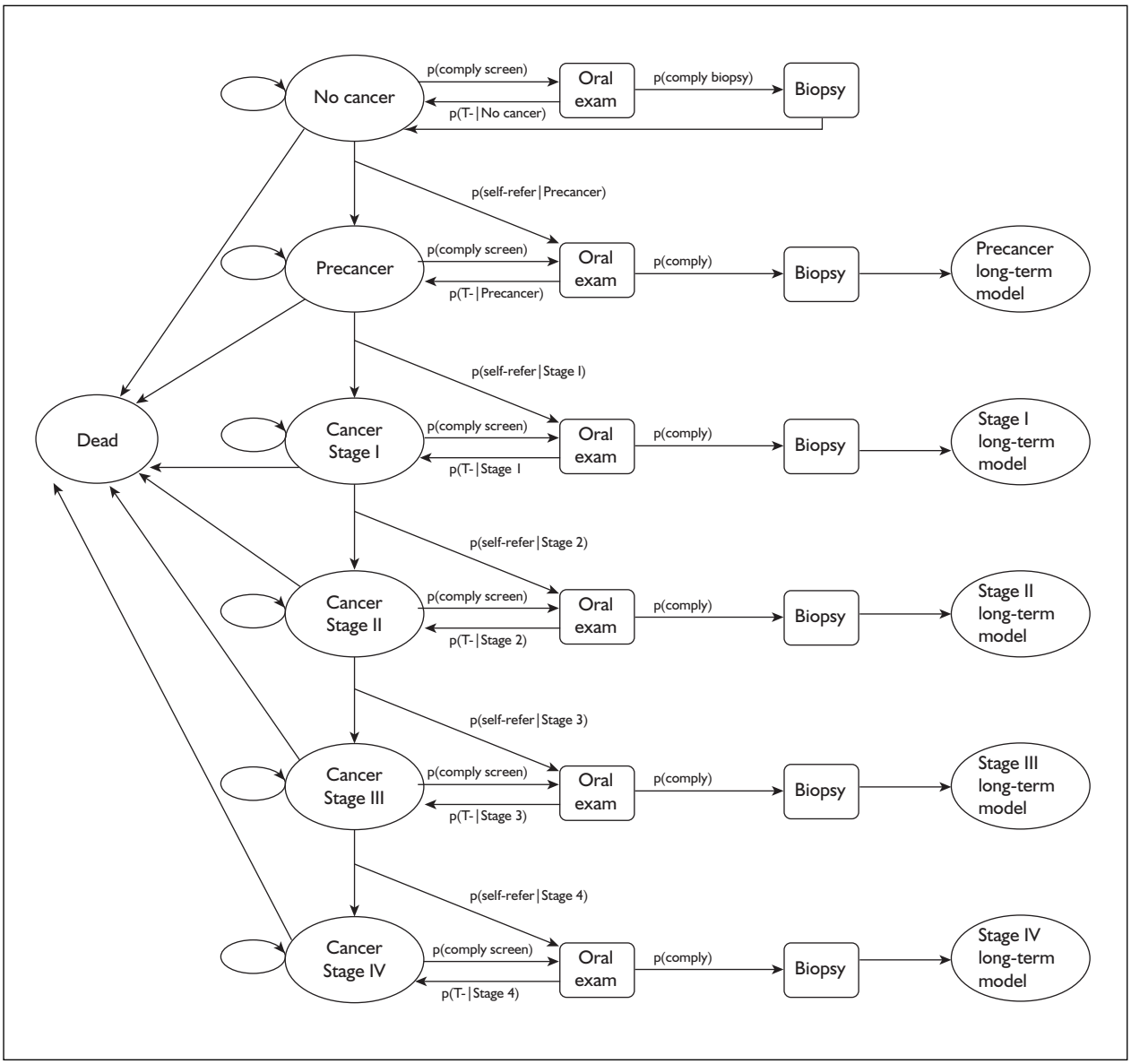

FIGURE 5 *Model structure*

low prevalence of oral cancer and precancer, and their association with known risk factors, it is possible to identify and target high-risk individuals for screening from *a priori* criteria. Speight and colleagues utilised a neural network to preselect patients at particularly high risk of the disease based on known risk factors based on demographic and lifestyle characteristics (e.g. age, gender, smoking and alcohol).[16] These strategies could be thought of as two-step screening strategies: the first test applied is the neural network, patients who are identified as being at high risk are then screened using a visual examination. Strategies F and G are restricted to screening dental and general medical patients known to be at high risk of oral cancer utilising the proposed neural network.

Description of the model

The structure of the decision model is illustrated in *Figures 5* and *6*. A Markov process is used to model the initial prevalence of undiagnosed (asymptomatic) oral precancer and cancer in the general population and the disease progression in people who remain undetected (and hence receive no intervention).[107] The various health states are represented using circles and possible transitions between the health states are represented with arrows. People with undetected precancer face an annual risk of mortality (based on the standard mortality rate estimated from life-tables) together with an annual risk of malignant transformation to cancer. People with undiagnosed cancer are assumed to have an elevated risk of mortality compared with the standard mortality rate and

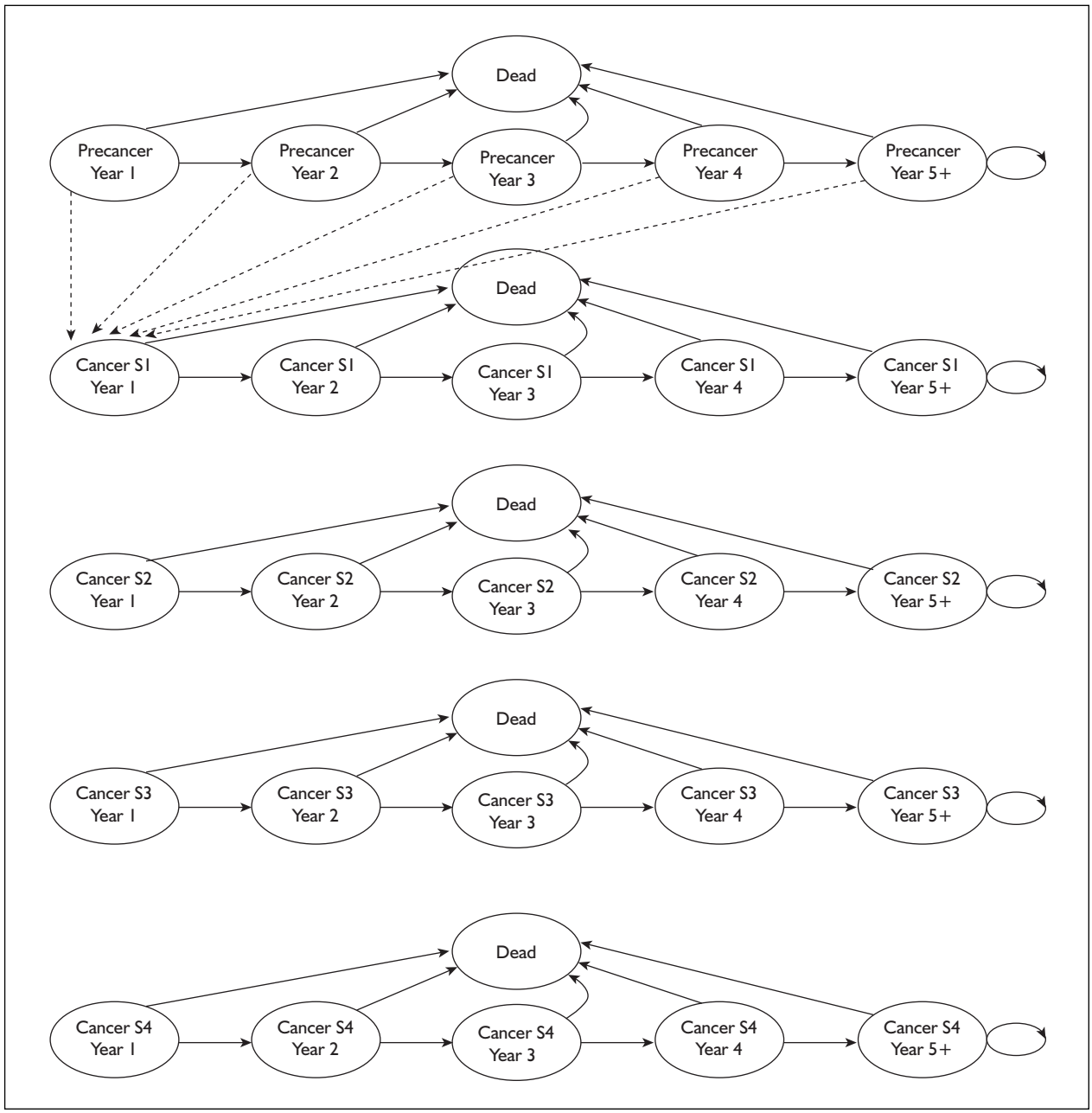

FIGURE 6 *Long-term model structure (diagnosed patients only)*

have an additional risk of progressing to a more advanced stage of cancer during each (annual) cycle of the model. The annual risk of mortality is assumed to increase with the stage of cancer. For the purposes of the model, all people developing cancer are assumed to have had a previous precancerous lesion (although this may not have been clinically detectable).

In the model, patients may be diagnosed with precancer and cancer either via self-referral/routine case finding or, for the screening strategies, as part of the formal screening programme. Those patients with positive screen results to the visual examination will be referred for a confirmatory test by biopsy in secondary care. Subsequent to receiving a positive test result to the visual screen (comprising both true positives and false positives), patients may or may not comply with the biopsy in secondary care. Patients who do not comply with the biopsy are assumed to re-enter the prognostic model for undetected patients. Patients who comply with the biopsy and receive a confirmatory test result from the biopsy enter the long-term prognostic model for diagnosed patients.

In addition to being detected via the screening programme itself, patients may also be detected within routine practice. The model assumes that a proportion of patients will be detected either via self-referral (either to a primary or secondary care setting) owing to becoming symptomatic or as part of routine clinical practice. Patients who are diagnosed with precancer or cancer (either via self-referral or via the screening programme) enter a separate long-term prognosis model and experience an expected survival duration and costs derived from separate UK observational data sources. Expected survival duration, quality of life (QoL) and associated costs of treatment for oral cancer are assumed to depend on the stage at diagnosis. Patients identified at an earlier stage of cancer are assumed to experience a better QoL and lower treatment costs than patients identified at a later stage.

The long-term model outlined in *Figure 6* is based on a separate Markov process using a series of tunnel states for patients based on the stage at diagnosis. The tunnel states are used to represent a sequence of health states representing the number of years post-diagnosis (according to presenting stage at diagnosis). The use of tunnel states allows the application of separate transition probabilities (e.g. mortality rates) and treatment costs to each year post-diagnosis. Patients detected with a precancerous lesion are assumed to follow the same annual mortality risk (based on the standard mortality rate derived from life-tables) as patients with undiagnosed precancerous lesions. The impact of diagnosis and subsequent treatment on the annual malignant transformation rate in diagnosed patients is modelled using a series of alternative assumptions. The assumptions reflect possible treatment effects on reducing the annual MTR (from a 0 to a 20% reduction). Patients diagnosed with precancer are assumed to be monitored regularly during the course of follow-up, such that if patients progress to cancer it is assumed that this is detected at the earliest stage (i.e. stage I).

The following sections provide detailed information related to the specific data inputs and assumptions applied in the model. Parameter estimates applied in the model are based on a series of systematic reviews, other published sources, observational data sets and expert opinion from a clinical advisory group. The first section provides details on the approach used to model the initial prevalence of undiagnosed oral precancer and oral cancer in the general population according to specific age and sex characteristics. The next section covers the natural history of precancer and oral cancer, including the approach used to derive mortality estimates and clinical upstaging based on the annual malignant transformation rate and stage-shift to more advanced stages of cancer. The final section comprises a description of the screening model and the relevant parameter inputs related to test performance of the alternative screeners and the compliance/attendance rates for the invitational and opportunistic approaches.

Prevalence of undiagnosed oral precancer and cancer

Prevalence data of undiagnosed precancer and oral cancer were obtained from a sample of 2201 patients included in a recent demonstration study of opportunistic cancer screening in a dental primary care environment.[17] Patients over the age of 35 years were prospectively recruited from 18 general dental practices. A positive diagnosis was defined as the presence of a white or a red patch or an ulcer of >2 weeks' duration. For the purposes of this study, lichen planus was defined as a negative lesion. In total, 72 patients (excluding lichen planus) were reported to have either malignant or potentially malignant lesions, giving an overall positive lesion prevalence of 3.3%. Of the 72 positive lesions identified, two were previously undetected squamous cell carcinomas.

Patient-level analysis, using logistic regression, was used to estimate age and sex-specific prevalence rates for positive lesions reported in *Table 21*. Dummy variables were used to adjust for the following characteristics of the sample: sex and age (based on 10-year age groupings). The coefficients from the logistic regression were used to calculate the probability of an asymptomatic positive lesion in each particular subgroup. The coefficients were combined using the predict command in STATA to ensure that any correlation between the separate coefficients for each covariate was reflected in the resulting parameter distributions.[108] The uncertainty in the resulting prediction (representing the log-odds) from the regression were characterised using a normal distribution. The log-odds were then converted into probabilities to provide the input parameters for the prevalence data. In summary, the log-odds were significantly higher in males than females, and the prevalence was lowest in the group aged 40–49 years.

The results from the logistic regression were then used to calculate the proportion of the general

TABLE 21 *Age and sex-specific prevalence rates from logistic regression*

Age (years)	Probability	Log-odds		Distribution
		Mean	SE	
Males				
40–49	0.0418	–3.1318	0.2579	Normal
50–59	0.0564	–2.8168	0.2338	Normal
60–69	0.0580	–2.7877	0.2607	Normal
70–79	0.0457	–3.0395	0.3698	Normal
80+	0.0647	–2.6705	0.5203	Normal
Females				
40–49	0.0158	–4.1321	0.3112	Normal
50–59	0.0215	–3.8170	0.2829	Normal
60–69	0.0221	–3.7880	0.3100	Normal
70–79	0.0173	–4.0398	0.4031	Normal
80+	0.0248	–3.6708	0.5448	Normal

TABLE 22 *Mean estimates of the age and sex-specific probabilities of initial health states*

Age (years)	No cancer	Precancer	Cancer stage I	Cancer stage II	Cancer stage III	Cancer stage IV
Males						
40–49	0.9582	0.0407	0.0003	0.0003	0.0003	0.0003
50–59	0.9436	0.0549	0.0004	0.0004	0.0004	0.0004
60–69	0.9420	0.0564	0.0004	0.0004	0.0004	0.0004
70–79	0.9543	0.0444	0.0003	0.0003	0.0003	0.0003
80+	0.9353	0.0629	0.0004	0.0004	0.0004	0.0004
Females						
40–49	0.9842	0.0154	0.0001	0.0001	0.0001	0.0001
50–59	0.9785	0.0209	0.0001	0.0001	0.0001	0.0001
60–69	0.9779	0.0215	0.0002	0.0002	0.0002	0.0002
70–79	0.9827	0.0168	0.0001	0.0001	0.0001	0.0001
80+	0.9752	0.0241	0.0002	0.0002	0.0002	0.0002

population starting the model in each of the six initial health states of the model (i.e. no cancer, precancer and cancer stages I–IV). The age and sex-specific prevalence rates from the logistic regression provided the proportion of people with no lesion and those with an asymptomatic positive lesion. For patients with a positive lesion, the initial distribution of patients within each of the five positive lesion health states (precancer and cancer stages I–IV) was modelled using the Dirichlet distribution.[109] The Dirichlet distribution is the multidimensional generalisation of the beta distribution and can be used to represent polychotomous (i.e. more than two events) transition probabilities to ensure that the sum of probabilities across multiple events equals 1. Of the 72 positive lesions identified in the demonstration screening study, two were classified as squamous cell carcinomas. Owing to the small number of carcinomas reported in the demonstration study, no attempt was made to provide separate prevalence rates for cancerous lesions by age and sex. Consequently, the probabilities of a positive lesion (including precancer and cancer) were adjusted using a Dirichlet (70,0.5,0.5,0.5,0.5) distribution to reflect the distributions of lesions in each stage. Mean estimates of the probabilities of entering the model in each specific health state are reported in *Table 22*.

Survival data – diagnosed patients

The survival data used to populate the decision model was obtained from the Thames Cancer Registry (TCR). The TCR is the largest cancer registry in Western Europe, covering the London region, south-east region and part of the eastern region of England. Twenty-six Health Authorities

TABLE 23 *Summary of patients included from the TCR*

Stage at diagnosis	Number (%)[a]	Male (%)	Female (%)	Age (years)	
				Mean	SD
Stage I	2712 (45)	59	41	66.13	13.55
Stage II	1445 (24)	65	35	66.04	12.42
Stage III	1506 (25)	65	35	63.56	12.86
Stage IV	430 (7)	65	35	65.62	13.62

[a] The sum of percentages exceeds 100% owing to rounding.

in the south-east of England, with a total population of 13.8 million, are part of the TCR. Its activities (along with the other cancer registries in England and Wales) are outlined in the national core contract issued in 1996.[110] The TCR data are recorded at the level of the individual tumour. For every tumour detected, full personal details are supplied. In most cases there is only one tumour per person. However, a single person may generate more than one record in the TCR database if they develop more than one tumour. Data were obtained from TCR for all people diagnosed with oral cancer between 1980 and 1995. This was the most recent time frame for which 'complete' registration data were available.

Patients were only included if they had complete details related to the following characteristics: age, sex and cancer stage at diagnosis. In total, 6093 patients were included in the analysis. The average age of the sample was 65.43 years and 62% of the sample was male (*Table 23*).

Transition probabilities were calculated from the TCR data using survival analysis techniques.[111] These methods allow for both censoring and differential follow-up of patients in the TCR. From the data, for each transition, an annual hazard (representing the instantaneous hazard of death) and the variance of the hazard were calculated by assuming a parametric survival distribution. Alternative parametric models based on exponential (constant hazard) and Weibull distributions (non-constant hazard) were undertaken to determine the appropriate distribution. The uncertainty associated with each transition was characterised by applying a normal distribution to the log-hazard rate. Following this procedure, the hazard rates were then converted into annual transition probabilities (plus variance) using standard techniques.[112] Further details on the approach are described below.

Transitions to death were initially modelled using a Weibull distribution to test formally the constant hazard assumption. Dummy variables were used to adjust for the following characteristics of the sample: sex, age (based on 10-year age groupings) and stage at diagnosis (stages I–IV). The Weibull distribution has the following probability density function:

$$f(t) = \lambda\gamma t^{\gamma-1} \exp(-\lambda t^{\gamma}) \quad (1)$$

that is characterised by two parameters, λ and γ. The hazard function is

$$h(t) = \lambda\gamma t^{\gamma-1} \quad (2)$$

When $\gamma = 1$, the Weibull expressions above reduce to those of the exponential distribution (i.e. the hazard is constant with respect to time).

Results from the Weibull regression are reported in Appendix 9. These results are based on the logarithms of relative hazard form such that the coefficients are the logs of the estimated parameters. The term $\ln\lambda$ is estimated by the linear function of the covariates and p is equivalent to γ in the above expression. Therefore, the t-test on $\ln p$ is the test for the exponential distribution. The results indicate that the exponential model is rejected at $p < 0.001$ and hence that the assumption of a constant hazard is not supported.

Age group, sex and cancer stage were significant in predicting survival in patients diagnosed with oral cancer. Estimates of $\ln\lambda$ were obtained using the predict command in STATA, ensuring that the correlation between the separate coefficients for each covariate was reflected in the resulting parameter distributions. *Table 24* presents the separate standard estimate of the mean (SE) of the separate standard estimates of $\ln\lambda$ for each combination of age/sex/stage reflected in the

TABLE 24 *Log hazard rates – results from the Weibull regression analysis*

	Mean (SE)				
Age (years)	**Stage I**	**Stage II**	**Stage III**	**Stage IV**	**Distribution**
Males					
40–49	–1.96 (0.06)	–1.42 (0.06)	–1.26 (0.06)	–0.93 (0.08)	Normal
50–59	–1.76 (0.05)	–1.22 (0.05)	–1.06 (0.05)	–0.73 (0.06)	Normal
60–69	–1.62 (0.04)	–1.08 (0.04)	–0.92 (0.04)	–0.59 (0.06)	Normal
70–79	–1.25 (0.04)	–0.71 (0.04)	–0.55 (0.04)	–0.22 (0.06)	Normal
80+	–0.84 (0.04)	–0.30 (0.05)	–0.14 (0.05)	0.19 (0.06)	Normal
Females					
40–49	–2.15 (0.07)	–1.61 (0.07)	–1.45 (0.07)	–1.12 (0.08)	Normal
50–59	–1.95 (0.05)	–1.41 (0.05)	–1.24 (0.05)	–0.92 (0.07)	Normal
60–69	–1.81 (0.04)	–1.27 (0.05)	–1.11 (0.05)	–0.78 (0.06)	Normal
70–79	–1.44 (0.04)	–0.90 (0.04)	–0.74 (0.04)	–0.41 (0.06)	Normal
80+	–1.03 (0.04)	–0.49 (0.05)	–0.33 (0.05)	0.00 (0.07)	Normal

model. Mortality rates were significantly higher in males than females, and rose markedly by age and the stage at which the cancer was detected.

Since hazards are instantaneous, they need to be converted to a transition probability for a given period, and as such require use of the integrated hazard function, which in the case of the Weibull distribution is

$$H(t) = \int_0^t h(u)\mathrm{d}u = \lambda u^{\gamma} \qquad (3)$$

Using this equation, the transition probabilities were estimated for each of the 5-year post-diagnosis states represented in the long-term model. The conditional probabilities of death in the first 5 years, based on the mean value from the estimated distribution, are reported in *Tables 25* and *26*. As with the estimate of the hazard, the conditional probabilities of death varied markedly by age, sex and stage at diagnosis. For males aged 40–49 years, the mean probability of death in the first year rises from 0.14 in stage I to 0.4 in stage IV. For females, the probabilities in each age group are lower across all stages; for females aged 40–49 years, the probability of death in the first year is about 0.12 in stage I compared with 0.33 in stage IV. Across all ages and stages, the risk of mortality is highest in the first year and declines rapidly thereafter. By years 4 and 5 post-diagnosis, the mortality rates in each stage are becoming close. After 5 years, patients are assumed to remain in the same state represented by the fifth year of the tunnel states and consequently face the same annual probability of death until they reach the next age band, at which point they assume the fifth-year risk of patients in this higher age band.

Survival data – undetected cancer

All data from the TCR reflect the survival data in diagnosed patients. Owing to the lack of relevant data on the prognosis of people who remained undetected, the survival data from the TCR was used as a proxy. The analysis assumed that people who remained undetected for each cancer stage would follow a similar prognosis to patients detected; however, in the absence of treatment it was assumed that they would face an additional risk of progressing to a more advanced cancer stage with a worse prognosis than patients detected at the previous stage. The probability of this additional risk is given in *Tables 24* and *25* and is further explained in the next section. Owing to the nature of the Markov process used to model the prognosis of patients who remained undetected, it was necessary to assume a constant hazard for the transitions to death for each stage, reflecting an average mortality rate from the 5-year survival data. Results from the exponential regression are provided in Appendix 9. *Table 27* presents the separate estimate of the mean probabilities of death for each combination of age/sex/stage reflected in the model. For the probabilistic analysis, the mean (SE) of the separate estimates of $\ln\lambda$ were modelled as a normal distribution and then converted to probabilities using the appropriate equation.

Modelling the malignant transformation rate and cancer stage-shift

Parameter estimates for the annual malignant transformation rate from precancer to cancer were derived from a recent systematic review and meta-analysis of oral leukoplakia studies. Petti calculated a weighted average of the annual transformation

TABLE 25 *Mean probability of death in males with diagnosed cancer: results from the exponential regression analysis*

Stage	Age	Year 1	Year 2	Year 3	Year 4	Year 5
I	40–49	0.1410	0.0861	0.0731	0.0657	0.0607
	50–59	0.1724	0.1053	0.0893	0.0803	0.0742
	60–69	0.1978	0.1208	0.1025	0.0921	0.0851
	70–79	0.2861	0.1748	0.1482	0.1333	0.1231
	80+	0.4316	0.2636	0.2236	0.2010	0.1858
II	40–49	0.2416	0.1476	0.1252	0.1126	0.1040
	50–59	0.2954	0.1805	0.1531	0.1376	0.1272
	60–69	0.3390	0.2071	0.1756	0.1579	0.1459
	70–79	0.4903	0.2995	0.2540	0.2284	0.2110
	80+	0.7396	0.4518	0.3832	0.3445	0.3183
III	40–49	0.2848	0.1740	0.1476	0.1327	0.1226
	50–59	0.3482	0.2127	0.1804	0.1622	0.1499
	60–69	0.3996	0.2441	0.2070	0.1861	0.1720
	70–79	0.5779	0.3530	0.2994	0.2692	0.2487
	80+	0.8717	0.5325	0.4516	0.4061	0.3752
IV	40–49	0.3953	0.2414	0.2048	0.1841	0.1701
	50–59	0.4833	0.2952	0.2504	0.2251	0.2080
	60–69	0.5546	0.3387	0.2873	0.2583	0.2387
	70–79	0.8021	0.4899	0.4156	0.3736	0.3452
	80+	1.0000	0.7390	0.6268	0.5636	0.5207

TABLE 26 *Mean probability of death in females with diagnosed cancer: results from the exponential regression analysis*

Stage	Age	Year 1	Year 2	Year 3	Year 4	Year 5
I	40–49	0.1167	0.0713	0.0604	0.0543	0.0502
	50–59	0.1426	0.0871	0.0739	0.0664	0.0614
	60–69	0.1637	0.1000	0.0848	0.0762	0.0704
	70–79	0.2367	0.1446	0.1226	0.1103	0.1019
	80+	0.3570	0.2181	0.1850	0.1663	0.1537
II	40–49	0.1999	0.1221	0.1036	0.0931	0.0860
	50–59	0.2444	0.1493	0.1266	0.1139	0.1052
	60–69	0.2805	0.1713	0.1453	0.1306	0.1207
	70–79	0.4056	0.2478	0.2102	0.1890	0.1746
	80+	0.6119	0.3738	0.3170	0.2850	0.2634
III	40–49	0.2356	0.1439	0.1221	0.1098	0.1014
	50–59	0.2881	0.1760	0.1493	0.1342	0.1240
	60–69	0.3306	0.2019	0.1713	0.1540	0.1423
	70–79	0.4781	0.2920	0.2477	0.2227	0.2058
	80+	0.7212	0.4405	0.3737	0.3359	0.3104
IV	40–49	0.3270	0.1998	0.1694	0.1523	0.1408
	50–59	0.3998	0.2442	0.2072	0.1862	0.1721
	60–69	0.4588	0.2802	0.2377	0.2137	0.1975
	70–79	0.6636	0.4053	0.3438	0.3091	0.2856
	80+	1.0000	0.6114	0.5186	0.4662	0.4308

rate of oral leukoplakia from studies conducted during the previous 20 years using the inverse variance weighting method.[113] The pooled estimate was reported to be 1.36% (95% CI: 0.69 to 2.03%). Uncertainty in the mean annual transformation rate was modelled using the beta distribution for the purposes of the probabilistic analysis. The beta distribution is a continuous distribution bounded by the limits of the interval 0–1 (in this model adapted to the interval 0–100%). Uncertainty in the beta distribution is characterised by two parameters ~ beta (α,β). The parameters of the beta distribution were solved using analytic methods (method-of-moments)

TABLE 27 *Mean annual probability of death in people with undetected cancer: results from the exponential regression analysis*

Age (years)	Stage I	Stage II	Stage III	Stage IV
Males				
40–49	0.1103	0.2101	0.2581	0.3780
50–59	0.1282	0.2442	0.3000	0.4394
60–69	0.1421	0.2707	0.3327	0.4872
70–79	0.1955	0.3724	0.4575	0.6701
80+	0.3013	0.5739	0.7051	0.9999
Females				
40–49	0.0932	0.1775	0.2181	0.3195
50–59	0.1083	0.2064	0.2535	0.3713
60–69	0.1201	0.2288	0.2812	0.4118
70–79	0.1652	0.3147	0.3867	0.5664
80+	0.2546	0.4850	0.5960	0.8729

TABLE 28 *Clinical upstaging in the absence of diagnosis/treatment (annual probabilities) – summary of clinical advisors' responses and parameter estimates applied in the model*

			Distribution and parameters		
Transition	**Mean**	**SD**	**Alpha**	**Beta**	**Distribution**
Stage I to II	0.53	0.27	1.34	1.17	Beta
Stage II to III	0.59	0.25	1.67	1.14	Beta
Stage III to IV	0.67	0.25	1.67	0.83	Beta

from the pooled estimate reported by Petti.[113] Method-of-moments fitting involves equating the means and variances observed in the data to the expressions for the mean and variance of the beta distribution.[105] The parameters of the beta distribution (α,β) can then be solved analytically. Applying this process, the uncertainty in the annual malignant transformation rate was characterised by a beta (1,73) distribution.

The systematic literature reviews did not provide any relevant data for the parameter estimates for clinical upstaging in oral cancer relevant to the UK. In the absence of appropriate estimates in the literature, parameter estimates were obtained from expert clinical opinion empirically derived using the Trial Roulette approach.[114] This approach has been widely used in healthcare and in particular has been applied in the field of cancer studies.[115] The method is appropriate when expert opinion is the best available source of information and when the focus of the study is concerned with quantifying the uncertainty in parameter estimates as opposed to trying to obtain a single value through consensus.

The expert group consisted of nine clinical experts experienced in the management of oral cancer (Appendix 10). The clinical experts were provided with a questionnaire to complete in order to quantify their beliefs in a series of parameters. The form completed by the experts is provided in Appendix 11. The diagrams provided on the questionnaire represent betting streets, similar to those used on a gaming table. Each column represents a range of potential values for a particular parameter. The expert clinical advisors were instructed that they had 20 gaming tokens (X) to place in some or all of the columns to represent their current belief and uncertainty in the parameters being discussed. Following a brief discussion of the question, the clinical advisors were asked to start by placing two of the counters at the upper and lower limits of their belief about the parameter value. They were then requested to place the remaining 18 counters so as to express their remaining uncertainty about the particular parameter value.

For the parameters related to clinical upstaging, the clinical advisors were asked, "In patients who are not diagnosed, what proportion will progress to a higher stage of cancer approximately one year after developing each of the following stages?". *Table 28* provides a summary of the clinical advisors' responses to the question

TABLE 29 *Health state costs from oral cancer case note exercise*

Year	Mean (£)	SD (£)	Distributional parameters[a]		
			Alpha	Beta	Distribution
Precancer					
Year 1	1123	237	22.45	50.02	Gamma
Year 2	368	93	15.66	23.50	Gamma
Year 3	378	76	24.74	15.28	Gamma
Cancer stage I					
Year 1	3948	547	52.09	75.79	Gamma
Year 2	552	116	22.64	24.38	Gamma
Year 3	414	173	5.73	72.29	Gamma
Cancer stage II					
Year 1	7132	1241	33.03	215.94	Gamma
Year 2	701	135	26.96	26.00	Gamma
Year 3	702	204	11.84	59.28	Gamma
Cancer stage III					
Year 1	10246	2067	24.57	416.99	Gamma
Year 2	848	278	9.30	91.14	Gamma
Year 3	789	392	4.05	194.76	Gamma
Cancer stage IV					
Year 1	9895	1110	79.47	124.52	Gamma
Year 2	1851	694	7.11	260.20	Gamma
Year 3	1768	1223	2.09	846.00	Gamma

[a] Parameters of distribution solved analytically using method-of-moments fitting from the observed cost data.

according to the starting health state. As with the annual malignant transformation rate, the beta distribution was used to characterise the uncertainty expressed by the clinical advisors. The responses indicated that the mean annual probability of progressing to a more advanced stage exceeded 50% in all cancer stages and increased from ~53% for the transition from stage I to stage II to ~67% for the transition from stage III to stage IV.

Modelling the impact of treatment of precancerous lesions on the annual malignant transformation rate

Only one study was identified which examined the impact of treatment on the malignant transformation of oral precancer.[116] The results were based on a study of 166 patients with oral leukoplakia in The Netherlands. The results from Schepman and colleagues indicated that patients who underwent any form of active treatment did not have a statistically significantly lower chance for malignant transformation than patients under surveillance.[116] The lack of statistical significance in this instance, however, does not rule out the possibility that treatment has an impact on reducing the transformation rate, particularly owing to the small numbers of patients in the study (87 had active treatment and 79 had surveillance). The survival curves presented in the study do not cross and therefore provide provisional support for a positive treatment effect for reducing the malignant transformation rate for premalignant lesions. In the absence of patient-level data with which to characterise the uncertainty, the model was run for three alternative scenarios representing possible treatment effects based on the results from Schepman and colleagues.[116] The first scenario reflects the most conservative assumption, that is, that treatment of premalignant lesions has no impact on reducing the annual malignant transformation rate. Two alternative scenarios are considered representing relative risk reductions of 10 and 20% on the malignancy transformation rate, which are within the range of possible treatment effects based on the survival curves reported in Schepman and colleagues.[116]

Oral cancer management costs and screening costs

Details of the approach used to derive the treatment costs of oral precancer and cancer were reported in Chapter 4. The total cost for each year post-diagnosis was applied in the decision model. Uncertainty in the health state costs for diagnosed

TABLE 30 *Unit cost estimates of screening*

Parameter	Unit cost (£)	Source
Oral examination by GP (invitational)	21	Netten and Curtis[117]
Oral examination by GDP (invitational)	10.25	GDS statement of dental remuneration[89]
Oral examination by specialist (invitational)	120	Netten and Curtis[117]
Oral examination by GP (opportunistic)	5	Netten and Curtis[117]
Oral examination by GDP (opportunistic)	3.4	GDS statement of dental remuneration[89]
Biopsy	50	Trust estimate
Neural network	1	Assumption
Invitation	1.31	MASS study[118]

TABLE 31 *Utility estimates for the general population[119]*

		Distribution and parameters		
Age (years)	**Mean (SE)**	**Alpha**	**Beta**	**Distribution**
Man				
35–44	0.91 (0.007)	659	65	Beta
45–54	0.85 (0.011)	341	65	Beta
55–64	0.80 (0.012)	334	94	Beta
65–74	0.78 (0.012)	388	110	Beta
75+	0.73 (0.015)	193	64	Beta
Females				
35–44	0.91 (0.009)	1009	100	Beta
45–54	0.85 (0.014)	546	96	Beta
55–64	0.81 (0.015)	530	124	Beta
65–74	0.78 (0.016)	556	157	Beta
75+	0.71 (0.019)	412	168	Beta

cases of oral precancer and cancer were modelled using the gamma distribution for the purposes of the probabilistic analysis. The gamma distribution is a continuous distribution bounded at the lower end by zero and with no positive upper bound. The properties of the gamma distribution are particularly appropriate to modelling cost data such that the resulting estimates are positive and reflect the positive skew typically seen in the sample cost data. Uncertainty in the gamma distribution is characterised by two parameters ~ gamma (α,β). The parameters of the gamma distribution were solved using analytic methods (method-of-moments) for each stage and each year post-diagnosis. These distributions are reported in *Table 29*.

In addition to the health state costs, the unit costs assigned to the screening programmes were also derived from relevant UK sources (*Table 30*). The costs of an oral examination by a specialist in a secondary care setting were based on the cost of an outpatient attendance undertaken in oncology.[117] The costs of the oral biopsy were obtained directly from the financial departments of the trusts involved in the case note exercise. The costs of an invitation were based on the invitational costs derived from a recent cost-effectiveness analysis of ultrasound screening in the UK.[118] A nominal cost of £1 was assigned to the neural network covering a similar range of costs to the administration costs reported in the MASS screening study (minus the relevant postage expenditure). The unit costs of the oral examination for the invitational and opportunistic programme were reported in Chapter 4.

Quality adjustment of survival data

In order to estimate QALYs, it is necessary to quality adjust the period during which the average person is alive within the model using an appropriate utility or preference score. A separate search of the literature identified one study which reported health state utility scores for oral precancer and cancer.[23] The study was based on a convenience sample of 100 members of the general public in the UK. Health state utilities were determined using the standard gamble

TABLE 32 *Registration and attendance rates (GP and GDP)*

	Registration rates – GDP and GP		Attendance rates – GP	
Age (years)	**GDP**	**GP**	**Males**	**Females**
40–44	0.51	0.99	0.70	0.84
45–54	0.47	0.99	0.74	0.86
55–64	0.49	0.99	0.80	0.86
65–74	0.43	0.99	0.85	0.86
75+	0.31	0.99	0.86	0.83

technique and were reported for three states: precancer, early cancer (stage I) and late cancer (including stages II–IV). The results indicated significant differences between the valuations reported for the three states. Mean (SD) health state utility values for the three states were oral precancer = 0.92 (0.18), early cancer = 0.88 (0.20) and late cancer = 0.68 (0.33). No studies were identified which provided utility estimates separately for each of the stages II–IV. As a result, the same utility value is assigned to patients with stages II–IV. Beta distributions were assigned to each of the three health state valuations for the probabilistic analysis.

The health state valuations reported here were elicited in relation to perfect health. For the purposes of the analysis, perfect health could be assigned a utility score of 1. However, this does not reflect that the general health of the population will naturally deteriorate over time. In order to encapsulate this in the model, the underlying utility of the general population was derived from a nationally representative UK sample.[119] The utility estimates for males and females according to 10-year age bands is presented in *Table 31*. Beta distributions were assigned to each separate age and sex grouping. These utility values were assigned to people in the 'no cancer' state. The three health state valuations for oral precancer and cancer were then applied to these utility estimates to derive the adjusted utility scores for these states allowing for the underlying utility of the general population. Thus, for example, if a 40-year-old man of the general population has a utility value of 0.91, a 40-year-old man with a precancerous lesion will have a utility value of 0.84 (0.91 × 0.92). This adjustment was necessary in order to re-scale the utility estimates to ensure that the values were bounded by the general health of the UK population (as opposed to perfect health). This ensured that the estimates were internally consistent, ensuring that the utility estimates for the cancer states could not exceed the health of the general population and also reflecting the fact that the health of the general population will naturally deteriorate over time.[120]

Registration, attendance rates and compliance with screening

Registration and attendance rates with NHS practices in both primary medical and dental care were obtained from national survey data[121] and the Dental Practice Board Archive (http://www.dpb.nhs.uk/gds/archive.shtml). These rates were used to determine the proportion of the general population who would be eligible for the invitational and opportunistic screening programmes. For the purposes of the model, the costs of the invitation for the invitational screening programmes were applied to all people registered with either a GP or a GDP. The compliance rate to the invitational screen was then applied to the proportion of the general population registered at either location. For the opportunistic programmes, the annual attendance rates were used to determine the proportion of the general population who could be screened opportunistically during an annual cycle.

Registration rates for males and females were not reported separately for either primary medical or dental practices. Separate registration rates by age were reported for NHS dental practices. Annual attendance rates in primary medical practices were reported separately by age and sex.[121] No separate data were available to determine the annual attendance in NHS dental practices. Since patients in NHS dental practices must attend on a regular basis to maintain their NHS registration (currently 15 months), the registration rates were used as a proxy for the annual attendance rates. *Table 32* provides a summary of the registration and attendance rates applied in the model for GPs and GDPs.

TABLE 33 *Self-referral/routine case-finding*

Stage	Mean	SD	Distributional parameters		
			Alpha	Beta	Distribution
Precancer	0.13	0.14	0.60	4.03	Beta
Stage I	0.27	0.19	1.19	3.17	Beta
Stage II	0.56	0.27	1.36	1.08	Beta
Stage III	0.68	0.28	1.27	0.59	Beta
Stage IV	0.71	0.30	0.89	0.37	Beta

Compliance with a postal invitation for the invitational screening strategies were taken from a UK pilot screening programme for oral cancer undertaken in general medical practice identified in the effectiveness review.[15] Compliance with a postal invitation (two rounds) from this programme was 26% (985/3826 patients). For the probabilistic analysis, compliance with the invitational screen was modelled using a beta (985,2841) distribution. Compliance with the follow-up biopsy, following an initial positive screen, was estimated to be approximately 76% (1162/1534 patients) based on an oral screening programme undertaken in the USA.[38] Compliance to the biopsy was modelled using a beta (1162,372) distribution.

Modelling the detection of precancer and cancer in routine practice

No evidence was identified in the systematic reviews regarding the probability that people will be detected as part of routine clinical practice (i.e. in the absence of a formal screening programme). Positive lesions may be detected in this manner either via self-referral, after the patient becomes symptomatic, or the lesion may be detected as part of a routine clinical examination. In the absence of relevant parameter estimates from the literature, expert clinical opinion was elicited using the Trial Roulette approach outlined earlier. The clinical advisors were asked to quantify their beliefs concerning the proportion of people who would be routinely detected for precancer and for each cancer stage. *Table 33* provides a summary of the responses from the clinical advisors. The responses indicated that the proportion of patients being detected increased from ~13% in precancer to ~71% for cancer stage IV. The uncertainty in the experts' responses was characterised using the beta distribution.

Diagnostic test performance for the visual screen

Parameter estimates for sensitivity and specificity were obtained using the SROC curve meta-analytical results described in detail in Chapter 2. For the purposes of the model, separate estimates for Sn and Sp were required for the alternative screeners considered in the various strategies (GDPs, GPs and hospital specialists). The studies identified as part of the systematic review did not identify separate studies of the alternative screeners. In Chapter 2, the main differences in the selected studies lay between the pilot and substantive studies conducted in the industrialised countries (England and Japan), which utilised dentists as screeners, and the much larger programmes from the Indian subcontinent that used specifically trained basic health workers. In the absence of specific estimates for each screener included in the model, estimates from the industrialised and non-industrialised countries were applied to GDPs and GPs, respectively. The estimates from the non-industrialised countries using trained basic health workers were thus used as a proxy for the potential test performance of GPs, reflecting that GPs will have less training than GDPs.

The values of Sn and Sp estimates calculated using the SROC are closely related. From the equation for the SROC curve, uncertainty in either the Sn or Sp (represented by the 95% CIs) is estimated in relation to a fixed value of the other. Although this process allows the 95% CI around both Sn and Sp to be shown, the distributions are not independent. Consequently, the distributions around the Sn and Sp cannot be modelled using separate distributions. For the purpose of the probabilistic model, it is necessary to fix either Sn or Sp in order to model the uncertainty in the other parameter. For this analysis, the weighted pooled value of Sn was fixed in the model. The weighted value of Sn was estimated to be 0.88 and 0.72 for GPs and GDPs, respectively. The corresponding uncertainty for Sp was then estimated from the SROC presented in Chapter 2.

No separate estimates of Sn and Sp were available for a secondary care specialist. In the absence of

specific estimates, we applied the most favourable assumption (i.e. Sn and Sp of 1). This represents a conservative assumption in relation to the invitational and opportunistic screening strategies in general medical and dental practice.

Analytic methods

The model was developed in Excel. The Monte Carlo simulation was run for 5000 iterations. The model was run several times to explore alternative scenarios. The main scenarios presented represent the uncertainty in the impact that early identification of precancerous lesions and subsequent treatment has on altering the malignant transformation rate from precancer to cancer outlined earlier:

1. Scenario 1: no treatment effect on malignant transformation rate
2. Scenario 2: relative risk reduction of 10% following treatment
3. Scenario 3: relative risk reduction of 20% following treatment.

The results of the model are presented in two ways. First, mean lifetime costs and QALYs of the alternative strategies are presented and their cost-effectiveness compared, estimating incremental cost-effectiveness ratios (ICERs) as appropriate, using standard decision rules.[122] The ICER examines the additional costs that one strategy incurs over another and compares this with the additional benefits. When more than two programmes are being compared, the ICERs are calculated using the following process:

1. The strategies are ranked in terms of cost (from the least expensive to the most costly).
2. If a strategy is more expensive and less effective than the previous strategy, then this strategy is said to be dominated and is excluded from the calculation of the ICERs.
3. The ICERs are calculated for each successive alternative, from the cheapest to the most costly. If the ICER for a given strategy is higher than that of the next more effective strategy, then this strategy is ruled out on the basis of extended dominance.
4. Finally, the ICERs are recalculated excluding any strategies that are ruled out using the notions of dominance and extended dominance.

The advantage of entering input parameters as uncertain variables is that this uncertainty can be propagated through the model and reflected in model outputs. To present the uncertainty in the cost-effectiveness of the alternative strategies, cost-effectiveness acceptability curves (CEACs) are used. These show the probability that each strategy is more cost-effective than the other three using alternative values for the maximum value that the health service is willing to pay for an additional QALY in these patients.[123,124]

Results

The results of the probabilistic analysis are presented for the entire population aged between 40 and 79 years, for males and females (aged 40–79 years) separately and for each age and sex subgroup (according to 10-year age bands). In all analyses and in each of alternative age/sex subgroups, strategy A (no screening) was always the cheapest and least effective strategy. Of the remaining strategies, strategies B (invitational screen – GDP), C (invitational screen – GP), E (opportunistic screen – GP) and H (invitational screen – secondary care specialist) were always ruled out either by dominance or extended dominance. Hence the strategies under consideration (i.e. non-dominated alternatives) in the calculation of the ICERs are A, no screen; G, opportunistic high-risk screening (GDP); F, opportunistic high-risk screening (GP); and D, opportunistic screening (GP). The ordering of these strategies is from least costly (and least effective) to most costly (and most effective). Since none of these alternatives are dominated, the ICERs are calculated between each successively more expensive (and more effective) strategy.

Combined results for the population analysis aged 40–79 years

A summary of the results of the ICER (excluding dominated strategies) is presented in *Tables 34–36* based on the combined analyses of males and females aged 40–79. A detailed set of results of the probabilistic results and the estimation of the ICER for males and females separately and for the various subgroups is presented in Appendices 12 and 13, respectively.

Assuming treatment of precancerous lesions has no effect on reducing the annual malignant transformation rate, the ICER of opportunistic high-risk screening by a GDP was about £22,850 per additional QALY compared with no screening. The ICER of opportunistic high-risk screening by a GP was £23,728 per QALY compared with the same screening strategy carried out by a GDP. Finally, the ICER of opportunistic screening by a GP was £25,961 per QALY compared with the opportunistic high-risk screening by a GP.

TABLE 34 *Population (males and females aged 40–79 years) – scenario 1: no treatment effect on progression from precancer to cancer*

Strategy	Screen option	Screener	Cost (£)	QALY	ICER (£)	Probability cost-effective for maximum WTP[a]		
						£20,000	£30,000	£40,000
A	No screen	NA	29.82	12.8740	NA	0.6566	0.2860	0.1140
C	Invitational screen	GDP	43.90	12.8745	ED	0.0000	0.0000	0.0000
B	Invitational screen	GP	67.04	12.8754	ED	0.0000	0.0000	0.0000
G	Opportunistic high-risk screen	GDP	73.80	12.8759	22,850	0.0308	0.0190	0.0056
E	Opportunistic screen	GDP	85.90	12.8764	ED	0.0232	0.0160	0.0050
H	Invitational screen	Spec.	92.70	12.8756	D	0.0000	0.0000	0.0000
F	Opportunistic high-risk screen	GMP	117.67	12.8778	23,728	0.1136	0.1540	0.1064
D	Opportunistic screen	GMP	142.32	12.8787	25,961	0.1758	0.5250	0.7690

D, option ruled out by dominance (more expensive and less effective); ED, option ruled out by extended dominance; NA, not applicable; Spec. hospital specialist.

[a] The probability that each strategy is more cost-effective than the others conditional on different maximum willingness to pay (WTP) for an additional QALY.

TABLE 35 *Population (males and females aged 40–79 years) – Scenario 2: 10% treatment effect on progression from precancer to cancer*

Strategy	Screen option	Screener	Cost (£)	QALY	ICER (£)	Probability cost-effective for maximum WTP[a]		
						£20,000	£30,000	£40,000
A	No screen	NA	29.76	12.8742	NA	0.4620	0.1394	0.0430
C	Invitational screen	GDP	43.97	12.8749	ED	0.0000	0.0000	0.0000
B	Invitational screen	GP	67.30	12.8759	ED	0.0000	0.0000	0.0000
G	Opportunistic high-risk screen	GDP	74.18	12.8765	18,919	0.0314	0.0088	0.0024
E	Opportunistic screen	GDP	86.43	12.8771	ED	0.0246	0.0112	0.0040
H	Invitational screen	Spec.	93.01	12.8761	D	0.0000	0.0000	0.0000
F	Opportunistic high-risk screen	GP	118.50	12.8788	19,703	0.1564	0.1254	0.0634
D	Opportunistic screen	GP	143.45	12.8799	21,623	0.3256	0.7152	0.8872

Footnotes as in *Table 34*.

Assuming that the treatment of precancerous lesions has a positive impact on reducing the annual malignant transformation made the ICER of all the screening strategies more favourable. The ICER of opportunistic high-risk screening by a GDP was £18,919 (based on a 10% reduction in the annual malignancy transformation rate) and £15,790 per additional QALY (20% reduction) compared with no screening. The ICER of opportunistic high-risk screening by a GP was £19,703 (10% reduction) and £16,443 per additional QALY (20% reduction) compared with the same screening strategy carried out by a GDP. The ICER of opportunistic screening by a GP was £21,623 (10% reduction) and £18,046 (20% reduction) per additional QALY compared with the opportunistic high-risk screening by a GP.

Although the results of the ICER can be used to determine the optimal decision based on a comparison of mean costs and QALYs, they do not incorporate the uncertainty surrounding this decision. The probability that each strategy is cost-effective is also presented in these tables for select values, representing possible maximum amounts that the NHS may be willing to pay for an additional QALY. The results across the full range of values considered (between £0 and £50,000 per QALY) are presented graphically using CEACs in Appendix 14. These curves detail the probability that each strategy is cost-effective over a range of potential maximum values that the health service is prepared to pay for an additional QALY. The results of the CEACs incorporate the uncertainty within the model in relation to both the estimates of mean costs and QALYs, and in the maximum willingness to pay for an additional QALY. The curves illustrate that there is considerable uncertainty in the optimal decision identified by the ICER, depending on both the maximum

TABLE 36 *Population (males and females aged 40–79 years): scenario 3: 20% treatment effect on progression from precancer to cancer*

						Probability cost-effective for maximum WTP[a]		
Strategy	**Screen option**	**Screener**	**Cost (£)**	**QALY**	**ICER (£)**	**£20,000**	**£30,000**	**£40,000**
A	No screen	NA	29.70	12.8746	NA	0.3024	0.0732	0.0232
C	Invitational screen	GDP	43.71	12.8754	ED	0.0000	0.0000	0.0000
B	Invitational screen	GP	66.76	12.8765	ED	0.0000	0.0000	0.0000
G	Opportunistic high-risk screen	GDP	£73.46	12.8773	15,790	0.0186	0.0052	0.0012
E	Opportunistic screen	GDP	85.50	12.8780	ED	0.0166	0.0046	0.0010
H	Invitational screen	Spec.	92.39	12.8768	D	0.0000	0.0000	0.0000
F	Opportunistic high-risk screen	GP	117.13	12.8800	16,443	0.1590	0.0842	0.0358
D	Opportunistic screen	GP	141.65	12.8814	18,046	0.5034	0.8328	0.9388

Footnotes as in *Table 34*.

TABLE 37 *Comparison of ICERs for strategies (non-dominated strategies): males*

			Summary of the ICERs for each age group (males) (£)			
Strategy	**Screen option**	**Screener**	**40–49 years**	**50–59 years**	**60–69 years**	**70–79 years**
Scenario 1: no treatment effect						
A	No screen	NA	NA	NA	NA	NA
G	Opportunistic high-risk screen	GDP	19,259	23,387	29,058	42,582
F	Opportunistic high-risk screen	GP	19,384	24,496	29,215	42,906
D	Opportunistic screen	GP	20,930	24,716	31,488	48,468
Scenario 2: 10% treatment effect						
A	No screen	NA	NA	NA	NA	NA
G	Opportunistic high-risk screen	GDP	15,460	18,938	24,569	35,711
F	Opportunistic high-risk screen	GP	15,560	19,028	24,700	35,981
D	Opportunistic screen	GP	16,678	19,605	26,247	41,415
Scenario 3: 20% treatment effect						
A	No screen	NA	NA	NA	NA	NA
G	Opportunistic high-risk screen	GDP	13,285	15,755	20,502	31,703
F	Opportunistic high-risk screen	GP	13,371	15,829	20,613	31,947
D	Opportunistic screen	GP	14,468	16,772	21,853	36,145

amount the NHS may be prepared to pay for an additional QALY and the impact that treatment has on the annual malignancy transformation rate.

Assuming that treatment of precancerous lesions results in a reduction in the annual malignant transformation rate improves the cost-effectiveness of these strategies. For scenario 1 (no treatment effect) there is a 66% probability that no screening is cost-effective at a threshold of £20,000 per QALY. Assuming a 20% reduction in the annual malignancy transformation rate, the probability that no screening is cost-effective falls to 30% for the same threshold value. As the maximum amount that the NHS is prepared to pay increases, the probability that the screening strategies are cost-effective rises in each scenario.

Results for the subgroup analyses

In the cost-effectiveness analysis, the ICER varied by age and sex and was most sensitive to the treatment effect applied to the malignant transformation rate. In all subgroups, opportunistic high-risk screening (GDP) had the lowest ICER, although the ICERs for opportunistic high-risk screening and opportunistic screening by a GP were only marginally higher than opportunistic high-risk screening by a GDP. These results are summarised in *Tables 37* and *38*.

Assuming treatment of precancerous lesions has no effect on reducing the annual malignant transformation rate, the ICER of opportunistic high-risk screening (compared with no screening)

TABLE 38 *Comparison of ICERs for strategies (non-dominated strategies): females*

Strategy	Screen option	Screener	Summary of the ICERs for each age group (females) (£)			
			40–49 years	50–59 years	60–69 years	70–79 years
Scenario 1: no treatment effect						
A	No screen	NA	NA	NA	NA	NA
G	Opportunistic high-risk screen	GDP	17,307	20,980	25,740	35,415
F	Opportunistic high-risk screen	GP	17,528	21,183	26,028	35,997
D	Opportunistic screen	GP	21,027	24,039	30,574	46,294
Scenario 2: 10% treatment effect						
A	No screen	NA	NA	NA	NA	NA
G	Opportunistic high-risk screen	GDP	16,230	16,586	21,992	31,786
F	Opportunistic high-risk screen	GP	16,416	16,748	22,242	32,306
D	Opportunistic screen	GP	18,758	19,560	26,226	41,118
Scenario 3: 20% treatment effect						
A	No screen	NA	NA	NA	NA	NA
G	Opportunistic high-risk screen	GDP	11,730	14,589	18,546	26,883
F	Opportunistic high-risk screen	GP	11,879	14,729	18,758	27,330
D	Opportunistic screen	GP	14,137	17,037	22,246	36,041

in a general dental practice ranged from £19,259 to £42,582 per QALY across each of the age groups in males. For females, the corresponding estimates of the ICER were from £17,307 to £35,415 per QALY. In both males and females, the screening programme was most cost-effective in the group aged between 40 and 49 years and least cost-effective in the age group 70–79 years. The ICER of opportunistic high-risk screening in a general medical practice (compared with opportunistic high-risk screening in a general dental practice) ranged from £19,384 to £42,906 per QALY for males and from £17,528 to £35,997 per QALY for females. Finally, the ICER of opportunistic screening in a general medical practice (compared with opportunistic high-risk screening in the same location) ranged from £20,930 to £48,468 per QALY for males and from £21,027 to £46,294 per QALY for females.

Assuming that the treatment of precancerous lesions has a positive impact on reducing the annual malignant transformation made the ICER of all the screening strategies more favourable. Assuming either a 10% relative risk reduction (the corresponding figures for a 20% risk reduction are given in parentheses), reduced the ICER for opportunistic high-risk screening for males to the range £15,460–35,711 per QALY (£13,285–31,703 per QALY). In this scenario, the ICER for opportunistic high-risk screening in general medical practice for males was £15,560–35,981 per QALY (£13,371–31,947 per QALY). Finally, the ICER for opportunistic screening in general medical practice was £16,678–41,415 per QALY (£14,468–36,145 per QALY). Similar reductions in the ICER were also evident for females under both these separate scenarios.

Clearly the key question is whether screening provides good value for money to the NHS. As a rough guide, recent decisions and guidance from the National Institute for Health and Clinical Excellence's Appraisal Committee suggests that a cost per QALY value of around £20,000–30,000 is considered value for money by the NHS.[94,125] Using this decision rule, the ICER of the opportunistic programmes would appear to be potentially cost-effective under a number of scenarios. In general, assuming no treatment effect on the premalignant transformation rate makes the cost-effectiveness of the three opportunistic screening programmes look least favourable. Under this scenario, the main benefit of screening is in ensuring that patients are identified at an earlier stage (all patients diagnosed with precancer are assumed to be detected at stage I) than would occur in routine practice progressed to cancer. However, even in this scenario, the opportunistic programmes seem potentially cost-effective for patients aged <70 years. For treatment effects between 10 and 20%, screening looks more favourable in people aged 40–69 years. In people aged >70 years, screening appeared markedly less cost-effective than patients aged<70 years in all scenarios.

Chapter 7
Value of information analysis

Introduction

Healthcare decision-making is inevitably undertaken under conditions of uncertainty. In the cost-effectiveness model, there is uncertainty in terms of both the resource implications (and hence costs) of alternative screening strategies and their associated outcomes. Within the proposed decision-theoretic framework, the primary reason to consider these uncertainties is to establish the value of acquiring additional information by conducting further research. This chapter explores the implications of the uncertainty associated with the cost-effectiveness of screening for oral cancer by undertaking value of information (VOI) analysis. This analysis produces an upper limit to the value of future research that could be undertaken to reduce the uncertainty associated with a decision regarding the adoption of screening for oral precancer and cancer in the NHS.

If the principal objective underlying health technology assessment is to make decisions that are consistent with maximising health gains from available NHS resources, then adoption/implementation decisions should be based on the expected cost-effectiveness given the existing information (i.e. using the mean differential costs and outcomes between the alternative strategies being compared). In Chapter 6, comparisons between the alternative screening policies evaluated in the model were made in relation to their ICER. The ICER indicates whether a particular strategy is cost-effective depending on the threshold/maximum willingness to pay for an additional unit of health outcome (i.e. per additional QALY). Uncertainty in the model was represented using CEACs. The curves demonstrated that although screening was potentially cost-effective across a range of threshold values, there was significant uncertainty surrounding the cost-effectiveness of the main screening strategies. Although this uncertainty is considered irrelevant to the adoption decision within the proposed framework, it has significant implications for the value of conducting further research to support this decision.[99,100]

Decisions based on existing information will be uncertain, and there will always be a chance that the wrong decision will be made. If the wrong decision is made, there will be costs in terms of health benefit and resources forgone. Therefore, the expected cost of uncertainty can be determined jointly by the probability that a decision based on existing information will be incorrect and the consequences of a wrong decision. Bayesian VOI analysis can be used to determine the expected costs of decision uncertainty predicted by the model and the maximum value that can be placed on additional research aimed at reducing this uncertainty. A VOI framework is used to provide an explicit measure of the cost associated with uncertainty surrounding the screening decision through formal consideration and valuation of the consequences associated with any uncertainty. This analysis can be used as the basis to inform policy decisions relating to future research priorities in this area and has recently been applied to several case studies in the NHS HTA programme.[104,126]

The expected costs of uncertainty can also be interpreted as the EVPI since perfect information would eliminate the possibility of making the wrong decision. Furthermore, the EVPI also represents the maximum amount that a decision-maker should be willing to pay for additional evidence to inform this decision in the future.[98,99,127] EVPI is used to provide an upper bound on the value of additional research to that provided by the model. This valuation can then be used as a necessary requirement for determining the potential efficiency of further primary research. Applying this decision rule, additional research should only be considered if the EVPI exceeds the expected cost of the research. In addition to providing a global estimate of the total cost of uncertainty related to all inputs in the model, EVPI can also be estimated for individual parameters (and groups of parameters) contained in the model. The objective of this analysis (termed partial EVPI) is to identify the model parameters where it would be most worthwhile in obtaining more precise estimates.

The results from these analyses will enable decision-makers to determine whether further primary research is required and provide an

indication of where research is most worthwhile. In this manner, modelling can help to prioritise future investment in research.

Methods

A non-parametric approach is used to determine the costs of uncertainty associated with the adoption decision.[124,126] The use of Monte Carlo simulation allows the expected costs of uncertainty associated with the initial adoption decision to be expressed as the proportion of iterations which results in an adoption decision other than that arising from maximising expected cost-effectiveness (the *a priori* adoption decision). The benefits forgone are simply the difference in the costs and outcomes (net benefit) between the optimal strategy for a given iteration and those of the strategy identified as optimal in the adoption decision (i.e. based on the expected cost-effectiveness estimates). The expectation of benefits forgone over all iterations represents the EVPI per individual.

Clearly, since information can be of value to more than one individual, EVPI can also be expressed for the total population who stand to benefit over the expected lifetime of the programme/technology. If the EVPI for the population of current and future patients exceeds the expected costs of additional research, then it is potentially cost-effective to conduct further research. The overall VOI for a population is determined by applying the individual EVPI estimate to the number of people that would be affected by the information over the anticipated lifetime of the technology:

$$\text{EVPI} \times \sum_{t=1}^{T} \frac{I_t}{(1+r)^t}$$

where I = incidence in period, t = period, T = total number of periods for which information from research would be useful and r = discount rate.

In the context of a national screening programme for oral cancer, the relevant population of interest considered by the model is all individuals currently aged 40–79 years, together with those who will become eligible over the lifetime of the programme (i.e. people currently aged <40 years). Population level EVPI is estimated using national population estimates from England and Wales (22.2 million aged 40–79 years), combined with the number of individuals who will become eligible each year thereafter (0.8 million aged 39 years).[128] The analysis assumes that the information would be valuable for 10 years. A 3.5% annual rate of discount is applied.

Results

Population EVPI

The population EVPI, based on the combined results for males and females aged 40–79 years, is illustrated in *Figure 7*. Separate estimates are provided based on the alternative assumptions applied concerning the impact that treatment has on reducing the MTR (i.e. no effect, 10% relative risk reduction, 20% relative risk reduction). When the threshold for cost-effectiveness (maximum willingness to pay for an additional QALY) is low (e.g. <£10,000 per QALY), screening is not considered to be cost-effective under any scenario and additional information is unlikely to change this decision. Consequently, the estimates of EVPI are low. Similarly, when the threshold is higher (e.g. >£40,000 per QALY) opportunistic screening is expected to be cost-effective and this decision is less likely to be changed by further research (and hence the EVPI falls). The population EVPI reaches a maximum when the threshold for cost-effectiveness is equal to the expected ICERs of the alternative screening strategies. In other words, the EVPI reaches a maximum when the decision is most uncertain whether to adopt or reject screening based on existing evidence.

A more detailed example illustrating the relationship between the ICER, based on the results reported in Chapter 6, and the VOI is provided. Assuming that treatment of precancerous lesions has no effect on reducing the annual MTR, the ICER of opportunistic high-risk screening by a GDP was ~£22,850 per additional QALY compared with no screening. The ICER of opportunistic high-risk screening by a GP was £23,728 per QALY compared with the same screening strategy carried out by a GDP. Finally, the ICER of opportunistic screening by a GP was £25,961 per QALY compared with the opportunistic high-risk screening by a GP. Consequently, the EVPI for this scenario reaches a peak between the ranges of these estimates of the ICER of the screening strategies. For threshold values <£22,850 per QALY, 'no screening' is considered the optimal decision based on the expected cost-effectiveness results. Clearly at threshold values close to this estimate there is significant uncertainty as to whether or not 'no

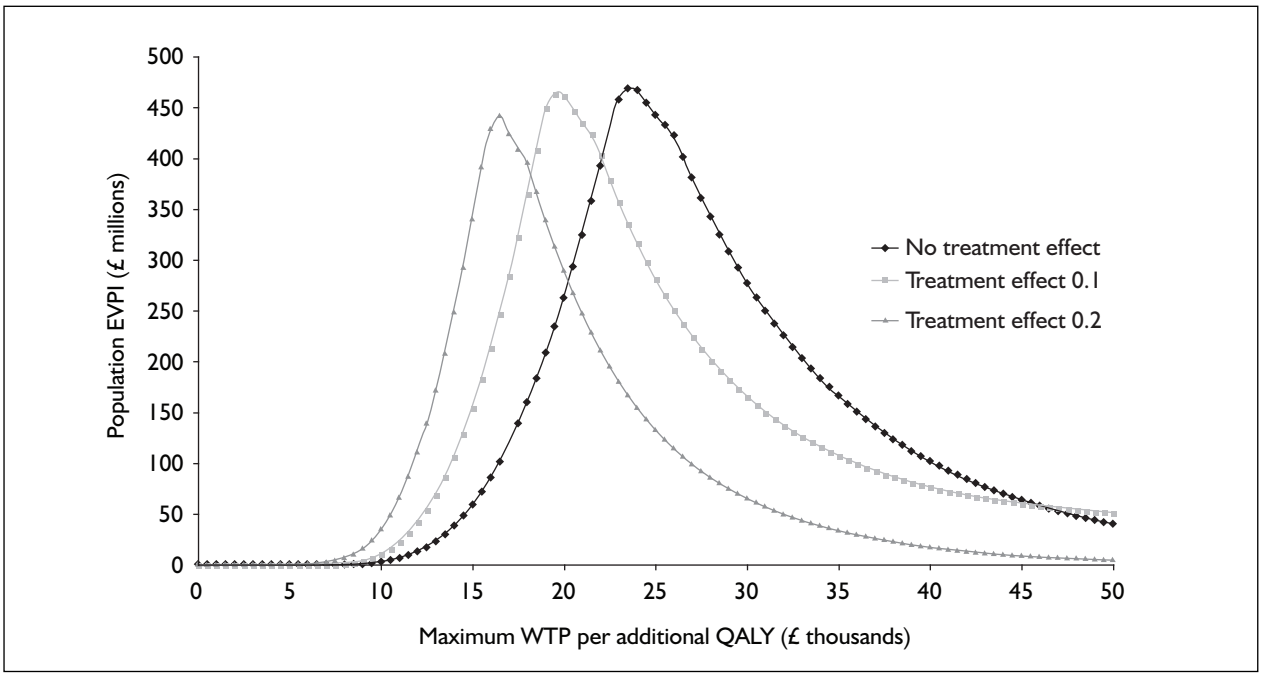

FIGURE 7 *VOI analysis for the population aged >40 (years) (males and females combined)*

screening' is the optimal decision, hence the associated EVPI is very high. However, as the threshold value is reduced, the uncertainty surrounding the 'no screening' strategy is significantly lower, hence the related EVPI is much less. Similarly, for threshold values between £22,000 and £26,000 per QALY there is significant uncertainty over which screening strategy is cost-effective (hence the EVPI estimate is highest in this range). As the threshold rises above £26,000 per QALY, then opportunistic screening by a GP appears cost-effective and the cost of uncertainty surrounding this decision reduces the higher the threshold value considered.

The results reported in Chapter 6 demonstrated that if treatment of precancerous lesions had a positive impact on reducing the annual MTR, then the ICER of all the screening strategies appeared more favourable. The impact of this on the population EVPI estimates is illustrated in the separate curves plotted in *Figure 7*. The lower ICER for the screening strategies in these scenarios results in a shift in the EVPI estimates, such that uncertainty is now highest at lower threshold values representing the maximum WTP per additional QALY.

Figures 8 and *9* present the results for males and females separately. The results clearly illustrate that the cost of uncertainty is significantly higher in males than females. This difference is due principally to the higher prevalence of oral precancer and cancer in males than in females (i.e. the consequences of making the wrong decision are higher in males than females). The estimates of EVPI also show important differences across the range of threshold value representing the maximum willingness to pay for an additional QALY.

Table 39 provides a summary of the population EVPI estimates for a select number of threshold values. The results indicate a considerable range in the population EVPI estimates depending on the threshold WTP value, the assumption concerning the treatment effect and the separate estimates for males and females. Despite the considerable range in these estimates, between £8 million and £462 million, further primary research would appear to be worthwhile, given the large cost of uncertainty in all scenarios.

Partial EVPI

Although estimates of the total EVPI provide a useful global estimate of the uncertainty surrounding the adoption decision, this estimate does not provide an indication of where further research would be of most value. The value of reducing the uncertainty surrounding particular input parameters in the decision model can also be established by estimating partial EVPI. This type of analysis can be used to focus further research by identifying those inputs for which more precise estimates would be most valuable. The analysis of the VOI associated with each of

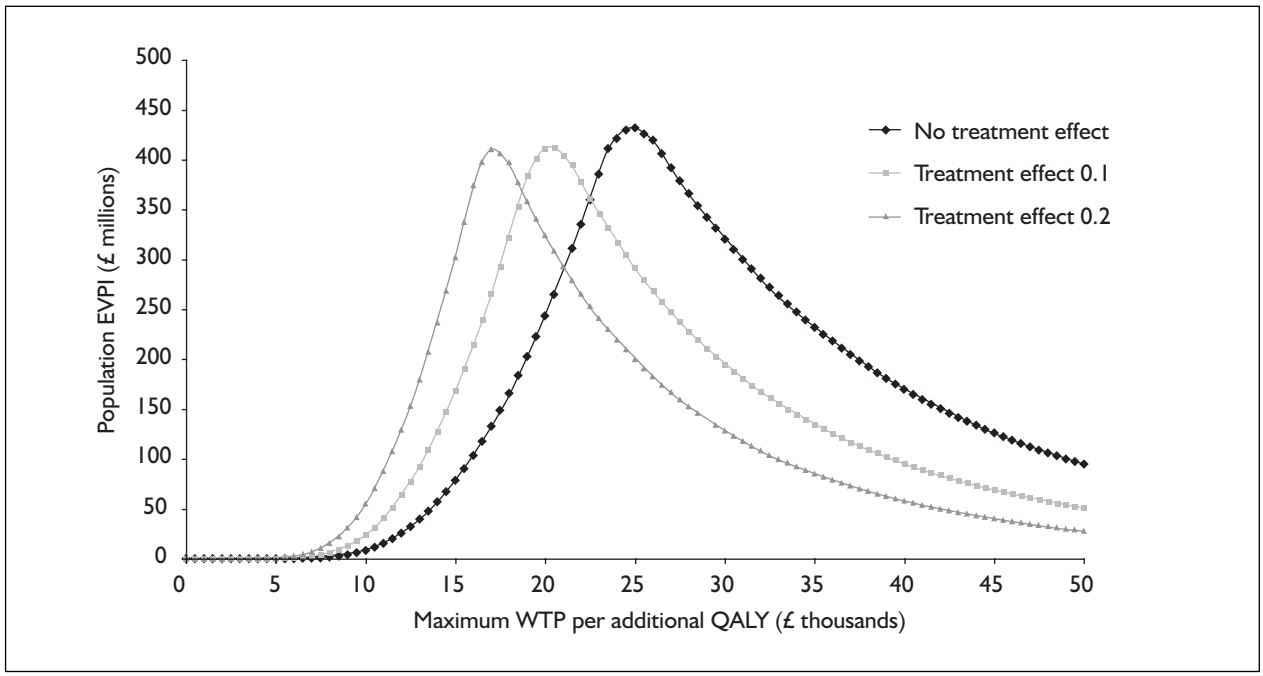

FIGURE 8 *VOI analysis for the population aged >40 years (males only)*

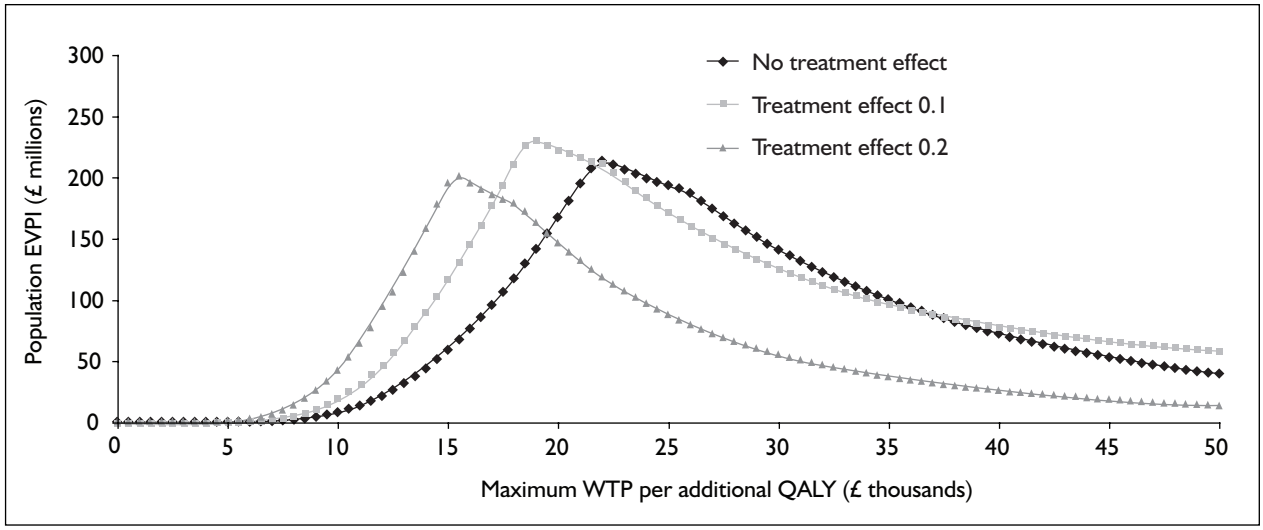

FIGURE 9 *VOI analysis for the population aged >40 years (females only)*

the model inputs can be conducted in a very similar way to the EVPI for the decision as a whole in cases where a linear relationship between the inputs and the expected costs and outcomes exists. However, where the relationship is non-linear, partial EVPI estimates require substantial additional computation. Owing to the complexity of the model presented here, a linear relationship has been assumed for ease of exposition and the partial EVPI results are presented for a single subgroup. Although estimates are presented for only one subgroup, the relative ordering of importance is likely to be similar across alternative subgroups/scenarios.

Table 40 provides the partial EVPI estimates for males aged 40–49 years (assuming treatment has no effect on the MTR). Estimates of EVPI presented are per patient estimates and have not been aggregated to provide population estimates, since only one scenario has been considered. In this example, the EVPI associated with the MTR is extremely high and appears to account for the majority of uncertainty surrounding the model.

TABLE 39 *Summary of population EVPI estimates (£ million)*

Scenario	Maximum WTP per additional QALY		
	£20,000	£30,000	£40,000
Total population (no treatment effect)	263	277	102
Total population (10% treatment effect)	462	165	77
Total population (20% treatment effect)	289	65	17
Males only (no treatment effect)	243	320	170
Males only (10% treatment effect)	411	195	95
Males only (20% treatment effect)	323	128	58
Females only (no treatment effect)	8	167	141
Females only (10% treatment effect)	20	223	125
Females only (20% treatment effect)	42	146	55

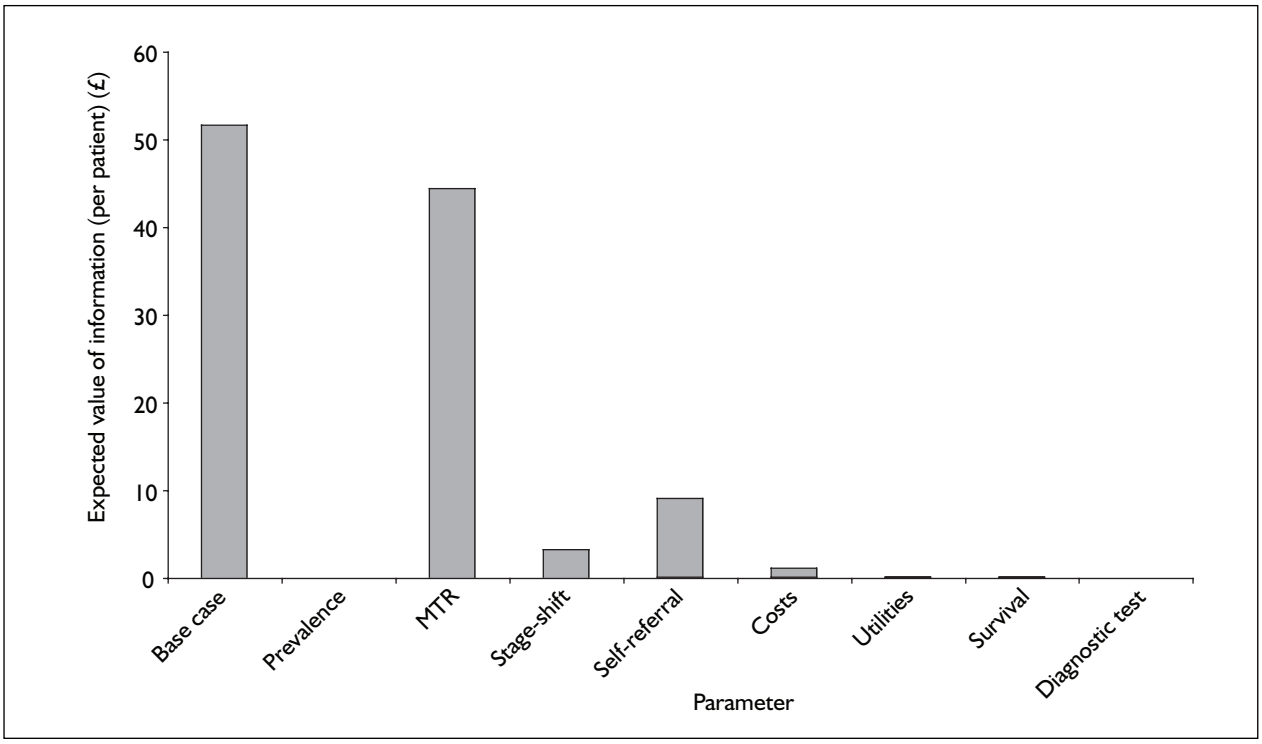

FIGURE 10 *Partial EVPI results (40–49-year-old males assuming no treatment effect)*

Other parameters which appear to have an important influence on the overall decision uncertainty include the proportion of people who will self-refer (with precancer and/or cancer), the probability of progressing to a more advanced stage of cancer (i.e. progression from stage I to stage II, etc.) and the costs of oral cancer. Estimates of the partial EVPI for a range of other parameters (e.g. prevalence data, diagnostic test performance, health state utilities) appear to have limited value in relation to obtaining further information. The estimates of partial EVPI for these parameters is illustrated graphically in *Figure 10*, based on a maximum threshold willingness to pay of £20,000 per QALY. The figure demonstrates the importance of the uncertainty surrounding the MTR in relation to the other parameters.

Discussion

The results from Chapter 6 indicated that there was considerable uncertainty in the adoption decision in each of the analyses over a range of key threshold values representing the maximum willingness to pay for an additional QALY. This uncertainty results in a significant cost of

TABLE 40 *Partial EVPI for individual parameters (per patient estimates) (£)*

	Maximum WTP per additional QALY		
Parameter(s)	**£20,000**	**£30,000**	**£40,000**
Base case (total)	51.61	37.77	28.10
Prevalence	0	0	0
MTR	44.37	30.83	22.87
Stage-shift (stages I–IV)	3.16	0.07	0
Self-referral	9.05	2.30	0.81
Costs of precancer/cancer	1.07	0	0
Utilities of precancer/cancer	0.01	0	0
Survival data	0.01	0	0
Compliance biopsy	0	0	0
Diagnostic test performance	0	0	0

uncertainty reflected in the high population EVPI estimates. The population EVPI estimates suggest that further research in this area is likely to be of significant value. EVPI for individual parameters highlighted that potential future research would be of most value directed toward obtaining more precise estimates of the MTR. Sensitivity analyses using alternative assumptions related to the impact of treatment on reducing the MTR indicate that EVPI is highly sensitive to the assumption, demonstrating that future research into the impact of treatment is also likely to be important.

Chapter 8

Conclusions and recommendations

This project used a simulation modelling approach to determine the cost-effectiveness of a number of possible oral cancer screening strategies in primary care environments. The advantage of this approach is that it allows greater flexibility in the number and scope of strategies that can be evaluated and avoids the costly implementation of an RCT in an area where there is uncertainty about the data. In this respect, the model also allows VOI analysis to be used to identify where this uncertainty lies and to place a value on areas of future research. The model is also generic in that it can be applied to multiple screening scenarios in any population setting.

The model was informed using data from the literature, including three systematic reviews, and also expert opinion and published data from cancer registries. Costs of management of oral cancer and precancer were gleaned from a case note review and from published UK sources.

Cost-effectiveness analysis

The cost-effectiveness of a range of alternative screening strategies for oral cancer was compared with no screening. The strategies were based on a one-off prevalence screen of a population age >40 years, including invitational and opportunistic programmes undertaken in both primary medical and dental locations. These strategies comprised invitational (population-based) screening programmes, opportunistic screening (case-finding) and targeted 'high-risk' screening. Eight strategies were compared from an NHS perspective using a probabilistic decision-analytic model:

A No screen
B Invitational screen – general medical practice
C Invitational screen – general dental practice
D Opportunistic screen – general medical practice
E Opportunistic screen – general dental practice
F Opportunistic high-risk screen – general medical practice
G Opportunistic high-risk screen – general dental practice
H Invitational screen – specialist

A review of the literature revealed a lack of data on the effects of treatment on the malignant potential of oral precancerous lesions. One major study found no advantage of surgical intervention over a 'watch and wait' strategy. Therefore, in the model, three scenarios were considered based on alternative assumptions concerning the potential effects of treatment on disease progression (no effect; 10% reduction in malignant transformation; 20% reduction in malignant transformation). The main results were estimated for a population aged between 40 and 79 years based on UK population demographics. A series of subgroup analyses were conducted to explore the impact of heterogeneity according to alternative age (10-year bands) and gender groupings.

Strategy A (no screening) was always the cheapest and least effective strategy. Of the remaining strategies, B, C, E and H were always ruled out by dominance or extended dominance. Assuming that treatment of precancerous lesions has no effect on reducing the annual MTR, the ICER of opportunistic high-risk screening by a GDP was ~£22,850 per additional QALY compared with no screening. The ICER of opportunistic high-risk screening by a GP was £23,728 per QALY compared with the same screening strategy carried out by a GDP. Finally, the ICER of opportunistic screening by a GP was £25,961 per QALY compared with the opportunistic high-risk screening by a GP. Assuming that the treatment of precancerous lesions has a positive impact on reducing the annual MTR made the ICER of all the screening strategies more favourable. For treatment effects between 10 and 20%, the ICER of opportunistic high-risk screening by a GDP ranged from £15,790 to £18,919 per QALY gained compared with no screening. The ICER of opportunistic high-risk screening by a GP was between £16,443 and £19,703 per QALY compared with the same screening strategy carried out by a GDP. The ICER of opportunistic screening by a GP was between £18,046 and £21,623 per QALY compared with the opportunistic high-risk screening by a GDP.

The same pattern of dominance and extended dominance found in the overall analysis was found

for the subgroup analyses. The ICER varied by age and sex and was most sensitive to the treatment effect applied to the MTR. In all subgroups, opportunistic high-risk screening (GDP) had the lowest ICER, although the ICER for opportunistic high-risk screening and opportunistic screening by a GP were only marginally higher than opportunistic high-risk screening by a GDP. The subgroup analysis demonstrated very similar results by sex, but important differences on age. One practical implication of this variation by age is that, from the point of view of policy, the population age mix will determine the potential cost-effectiveness and should be factored into decision-making. In other words, in a population with a higher prevalence of older individuals, screening will be less efficient.

Overall, set against a benchmark figure of £20,000–£30,000 per QALY, the results indicate that opportunistic screening for oral cancer may be cost-effective. In particular, opportunistic high-risk screening by GDPs who are already trained to examine the mouth, with an ICER of £18,919 may be a practical proposition. These data, however, assume that interventive treatment of precancerous lesions will prevent disease progression and reduce the MTR. Literature reviews revealed conflicting evidence that this is the case.

Owing to a lack of available data, the model does not allow for the potential negative effects of screening. Possible negative impacts of QoL may arise from case detection (anxiety) and treatment (pain, anxiety). Similarly the model cannot allow for possible positive psychosocial effects of screening.

Value of information analysis

Bayesian VOI analysis was undertaken to determine the expected costs of decision uncertainty predicted by the model and the maximum value that can be placed on additional research aimed at reducing this uncertainty. The estimates of EVPI provide an upper bound on the value of additional research (to that provided by the model) and provide a necessary hurdle for determining the potential efficiency of further primary research. This analysis can therefore be used as the basis to inform policy decisions relating to future research priorities and study design issues in this area.

The population EVPI estimates suggest that further research in the area of oral cancer screening is likely to be of significant value. The results indicate a considerable range in the population EVPI estimates, between £8 million and £462 million. Further primary research would appear to be worthwhile given the large cost of uncertainty. Partial EVPI for individual parameters indicated that future research would be of most value directed towards obtaining more precise estimates of the malignant transformation rate. Sensitivity analyses also demonstrated that the EVPI is highly sensitive to the assumption concerning the impact of treatment on reducing the malignant transformation rate.

Conclusions

- Opportunistic high-risk screening, particularly in general dental practice, may be cost-effective. Screening by GPs was only marginally more expensive despite their lack of specific training and lower sensitivities and specificities in the oral examination. This is probably due to the higher population coverage in medical practice. Screening may more effectively be targeted to younger age groups, particularly 40–60-year-olds.
- There is considerable uncertainty in the parameters used in the model, particularly MTR and disease progression.
- Given this high uncertainty, further research is required in a number of key areas.

The relevance of this report to the National Screening Committee criteria for appraising a screening programme is given in Appendix 15.

Recommendations for further research

There is an urgent need to learn more about the natural history of oral cancer and precancer.

- Studies are needed to determine the MTRs of oral potentially malignant lesions. Results from the model suggest that the MTR and the impact of active treatment on this rate are the highest priorities for future research aimed at further defining the potential cost-effectiveness of oral cancer screening. Further information on the MTR could be collected using surveillance methods, possibly by expanding existing cancer registries. In this respect, careful analysis of cancer registries in other countries, where oral dysplastic lesions are registered, may be useful. The current estimates for the impact of

treatment on the MTR were based on estimates from a non-randomised study and there may be legitimate concerns about the potential for bias in these estimates. However, the evidence suggests that active intervention may have no greater benefit than a 'watch and wait' policy. Hence further primary research in the form of an RCT to compare the effectiveness and cost-effectiveness of active treatment (intervention) compared with surveillance ('watch and wait') may be now be justified.
- Studies are needed to determine the rates of progression of oral cancer. The model revealed considerable uncertainty around estimates of disease progression from early to late stage disease. Review of the literature showed few data in this area and consultation of experts produced divergent views.
- Studies are needed on referral pathways from primary to secondary care and the possible impact on delay and stage of presentation.

There is a need to evaluate high-risk opportunistic screening in general dental practice.

- Prospective studies are needed to determine the feasibility, effectiveness and cost-effectiveness of high-risk, opportunistic screening or case-finding in general dental and medical practice. 'Options for change', the Chief Dental Officer's paper on reorganising the NHS dental fee structure, recommends a common oral health assessment for all patients, which implicitly includes an examination for oral malignant and premalignant lesions. This framework could be used to commission trial areas using demographically similar areas as controls. Determination of population-based mortality as the end-point, however, would be extremely difficult for a disease of relatively low prevalence. Consideration should be given to using yield and disease progression as end-points.
- Studies are needed to determine the sensitivities and specificities, effectiveness and cost-effectiveness of an oral examination by ancillary personnel in other healthcare settings, including, for example, dental therapists and practice nurses.

The decision model is generic and can be applied to other populations or screening scenarios.

- The decision model should be run on data obtained from sources with less heterogeneity or uncertainty in the data, for example, using data from small, carefully controlled registries, or in countries where potentially malignant lesions are also registered and monitored.
- The model should be developed to determine effectiveness and cost-effectiveness of repeat screening in the context of an ongoing screening programme.
- Simulation modelling may be used to determine the cost-effectiveness and EVPI of new screening methodologies, before committing to clinical trials. This may include, for example, the application of brush biopsy/cytology in general dental practice.

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Contribution of authors

Paul M Speight (Professor of Oral Pathology) was principal investigator and team leader, conceived and wrote the original protocol, carried out systematic reviews, supervised the acquisition of primary data, literature reviews and data analysis and was responsible for overall management of the project and prepared the final report. Stephen Palmer (Senior Research fellow) had overall responsibility and supervision of the development and construction of the computer model, supervised the input of data and data analysis, interpretation of data and model results, carried out systematic and literature reviews and co-wrote the protocol and the final report. David R Moles (Senior Clinical Lecturer) was responsible for acquisition of data and statistical analyses and systematic reviews and co-wrote the protocol and final report. Martin C Downer (Honorary Professor) was responsible for data analysis and literature reviews, carried out and supervised systematic reviews and co-wrote the protocol and final report. David H Smith (Investigator) developed and constructed the computer model and co-wrote the protocol. Martin Henriksson (Research fellow) was responsible for populating the computer model and final data analysis. Federico Augustovski (Professor of Public Health) was responsible for populating the computer model and final data analysis. All authors approved the final version of the report.

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Appendix 1

Example MEDLINE search strategy for systematic review reported in Chapter 2

MEDLINE: 1980–October 2001
Searched 3 January 2002

No.	Records	Request
1	11281	"Mouth-Neoplasms"/ all subheadings
2	1039	"Gingival-Neoplasms"/ all subheadings
3	1891	explode "Leukoplakia-Oral"/ all subheadings
4	2927	"Lip-Neoplasms"/ all subheadings or "Palatal-Neoplasms"/ all subheadings
5	3557	"Tongue-Neoplasms"/ all subheadings
6	1256	(((intra oral*) or intraoral* or intra-oral* or oral* or mucosa*) near2 (scc or squamous cell carcinoma*)) in ti,ab
7	7781	(((intra oral*) or intraoral* or intra-oral* or oral* or mouth or tongue or lip or lips or palate or palatal) near2 (cancer* or neoplas* or malignan* or carcinoma* or tumo?r* or growth* or mass or masses or lesion* or cis or premalig* or pre-malig* or (pre malig*))) in ti,ab
8	421	((gum or gums or gumline or gum-line or gum line or gingiva* or buccal mucosa or retromolar trigone) near2 (cancer* or neoplas* or malignan* or carcinoma* or tumo?r* or growth* or mass or masses or lesion* or cis or premalig* or pre-malig* or (pre malig*))) in ti,ab
9	1858	((mucosa or oropharynx or oro-pharynx or oropharyngeal or oro-pharyngeal) near2 (cancer* or neoplas* or malignan* or carcinoma* or tumo?r* or growth* or mass or masses or lesion* or cis or premalig* or pre-malig* or (pre malig*))) in ti,ab
10	15	((lingual tonsil or alveolar ridge or alveolar mucosa or uvula or buccal sulcus or labial sulcus) near2 (cancer* or neoplas* or malignan* or carcinoma* or tumo?r* or growth* or mass or masses or lesion* or cis or premalig* or pre-malig* or (pre malig*))) in ti,ab
11	1	((retromolar region or retromolar area or interdental papillae) near2 (cancer* or neoplas* or malignan* or carcinoma* or tumo?r* or growth* or mass or masses or lesion* or cis or premalig* or pre-malig* or (pre malig*))) in ti,ab
12	0	((skin vermillion border*) near2 (cancer* or neoplas* or malignan* or carcinoma* or tumo?r* or growth* or mass or masses or lesion* or cis or premalig* or pre-malig* or (pre malig*))) in ti,ab
13	0	((skin-vermillion border*) near2 (cancer* or neoplas* or malignan* or carcinoma* or tumo?r* or growth* or mass or masses or lesion* or cis or premalig* or pre-malig* or (pre malig*))) in ti,ab
14	0	((vermillion border*) near2 (cancer* or neoplas* or malignan* or carcinoma* or tumo?r* or growth* or mass or masses or lesion* or cis or premalig* or pre-malig* or (pre malig*))) in ti,ab
15	2	((lipstick border* or circumvallate papillae or tonsillar fossa or tonsillar pillar*) near2 (cancer* or neoplas* or malignan* or carcinoma* or tumo?r* or growth* or mass or masses or lesion* or cis or premalig* or pre-malig* or (pre malig*))) in ti,ab
16	650	((anterior epiglottis or tonsil or hypopharynx or hypo-pharynx or hypopharyngeal or hypo-pharyngeal) near2 (cancer* or neoplas* or malignan* or carcinoma* or tumo?r* or growth* or mass or masses or lesion* or cis or premalig* or pre-malig* or (pre malig*))) in ti,ab

No.	Records	Request
17	16	((waldeyer* ring) near2 (cancer* or neoplas* or malignan* or carcinoma* or tumo?r* or growth* or mass or masses or lesion* or cis or premalig* or pre-malig* or (pre malig*))) in ti,ab
18	12	oed in ti,ab
19	70	oral epithel* dysplasia* in ti,ab
20	142	white patch* in ti,ab
21	28	((lichen planus or submucus fibrosis or sub-mucus fibrosis or sub mucus fibrosis or keratosis) near3 (precancer*or pre-cancer* or pre cancer* or premalig* or pre-malig* or pre malig* or (potential* malig*))) in ti,ab
22	1711	((erythroplastic lesion*) or leukoplak*) in ti,ab
23	1891	explode "Leukoplakia-Oral"/ all subheadings
24	0	smoker* keratosis in ti,ab
25	23997	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24
26	659	"Diagnosis-Oral"/ all subheadings
27	723	"Tolonium-Chloride"/ all subheadings
28	4540	((dental or oral* or intraoral* or intra-oral* or intra oral*) near2 (exam* or test* or screen* or checkup* or check-up* or "check up" or "check ups")) in ti,ab
29	10339	(screening test* in ti,ab)
30	7422	((screening program*) or (screening attend*)) in ti,ab
31	247	((dental or oral* or intraoral* or intra-oral* or intra oral*) near2 screening) in ti,ab
32	39	(oral mucosa* exam* in ti,ab)
33	14963	(oral soft tissue exam* in ti,ab) or (early detect* in ti,ab)
34	21200	(mucosa* exam* in ti,ab) or (early diagnos* in ti,ab)
35	1236	(visual near2 (exam* or check*)) in ti,ab
36	4800	(toluidine blue in ti,ab) or (early identif* in ti,ab)
37	4611	(tolonium chloride in ti,ab) or (early recog* in ti,ab)
38	428	(screening service*) in ti,ab
39	67037	#26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38
40	927	#25 and #39
41	753	#40 and (LA = "ENGLISH")
42	688	#41 and (PY >= "1980")
43	581507	(letter or editorial or comment) in pt
44	661	#42 not #43
45	296136	efficacy or accurac* or accurat*
46	90879	"sensitivity and specificity" in ti,ab,mesh
47	905877	diagnosis in mesh
48	75189	radionuclide imaging in mesh
49	249146	diagnostic use in mesh
50	346362	specificity in ti,ab,mesh
51	63984	((predictive near5 value*) in ti,ab,mesh) or ((prognos* near5 value*) in ti,ab)
52	1898	diagnostic yield*
53	9380	"False-Negative-Reactions"
54	13012	"False-Positive-Reactions"
55	4668	"ROC-Curve"
56	281135	sensitivity in ti,ab,mesh
57	7716	test* perform* in ti,ab
58	356	screen* perform* in ti,ab
59	814	diagnos* efficac* in ti,ab
60	842	diagnos* efficien* in ti,ab
61	880	diagnos* effective* in ti,ab
62	16247	false positive in ti,ab
63	1749	true positive in ti,ab
64	10292	false negative in ti,ab

No.	Records	Request
65	860	true negative in ti,ab
66	31585	compliance in ti,ab
67	64115	"Reproducibility-of-Results" in MIME,MJME
68	33741	validity in ti,ab
69	57051	agreement in ti,ab
70	18365	population stud* in ti,ab
71	1908488	#45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62 or #63 or #64 or #65 or #66 or #67 or #68 or #69 or #70
72	2645688	animal in tg
73	6206484	human in tg
74	2043663	#72 not (#72 and #73)
75	1617412	#71 not #74
76	**343**	**#44 and #75**

Appendix 2

Study selection form for systematic review reported in Chapter 2

Study selection exercise

Reviewer:

Title (abbreviated if appropriate):

First author:

Title of journal or other work:

Year of publication:

Review code number:

	Yes	No
Is the investigation a prospective, clinical field study?	❑	❑
Are the criteria for a positive screen defined?	❑	❑
Is there a defined gold standard?	❑	❑
Is the gold standard applied to at least a proportion of negatives?	❑	❑
Is it possible to derive a full 2×2 contingency table from the data?	❑	❑
Is this the most current primary report of this investigation?	❑	❑

Please tick the presumed correct response. A negative response to any of the above six questions excludes the study from the review if a majority of reviewers are in agreement.

Appendix 3

Example of data extraction form for studies included in the systematic review reported in Chapter 2

General information	
Identification features of study	
Author(s), reference number	Downer *et al.*[13]
Journal, year, volume, page numbers	*Community Dent Oral Epidemiol* 1995, 23, 84–8
Notes	–
Specific information	
Population characteristics	
Target population	Commercial company headquarters staff
Country	England
Locality	London
Characteristics of participants	
Age	≥ 40 years
Gender	M and F
Socio-economic status	Managerial 72.6%, clerical/secretarial 21.6%, service 5.8%
Ethnicity	Mostly indigenous British
Health status	Assumed disease free
Occupation/industry	Employees in a company headquarters
Drinkers? (%)	Proportion not specified
Smokers? (%)	Proportion not specified
Smokers and drinkers (%)	Proportion not specified
Tobacco chewers? (%)	Not recorded
Characteristics of study	
Target lesions	Yes
Specified? Yes/no	Carcinoma, leukoplakia, erythroplakia, lichen planus, lupus erythematosus,
If yes, list the lesions	submucous fibrosis, actinic keratosis
Definitive programme or pilot?	Pilot
Recruitment procedure	
Invitational, opportunistic, case-finding?	Invitational
Screeners	
Category of personnel (number)	General dental practitioners (2)
Specific training? (yes, no, unreported)	No
Calibration? (yes, no, unreported)	No
Gold standard examiners	
Category of personnel (number)	Oral medicine specialist (1)
Verification [complete, partial (%)]	Complete
Screening setting	Company dental surgery
Reference examination setting	Adjacent company dental surgery
Test results blind? (yes, no, unreported)	Yes
Diagnostic aids? (type of aid or none)	No

Results

Two-by-two contingency table

Target disorder test	Lesion present	Lesion absent	Total
Positive	12	2	14
	a	*b*	*a*+*b*
Negative	5	290	295
	c	*d*	*c*+*d*
Total	17	292	309
	a + *b*	*b* + *d*	*a* + *b* + *c* + *d*

Result summary

Number contacted (*N*)	570
Number screened (*n*)	309
Uptake (%)	54.21
Lesion prevalence (% of *n*) = (*a* + *c*)/(*a* + *b* + *c* + *d*)	5.50
Sn = *a*/(*a* + *c*)	0.71
Sp = *d*/(*b* + *d*)	0.99
PPV = *a*/(*a* + *b*)	0.86
NPV = *d*/(*c* + *d*)	0.98
Likelihood ratio (positive) = Sn/(1 – Sp)	71.00
Likelihood ratio (negative) = (1 – Sn)/Sp	0.29

Appendix 4

Example MEDLINE search strategy for systematic review reported in Chapter 3

Effectiveness of oral cancer screening
Third draft: medq1a3.his
MEDLINE: 1990–October 2001
Searched 4 December 2001
Strategy with (oral + screen*)

No.	Records	Request
1	6065	"Mouth-Neoplasms"/ all subheadings
2	521	"Gingival-Neoplasms"/ all subheadings
3	1035	explode "Leukoplakia-Oral"/ all subheadings
4	1237	"Lip-Neoplasms"/ all subheadings or "Palatal-Neoplasms"/ all subheadings
5	1800	"Tongue-Neoplasms"/ all subheadings
6	1204	(((intra oral*) or intraoral* or intra-oral* or oral* or mucosa*) near2 (scc or squamous cell carcinoma*)) in ti,ab
7	5302	(((intra oral*) or intraoral* or intra-oral* or oral* or mouth or tongue or lip or lips or palate or palatal) near2 (cancer* or neoplas* or malignan* or carcinoma* or tumo?r* or growth* or mass or masses or lesion* or cis or premalig* or pre-malig* or (pre malig*))) in ti,ab
8	257	((gum or gums or gumline or gum-line or gum line or gingiva* or buccal mucosa or retromolar trigone) near2 (cancer* or neoplas* or malignan* or carcinoma* or tumo?r* or growth* or mass or masses or lesion* or cis or premalig* or pre-malig* or (pre malig*))) in ti,ab
9	1362	((mucosa or oropharynx or oro-pharynx or oropharyngeal or oro-pharyngeal) near2 (cancer* or neoplas* or malignan* or carcinoma* or tumo?r* or growth* or mass or masses or lesion* or cis or premalig* or pre-malig* or (pre malig*))) in ti,ab
10	12	((lingual tonsil or alveolar ridge or alveolar mucosa or uvula or buccal sulcus or labial sulcus) near2 (cancer* or neoplas* or malignan* or carcinoma* or tumo?r* or growth* or mass or masses or lesion* or cis or premalig* or pre-malig* or (pre malig*))) in ti,ab
11	1	((retromolar region or retromolar area or interdental papillae) near2 (cancer* or neoplas* or malignan* or carcinoma* or tumo?r* or growth* or mass or masses or lesion* or cis or premalig* or pre-malig* or (pre malig*))) in ti,ab
12	0	((skin vermillion border*) near2 (cancer* or neoplas* or malignan* or carcinoma* or tumo?r* or growth* or mass or masses or lesion* or cis or premalig* or pre-malig* or (pre malig*))) in ti,ab
13	0	((skin-vermillion border*) near2 (cancer* or neoplas* or malignan* or carcinoma* or tumo?r* or growth* or mass or masses or lesion* or cis or premalig* or pre-malig* or (pre malig*))) in ti,ab
14	0	((vermillion border*) near2 (cancer* or neoplas* or malignan* or carcinoma* or tumo?r* or growth* or mass or masses or lesion* or cis or premalig* or pre-malig* or (pre malig*))) in ti,ab
15	2	((lipstick border* or circumvallate papillae or tonsillar fossa or tonsillar pillar*) near2 (cancer* or neoplas* or malignan* or carcinoma* or tumo?r* or growth* or mass or masses or lesion* or cis or premalig* or pre-malig* or (pre malig*))) in ti,ab

No.	Records	Request
16	480	((anterior epiglottis or tonsil or hypopharynx or hypo-pharynx or hypopharyngeal or hypo-pharyngeal) near2 (cancer* or neoplas* or malignan* or carcinoma* or tumo?r* or growth* or mass or masses or lesion* or cis or premalig* or pre-malig* or (pre malig*))) in ti,ab
17	8	((waldeyer* ring) near2 (cancer* or neoplas* or malignan* or carcinoma* or tumo?r* or growth* or mass or masses or lesion* or cis or premalig* or pre-malig* or (pre malig*))) in ti,ab
18	12	oed in ti,ab
19	78	oral epithel* dysplasia* in ti,ab
20	107	white patch* in ti,ab
21	25	((lichen planus or submucus fibrosis or sub-mucus fibrosis or sub mucus fibrosis or keratosis) near3 (precancer*or pre-cancer* or pre cancer* or premalig* or pre-malig* or pre malig* or (potential* malig*))) in ti,ab
22	1040	((erythroplastic lesion*) or leukoplak*) in ti,ab
23	1035	explode "Leukoplakia-Oral"/ all subheadings
24	0	smoker* keratosis in ti,ab
25	13501	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24
26	429	"Diagnosis-Oral"/ all subheadings
27	401	"Tolonium-Chloride"/ all subheadings
28	3116	((dental or oral* or intraoral* or intra-oral* or intra oral*) near2 (exam* or test* or screen* or checkup* or check-up* or "check up" or "check ups")) in ti,ab
29	6869	(screening test* in ti,ab)
30	5736	((screening program*) or (screening attend*)) in ti,ab
31	194	((dental or oral* or intraoral* or intra-oral* or intra oral*) near2 screening) in ti,ab
32	22	(oral mucosa* exam* in ti,ab)
33	10767	(oral soft tissue exam* in ti,ab) or (early detect* in ti,ab)
34	13495	(mucosa* exam* in ti,ab) or (early diagnos* in ti,ab)
35	880	(visual near2 (exam* or check*)) in ti,ab
36	3433	(toluidine blue in ti,ab) or (early identif* in ti,ab)
37	2855	(tolonium chloride in ti,ab) or (early recog* in ti,ab)
38	371	(screening service*) in ti,ab
39	45449	#26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38
40	671	#25 and #39
41	585	#40 and (LA = "ENGLISH")
42	585	#41 and (PY >= "1980")
43	410474	(letter or editorial or comment) in pt
44	**559**	**#42 not #43**

Appendix 5

Excluded studies for systematic review reported in Chapter 3, with reasons

Reference	Reasons
WHO. control of oral cancer in developing countries, WHO meeting. *Bull World Health Organ* 1984;**62**:817–30.	No outcome (review) No data
Abd Jalil N. Oral precancer cancer screening project in Kota Belud, Sabah. *J Dent Res* 1999;**78**:1180.	No outcomes No data
Ahluwalia KP, Yellowitz JA, Goodman HS, Horowitz AM. An assessment of oral cancer prevention curricula in U.S. medical schools. *J Cancer Educ* 1998;**13**:90–5.	No outcomes
Arbes SJ, Slade GD. Racial differences in stage at diagnosis of screenable oral cancers in North Carolina. *J Public Health Dent* 1996;**56**:352–4.	No outcomes
Arotiba JT, Obiechina AE, Fasola OA, Fawole OI, Ajagbe HA. Oral squamous cell carcinoma: a review of 246 Nigerian cases. *Afr J Med Med Sci* 1999;**28**:141–4.	No outcomes
Banoczy J, Rigo O. Prevalence study of oral precancerous lesions within a complex screening system in Hungary. *Community Dent Oral Epidemiol* 1991;**19**:265–7.	No outcomes
Burzynski NJ, Firriolo FJ, Butters JM, Sorrell CL. Evaluation of oral cancer screening. *J Cancer Educ* 1997;**12**:95–9.	No outcomes
Chiodo GT, Eigner T, Rosenstein DI. Oral cancer detection. The importance of routine screening for prolongation of survival. *Postgrad Med*1986;**80**:231–6.	No outcomes No data
Clayman GL, Chamberlain RM, Lee JJ, Lippman SM, Hong WK. Screening at a health fair to identify subjects for an oral leukoplakia chemoprevention trial. *J Cancer Educ* 1995;**10**:88–90.	No data No outcomes
Cowan CG, Gregg TA, Napier SS, McKenna SM, Kee F. Potentially malignant oral lesions in northern Ireland: a 20-year population-based perspective of malignant transformation. *Oral Dis* 2001;**7**:18–24.	No outcomes
Denton DW, Reed LE. Oral cancer in primary care: reducing mortality through early recognition and prompt referral … recertification series. *Physician Assistant* 1998;**22**:36–59	No outcomes No data (review)
Dombi C, Voros Balog T, Czegledy A, Hermann P, Vincze N, Banoczy J. Risk group assessment of oral precancer attached to X-ray lung-screening examinations. *Community Dent Oral Epidemiol* 2001;**29**:9–13.	No outcomes
Downer MC, Jullien JA, Speight PM. An interim determination of health gain from oral cancer and precancer screening: 2. Developing a model of population screening. *Community Dent Health* 1997;**14**:227–32.	No outcomes
Downer MC, Jullien JA, Speight PM. An interim determination of health gain from oral cancer and precancer screening: 3. Preselecting high risk individuals. *Community Dent Health* 1998;**15**:72–6.	No outcomes
Eddy DM. Secondary prevention of cancer: an overview. *Bull World Health Organ* 1986;**64**:421–429.	No data No outcomes
Elwood JM, Gallagher RP. Factors influencing early diagnosis of cancer of the oral cavity. *CMAJ* 1985;**133**:651–6.	No data No outcomes
Epstein JB, Oakley C, Millner A, Emerton S, van der Meij E, Le N. The utility of toluidine blue application as a diagnostic aid in patients previously treated for upper oropharyngeal carcinoma. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1997;**83**:537–47.	No outcomes

continued

Reference	Reasons
Feaver GP. Oral squamous-cell carcinoma – results of screening are encouraging. *BMJ* 1994;**308**:1103.	No data No outcomes
Freije J, Kumar JV. Prevention of cancers of oral cavity and pharynx in New York State. *N Y State Dent J* 2001;**67**:26–30.	No data No outcomes
Gray M, Gold L, Burls, A, Elley K. *The effectiveness of toluidine blue dye as an adjunct to oral cancer screening in general dental practice*. 0704421755. DPHE Report No. 24. Birmingham: Department of Public Health and Epidemiology, University of Birmingham; 2000 (Collaborative effort with Wessex Institute). New Zealand Health Technology Assessment (NZHTA).	No data No outcomes
Gronbaek M, Becker U, Johansen D, Tonnesen H, Jensen G, Sorensen TIA. Population based cohort study of the association between alcohol intake and cancer of the upper digestive tract. *BMJ* 1998;**317**:844–7.	No outcomes
Hawkins RJ, Wang EE, Leake JL. Preventive health care, 1999 update: prevention of oral cancer mortality. The Canadian Task Force on Preventive Health Care. *J Can Dent Assoc* 1999;**65**:617.	No data No outcomes
Hollows P, McAndrew PG, Perini MG. Delays in the referral and treatment of oral squamous cell carcinoma. *Br Dent J* 2000;**188**:262–5.	No outcomes
Horiuchi M, Makuuchi H, Machimura T, Tamura Y, Sakai M. Survival benefit of screening for early esophageal carcinoma in head and neck cancer patients. *Dig Endosc* 1998:110–15.	Not oral cancer
Horowitz AM, Nourjah PA. Factors associated with having oral cancer examinations among US adults 40 years of age or older. *J Public Health Dent* 1996;**56**:331–5.	No outcomes
Horowitz AM, Drury TF, Goodman HS, Yellowitz JA. Oral pharyngeal cancer prevention and early detection. Dentists' opinions and practices. *J Am Dent Assoc* 2000;**131**:453–62.	No outcomes
Horowitz AM, Drury TF, Canto MT. Practices of Maryland dentists: oral cancer prevention and early detection – baseline data from 1995. *Oral Dis* 2000;**6**:282–8.	No outcomes
Horowitz AM, Siriphant P, Sheikh A, Child WL. Perspectives of Maryland dentists on oral cancer. *J Am Dent Assoc* 2001;**132**:65–72.	No outcomes
Humphris GM, Ireland RS, Field EA. Randomised trial of the psychological effect of information about oral cancer in primary care settings. *Oral Oncol* 2001;**37**:548–52.	No outcomes
Ildstad ST, Tollerud DJ, Bigelow ME, Remensnyder JP. A multivariate analysis of determinants of survival for patients with squamous cell carcinoma of the head and neck. *Ann Surg* 1989;**209**:237–41.	No outcomes
Jorge Junior J, de Almeida OP, Bozzo L, Scully C, Graner E. Oral mucosal health and disease in institutionalized elderly in Brazil. *Community Dent Oral Epidemiol* 1991;**19**:173–5.	No outcomes
Jullien JA. *Evaluation of aspects of screening for oral cancer*. London: University of London; 1996.	Data reported elsewhere (PhD thesis)
Kovac Kovacic M, Skaleric U. The prevalence of oral mucosal lesions in a population in Ljubljana, Slovenia. *J Oral Pathol Med* 2000;**29**:331–5.	No outcomes
Martin IC, Kerawala CJ, Reed M. The application of toluidine blue as a diagnostic adjunct in the detection of epithelial dysplasia. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 1998;**85**:444–6.	No outcomes
Martin LM, Bouquot JE, Wingo PA, Heath CW. Cancer prevention in the dental practice: oral cancer screening and tobacco cessation advice. *J Public Health Dent* 1996;**56**:336–40.	No outcomes
Mashberg A. Final evaluation of tolonium chloride rinse for screening of high-risk patients with asymptomatic squamous carcinoma. *J Am Dent Assoc* 1983;**106**:319–23.	No outcomes

continued

Reference	Reasons
Mashberg A, Barsa P. Screening for oral and oropharyngeal squamous carcinomas. *CA Cancer J Clin* 1984;**34**:262–8.	No outcomes No data
Mashberg A, Feldman LJ. Clinical criteria for identifying early oral and oropharyngeal carcinoma: erythroplasia revisited. *Am J Surg* 1988;**156**:273–5.	No outcomes No data
McCunniff MD, Barker GJ, Barker BE, Williams K. Health professionals' baseline knowledge of oral/pharyngeal cancers. *J Cancer Educ* 2000;**15**:79–81.	No outcomes
Miller AB. An epidemiological perspective on cancer screening. *Clin Biochem* 1995;**28**:41–8.	Not oral cancer
Nair MK, Varghese C, Mathew B, Sankaranarayanan R. Prevention and early detection of oral, breast and cervical cancers: a practical approach in Indian context. *J Indian Med Assoc* 1993;**91**:94–6.	No data No outcomes
Onofre MA, Sposto MR, Navarro CM. Reliability of toluidine blue application in the detection of oral epithelial dysplasia and in situ and invasive squamous cell carcinomas. *Oral Surg Oral Med Oral Pathol Oral Rad Endod* 2001;**91**:535–40.	No outcomes
Pearson N, Croucher R, Marcenes W, O'Farrell M. Dental service use and the implications for oral cancer screening in a sample of Bangladeshi adult medical care users living in Tower Hamlets, UK. *Br Dent J* 1999;**186**:517–21.	No outcomes
Petit T, Georges C, Jung GM, *et al*. Systematic esophageal endoscopy screening in patients previously treated for head and neck squamous-cell carcinoma. *Ann Oncol* 2001;**12**:643–6.	No data No outcomes
Prorok PC, Chamberlain J, Day NE, Hakama M, Miller AB. UICC Workshop on the evaluation of screening programmes for cancer. *Int J Cancer* 1984;**34**:1–4.	No data No outcomes
Rajkumar R, Sankaranarayanan R, Esmi A, Jayaraman R, Cherian J, Parkin DM. Leads to cancer control based on cancer patterns in a rural population in South India. *Cancer Causes Control* 2000;**11**:433–9.	No outcomes
Reichart PA. Oral mucosal lesions in a representative cross-sectional study of aging Germans. *Community Dent Oral Epidemiol* 2000;**28**:390–8.	No outcomes
Sankaranarayanan R, Nair MK, Mathew B, Balaram P, Sebastian P, Dutt SC. Recent results of oral cancer research in Kerala, India. *Head Neck* 1992;**14**:107–12.	No data No outcomes
Sankaranarayanan R. Health care auxiliaries in the detection and prevention of oral cancer. *Oral Oncol* 1997;**33**:149–54.	No data No outcomes
Sankaranarayanan R. Integration of cost-effective early detection programs into the health services of developing countries. *Cancer* 2000;**89**:475–81.	No data No outcomes
Satyanarayana G. Profile of a cancer detection camp. *J Indian Med Assoc* 1991;**89**:3–6.	No outcomes
Seoane J, Varela Centelles PI, Gonzalez Reforma N, Aguado A, Esparza G. Assessment of dental students' ability to recognise precancerous lesions and conditions. *Eur J Dent Educ* 1997;**1**:172–5.	No outcomes
Speight PM, Downer MC, Zakrzewska J. Screening for oral cancer and precancer. *Community Dent Health* 1993;Suppl 1: 1–79.	No data No outcomes
Stjernsward J, Stanley K, Eddy D, *et al*. National cancer control programs and setting priorities. *Cancer Detect Prev* 1986;**9**:113–24.	No data No outcomes
Succo G, Beatrice F, Giordano C, Sorrentino R, Pecorari G, Sartoris A. Early detection of oral cavity cancer: Identification of high risk groups. *Med Sci Res* 1990;**18**:25–6.	No outcomes
Syme SE, Drury TF, Horowitz AM. Maryland dental hygienists' knowledge and opinions of oral cancer risk factors and diagnostic procedures. *Oral Dis* 2001;**7**:177–84.	No outcomes
Warnakulasuriya KA, Johnson NW. Dentists and oral cancer prevention in the UK: opinions, attitudes and practices to screening for mucosal lesions and to counselling patients on tobacco and alcohol use: baseline data from 1991. *Oral Dis* 1999;**5**:10–14.	No outcomes

continued

Reference	Reasons
Woodward L, Charlton A. The BMA TP Gunton Award 1995: development of a health education leaflet to promote early detection of oral cancer. *Int J Health Promot Educ* 1999;**37**:5–10.	No outcomes
Yellowitz J, Horowitz AM, Goodman HS, Canto MT, Farooq NS. Knowledge, opinions and practices of general dentists regarding oral cancer: a pilot survey. *J Am Dent Assoc* 1998;**129**:579–83.	No outcomes
Yellowitz JA, Goodman HS, Farooq NS. Knowledge, opinions, and practices related to oral cancer: results of three elderly racial groups. *Spec Care Dentist* 1997;**17**:100–4.	No outcomes
Yellowitz JA, Horowitz AM, Drury TF, Goodman HS. Survey of U.S. dentists' knowledge and opinions about oral pharyngeal cancer. *J Am Dent Assoc* 2000;**131**:653–61.	No outcomes
Yokoyama A, Ohmori T, Makuuchi H, *et al*. Successful screening for early esophageal cancer in alcoholics using endoscopy and mucosa iodine staining. *Cancer* 1995;**76**:928–934.	No outcomes Not oral cancer

Appendix 6

Proforma for collection of treatment episodes for calculation of costs (Chapter 4)

Surname

Forename

Date of verification

D	D	-	M	M	-	Y	Y
		-			-		

Hospital number

1	
2	
3	

Hospital name

Address

Post code

Date of birth

D	D	-	M	M	-	Y	Y
		-			-		

Gender

F	M

Data source

Disease stage:

1. Pre-cancer lesions ( )
2. Stage I ( )
3. Stage II ( )
4. Stage III ( )
5. Stage IV ( )

Smoking:

1. Yes ( ) 1.a How many cigarettes? _____
2. No ( )

Alcohol:

1. Yes ( ) 2. No ( )

INPATIENT HOSPITALIZATION SUMMARY

No. of admissions : _____

First admission
Specialty

Date of admission D D - M M - Y Y

Date of discharge D D - M M - Y Y

Did she/he stay on ICU?
Yes 1 ( ) How many days?_____
No 0

Second admission
Specialty

Date of admission D D - M M - Y Y

Date of discharge D D - M M - Y Y

Did she/he stay on ICU?
Yes 1 ( ) How many days?_____
No 0 ( )

INPATIENT HOSPITALIZATION SUMMARY

Third admission
Specialty

Date of admission D D - M M - Y Y

Date of discharge D D - M M - Y Y

Did she/he stay on ICU?
Yes 1 ( ) How many days?_____
No 0 ( )

Fourth admission
Specialty

Date of admission D D - M M - Y Y

Date of discharge D D - M M - Y Y

Did she/he stay on ICU?
Yes 1 ( )
No 0 ( )

How many days?_____

OUTPATIENT ATTENDANCE SUMMARY

No	Hospital	Specialty	Date attended D D - M M - Y Y
1			
2			
3			
4			
5			
6			
7			
8			

DAY CARE ATTENDANCE SUMMARY

No	Specialty	Date attended D D - M M - Y Y
1		
2		
3		
4		
5		
6		
7		
8		
9		

DIAGNOSTIC TEST

Name of the Test	Test No	Date of the Test (D D - M M - Y Y)
PET	1	
	2	
	3	
	4	
	5	

Name of the Test	Test No	Date of the Test (D D - M M - Y Y)
CT SCAN	1	
	2	
	3	
	4	
	5	

Name of the Test	Test No	Date of the Test (D D - M M - Y Y)
MRI	1	
	2	
	3	
	4	
	5	

☐

Name of the Test	Test No	Date of the Test (D D - M M - Y Y)
INTRAORAL ULTRASONOGRAPHY	1	
	2	
	3	
	4	
	5	

Name of the Test	Test No	Type of the examination	Date of the Test (D D - M M - Y Y)
PATHOLOGY	1		
	2		
	3		
	4		
	5		

Name of the Test	Test No	Date of the Test (D D - M M - Y Y)
OTHER CATEGORIES	1	
	2	
	3	
	4	
	5	

RADIOTHERAPY

Numbers of sessions _____

Date of started D D - M M - Y Y

Date of completed D D - M M - Y Y

Frequency and regime

CHEMOTHERAPY

Numbers of sessions_____

Date of started D D - M M - Y Y

Date of completed D D - M M - Y Y

Frequency and regime

Type of drug

PHOTODYNAMIC THERAPY

No	Drug and regime	Date of procedure
		D D - M M - Y Y
1		- -
2		- -
3		- -
4		- -

SURGICAL PROCEDURES

No	Type of procedure	Inpatient/ outpatient	OPCS code	Date
				D D - M M - Y Y
1				- -
2				- -
3				- -
4				- -
5				- -

PROSTHESES

Procedure

1. **Fixed prostheses ( )**
2. **Over-denture prostheses ( )**
3. **Obturator ( )**

No	Type of procedure	Date of procedure D D - M M - Y Y
1		- -
2		- -
3		- -
4		- -

Appendix 7

Search strategy for cost-effectiveness analyses (Chapter 5)

No.	Records	Request
1	11172	"Mouth-Neoplasms"/ all subheadings
2	1030	"Gingival-Neoplasms"/ all subheadings
3	1876	explode "Leukoplakia-Oral"/ all subheadings
4	2914	"Lip-Neoplasms"/ all subheadings or "Palatal-Neoplasms"/ all subheadings
5	3530	"Tongue-Neoplasms"/ all subheadings
6	1229	(((intra oral*) or intraoral* or intra-oral* or oral* or mucosa*) near2 (scc or squamous cell carcinoma*)) in ti,ab
7	7693	(((intra oral*) or intraoral* or intra-oral* or oral* or mouth or tongue or lip or lips or palate or palatal) near2 (cancer* or neoplas* or malignan* or carcinoma* or tumo?r* or growth* or mass or masses or lesion* or cis or premalig* or pre-malig* or (pre malig*))) in ti,ab
8	409	((gum or gums or gumline or gum-line or gum line or gingiva* or buccal mucosa or retromolar trigone) near2 (cancer* or neoplas* or malignan* or carcinoma* or tumo?r* or growth* or mass or masses or lesion* or cis or premalig* or pre-malig* or (pre malig*))) in ti,ab
9	1830	((mucosa or oropharynx or oro-pharynx or oropharyngeal or oro-pharyngeal) near2 (cancer* or neoplas* or malignan* or carcinoma* or tumo?r* or growth* or mass or masses or lesion* or cis or premalig* or pre-malig* or (pre malig*))) in ti,ab
10	15	((lingual tonsil or alveolar ridge or alveolar mucosa or uvula or buccal sulcus or labial sulcus) near2 (cancer* or neoplas* or malignan* or carcinoma* or tumo?r* or growth* or mass or masses or lesion* or cis or premalig* or pre-malig* or (pre malig*))) in ti,ab
11	1	((retromolar region or retromolar area or interdental papillae) near2 (cancer* or neoplas* or malignan* or carcinoma* or tumo?r* or growth* or mass or masses or lesion* or cis or premalig* or pre-malig* or (pre malig*))) in ti,ab
12	0	((skin vermillion border*) near2 (cancer* or neoplas* or malignan* or carcinoma* or tumo?r* or growth* or mass or masses or lesion* or cis or premalig* or pre-malig* or (pre malig*))) in ti,ab
13	0	((skin-vermillion border*) near2 (cancer* or neoplas* or malignan* or carcinoma* or tumo?r* or growth* or mass or masses or lesion* or cis or premalig* or pre-malig* or (pre malig*))) in ti,ab
14	0	((vermillion border*) near2 (cancer* or neoplas* or malignan* or carcinoma* or tumo?r* or growth* or mass or masses or lesion* or cis or premalig* or pre-malig* or (pre malig*))) in ti,ab
15	2	((lipstick border* or circumvallate papillae or tonsillar fossa or tonsillar pillar*) near2 (cancer* or neoplas* or malignan* or carcinoma* or tumo?r* or growth* or mass or masses or lesion* or cis or premalig* or pre-malig* or (pre malig*))) in ti,ab
16	633	((anterior epiglottis or tonsil or hypopharynx or hypo-pharynx or hypopharyngeal or hypo-pharyngeal) near2 (cancer* or neoplas* or malignan* or carcinoma* or tumo?r* or growth* or mass or masses or lesion* or cis or premalig* or pre-malig* or (pre malig*))) in ti,ab
17	16	((waldeyer* ring) near2 (cancer* or neoplas* or malignan* or carcinoma* or tumo?r* or growth* or mass or masses or lesion* or cis or premalig* or pre-malig* or (pre malig*))) in ti,ab

No.	Records	Request
18	11	oed in ti,ab
19	69	oral epithel* dysplasia* in ti,ab
20	139	white patch* in ti,ab
21	28	((lichen planus or submucus fibrosis or sub-mucus fibrosis or sub mucus fibrosis or keratosis) near3 (precancer*or pre-cancer* or pre cancer* or premalig* or pre-malig* or pre malig* or (potential* malig*))) in ti,ab
22	1694	((erythroplastic lesion*) or leukoplak*) in ti,ab
23	1876	explode "Leukoplakia-Oral"/ all subheadings
24	0	smoker* keratosis in ti,ab
25	23766	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24
26	654	"Diagnosis-Oral"/ all subheadings
27	714	"Tolonium-Chloride"/ all subheadings
28	4213	((dental or oral* or intraoral* or intra-oral* or intra oral*) near2 (exam* or test* or checkup* or check-up* or "check up" or "check ups")) in ti,ab
29	145678	(testing program* in ti,ab) or screen* in ti,ab
30	7325	((screening program*) or (screening attend*)) in ti,ab
31	830615	(screening service* in ti,ab) or (test* in ti,ab) or (preventative health* in ti,ab)
32	241	((dental or oral* or intraoral* or intra-oral* or intra oral*) near2 screening) in ti,ab
33	3394	(oral mucosa* exam* in ti,ab) or (secondary prevention in ti,ab)
34	14792	(oral soft tissue exam* in ti,ab) or (early detect* in ti,ab)
35	20946	(mucosa* exam* in ti,ab) or (early diagnos* in ti,ab)
36	2658	((visual near2 (exam* or check*)) in ti,ab) or (preventive health* in ti,ab)
37	4731	(toluidine blue in ti,ab) or (early identif* in ti,ab)
38	4561	(tolonium chloride in ti,ab) or (early recog* in ti,ab)
39	972482	#26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 or #36 or #37 or #38
40	2232	#25 and #39
41	2046	#40 and (PY >= "1980")
42	1716	#41 and (LA = "ENGLISH")
43	432747	letter in pt
44	126251	editorial in pt
45	174472	comment in pt
46	575296	#43 or #44 or #45
47	1684	#42 not #46
48	6783	"Economics"/ all subheadings
49	85104	explode "Costs-and-Cost-Analysis"/ all subheadings
50	862	"Economic-Value-of-Life" in MIME,MJME
51	9441	explode "Economics-Hospital"/ all subheadings
52	1752	explode "Economics-Dental"/ all subheadings
53	5676	explode "Economics-Medical"/ all subheadings
54	2569	"Economics-Nursing"/ all subheadings
55	804	"Economics-Pharmaceutical"/ all subheadings
56	7003	explode "Budgets"/ all subheadings
57	150363	(cost or costs or costly or costed or costing or budget*) in ti,ab,mesh
58	196979	(econom* or pharmacoeconom* or pharmaco-econom* or price* or pricing) in ti,ab,mesh
59	265	(value near5 money) in ti,ab,mesh
60	11918	(expenditure* not energy) in ti,ab,mesh
61	270550	#48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60
62	**56**	**#47 and #61**

Appendix 8

Details of quality assessment for economic studies (Chapter 5)

All items are graded as either 'yes' (item adequately addressed), 'no' (item not adequately addressed), '?' (unclear or not enough information), NA (not applicable) or NS (not stated).

Study question	Answer	Comments
1. Costs and effects examined	Yes	
2. Alternatives compared	Yes	
3. The viewpoint(s)/perspective of the analysis is clearly stated (e.g. NHS, society)	No	
Selection of alternatives		
4. All relevant alternatives are compared (including do nothing if applicable)	No	No consideration of screening high-risk patients only or screening conducted by other practitioners
5. The alternatives being compared are clearly described (who did what, to whom, where and how often)	No	Unclear whether the strategies considered were based on opportunistic approaches or via a formal invitation
6. The rationale for choosing the alternative programmes or interventions compared is stated	No	
Form of evaluation		
7. The choice of form of economic evaluation is justified in relation to the questions addressed	Yes	
8. If a cost-minimisation design is chosen, have equivalent outcomes been adequately demonstrated?	NA	
Effectiveness data		
9. The source(s) of effectiveness estimates used are stated (e.g. single study, selection of studies, systematic review, expert opinion)	No	The sources for a number of key parameters are not explicitly stated
10. Effectiveness data from RCT or review of RCTs	No	
11. Potential biases identified (especially if data not from RCTs)	No	
12. Details of the method of synthesis or meta-analysis of estimates are given (if based on an overview of a number of effectiveness studies)	No	No synthesis undertaken
Costs		
13. All the important and relevant resource use included	?	Source of cost data for cancer treatment are not specified
14. All the important and relevant resource use measured accurately (with methodology)	?	No details of the resource use assigned for cancer are presented
15. Appropriate unit costs estimated (with methodology)	?	Insufficient details provided
16. Unit costs reported separately from resource use data	No	
17. Productivity costs treated separately from other costs	NA	
18. The year and country to which unit costs apply is stated with appropriate adjustments for inflation and/or currency conversion	No	

continued

Study question	Answer	Comments
Benefit measurement and valuation		
19. The primary outcome measure(s) for the economic evaluation are clearly stated (cases detected, life years, QALYs, etc.)	Yes	
20. Methods to value health states and other benefits are stated (e.g. time trade-off)	NA	
21. Details of the individuals from whom valuations were obtained are given (patients, members of the public, healthcare professionals, etc.)	NA	
Decision modelling		
22. Details of any decision model used are given (e.g. decision tree, Markov model)	Yes	
23. The choice of model used and the key input parameters on which it is based are adequately detailed and justified	No	Only limited justification for a range of parameters is provided
24. All model outputs described adequately	No	Only limited details for one of the screening strategies are reported
Discounting		
25. Discount rate used for both costs and benefits	No	
26. Do discount rates accord with NHS guidance?	No	No discounting applied
Allowance for uncertainty		
Stochastic analysis of patient-level data		
27. Details of statistical tests and CIs are given for stochastic data	NA	
28. Uncertainty around cost-effectiveness expressed (e.g. CI around ICER, CEACs	NA	
29. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data)	NA	A limited range of parameters are included in a sensitivity analysis
Stochastic analysis of decision models		
30. Are all appropriate input parameters included with uncertainty?	NA	
31. Is second-order uncertainty (uncertainty in means) included rather than first-order (uncertainty between patients)?	NA	
32. Are the probability distributions adequately detailed and appropriate?	NA	
33. Sensitivity analysis used to assess uncertainty in non-stochastic variables (e.g. unit costs, discount rates) and analytic decisions (e.g. methods to handle missing data)	NA	
Deterministic analysis		
34. The approach to sensitivity analysis is given (univariate, threshold analysis, etc)	No	
35. The choice of variables for sensitivity analysis is justified	No	
36. The ranges over which the variables are varied are stated	No	
Presentation of results		
37. Incremental analysis is reported using appropriate decision rules	No	
38. Major outcomes are presented in a disaggregated as well as aggregated form	Yes	
39. Applicable to the NHS setting	?	Not clear owing to lack of transparency in a number of key parameters

Appendix 9

Results of survival analyses (Chapter 6)

Weibull regression results

Weibull regression – log relative hazard form

No. of subjects = 5840
No. of observations = 5840
No. of failures = 4295
Time at risk = 25331.73173
LR $\chi^2(8)$ = 910.91
Log likelihood = –10112.57
Probability > χ^2 = 0.0000

_t |	Coeff.	SE	z	p > |z|	95% CI	
_lage_10_2 |	0.2009864	0.066105	3.04	0.002	0.0714229	0.3305498
_lage_10_3 |	0.3385861	0.0627858	5.39	0.000	0.2155281	0.461644
_lage_10_4 |	0.7075981	0.0625167	11.32	0.000	0.5850676	0.8301287
_lage_10_5 |	1.118652	0.0679869	16.45	0.000	0.9854	1.251904
sex |	–0.1895643	0.0322141	–5.88	0.000	–0.2527028	–0.1264259
_lstage_2 |	0.5386838	0.0389727	13.82	0.000	0.4622987	0.615069
_lstage_3 |	0.7030153	0.0385593	18.23	0.000	0.6274405	0.77859
_lstage_4 |	1.030819	0.0589379	17.49	0.000	0.9153031	1.146336
_cons |	–1.769433	0.075251	–23.51	0.000	–1.916922	–1.621944
/ln_p |	–0.3742472	0.012524	–29.88	0.000	–0.3987937	–0.3497007
p |	0.6878069	0.0086141			0.6711291	0.7048991
1/p |	1.453896	0.0182085			1.418643	1.490026

Exponential regression – log relative hazard form

No. of subjects = 5840
No. of observations = 5840
No. of failures = 1864
Time at risk = 4861.218333
LR $\chi^2(8)$ = 584.51
Log likelihood = –5356.1414
Probability > χ^2 = 0.0000

_t |	Coeff.	SE	z	p > |z|	95% CI	
_lage_10_2 |	0.2518029	0.1084782	2.32	0.020	0.0391895	0.4644164
_lage_10_3 |	0.450839	0.1029313	4.38	0.000	0.2490972	0.6525807
_lage_10_4 |	0.748236	0.1019285	7.34	0.000	0.5484598	0.9480123
_lage_10_5 |	1.254055	0.1065165	11.77	0.000	1.045286	1.462823
sex |	–0.1543153	0.0492873	–3.13	0.002	–0.2509167	–0.0577139
_lstage_2 |	0.7278286	0.0622401	11.69	0.000	0.6058402	0.849817
_lstage_3 |	0.944713	0.0600679	15.73	0.000	0.8269822	1.062444
_lstage_4 |	1.292698	0.0804127	16.08	0.000	1.135092	1.450304
_cons |	–1.898452	0.1202792	–15.78	0.000	–2.134195	–1.662709

Appendix 10

Members of expert group (Chapter 6)

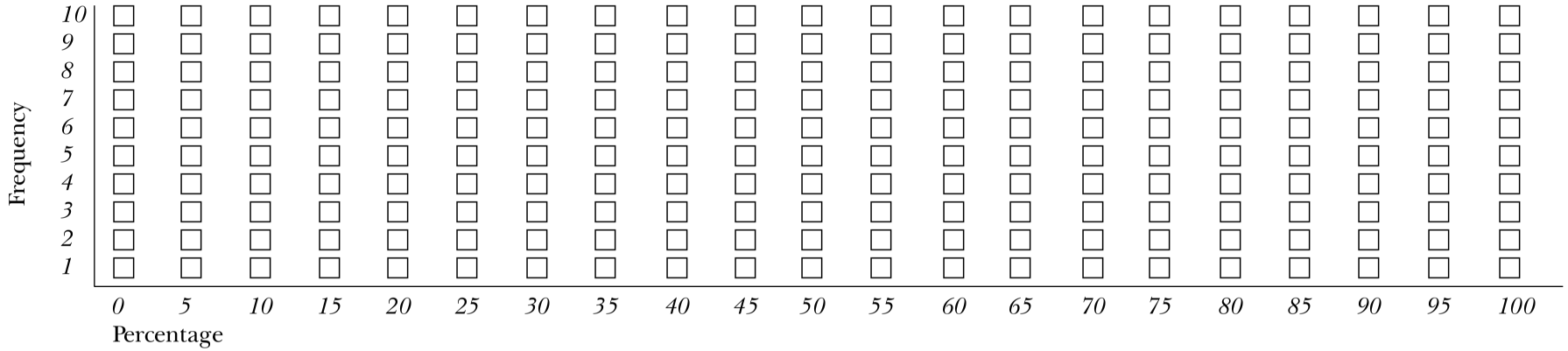
Members were asked to participate in the Trial Roulette technique to determine parameter estimates relating to disease progression.

Dr Bill Barrett	Consultant oral pathologist
Mr Colin Hopper	Consultant oral and maxillofacial surgeon specialising in surgical oncology of the head and neck and in management of premalignant disease
Prof. Mark McGurk	Consultant oral and maxillofacial surgeon specialising in surgical oncology of the head and neck
Prof. Peter Morgan	Consultant oral pathologist
Mr Lawrence Newman	Consultant oral and maxillofacial surgeon specialising in surgical oncology of the head and neck
Prof. Michelle Saunders	Consultant clinical oncologist specialising in oral cancer
Prof. Paul Speight	Consultant oral pathologist
Prof. Saman Warnakulasuriya	Consultant in oral medicine and Professor of experimental oral pathology, specialising in oral cancer and oral cancer screening
Ms Margaret Witcher	Nurse specialist in head and neck oncology

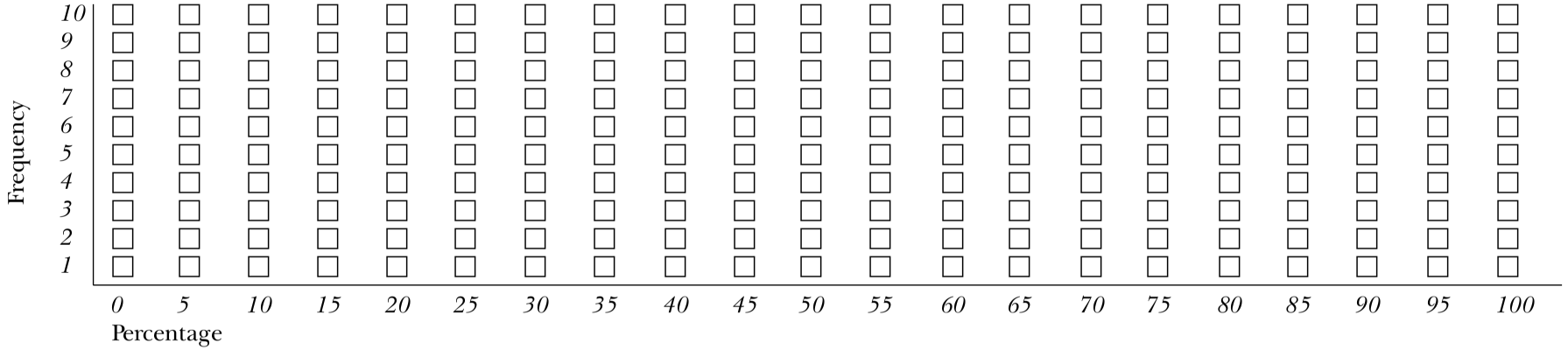
Appendix 11

Questionnaires used to elicit expert opinion (Chapter 6)

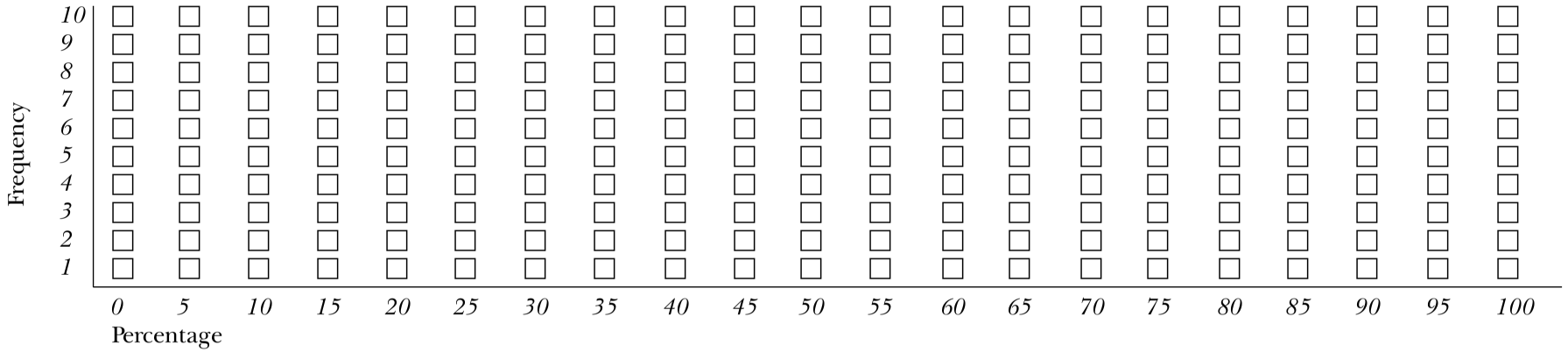
1a: Precancer (% of undiagnosed patients progressing to stage I without treatment)



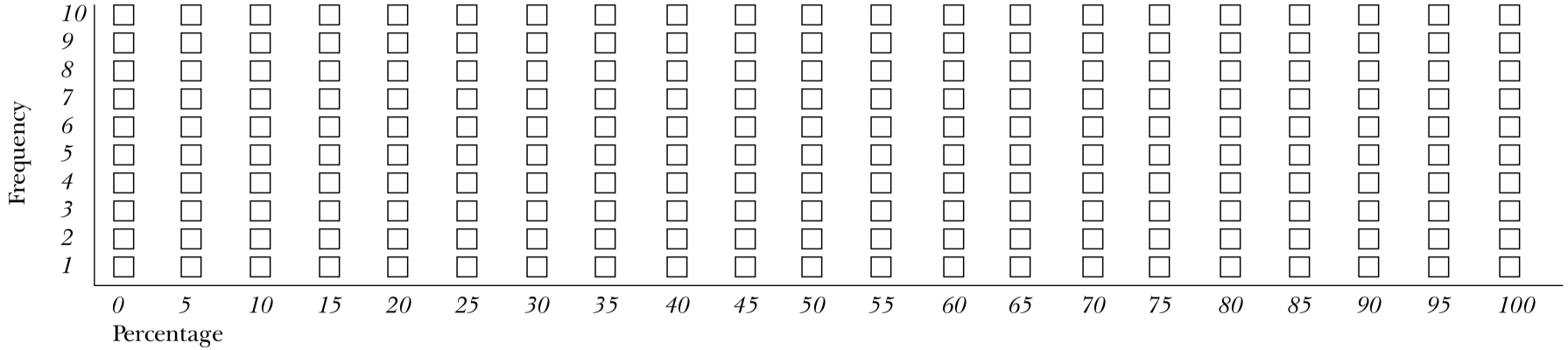
1b: Cancer stage I (% of undiagnosed patients progressing to stage II without treatment)



1c: Cancer stage II (% of undiagnosed patients progressing to stage III without treatment)



1d: Cancer stage III (% of undiagnosed patients progressing to stage IV without treatment)



Appendix 12

Results of the probabilistic analysis for males and females aged 40–79 years (Chapter 6)

Males aged 40–79 years (no treatment effect on progression from precancer to cancer)

Strategy	Screen option	Screener	Cost (£)	QALY	ICER (£)	Probability cost-effective for maximum WTP[a]		
						£20,000	£30,000	£40,000
A	No screen	NA	41.40	12.3665	NA	0.6600	0.3792	0.2258
C	Invitational screen	GDP	60.88	12.3673	ED	0.0000	0.0000	0.0000
B	Invitational screen	GP	92.17	12.3684	ED	0.0000	0.0000	0.0000
G	Opportunistic high-risk screen	GDP	104.50	12.3692	23,550	0.0252	0.0190	0.0112
H	Invitational screen	Spec.	119.76	12.3687	D	0.0000	0.0000	0.0000
E	Opportunistic screen	GDP	121.34	12.3699	ED	0.0226	0.0168	0.0110
F	Opportunistic high-risk screen	GP	162.04	12.3715	24,795	0.0912	0.1178	0.0966
D	Opportunistic screen	GP	194.65	12.3728	26,024	0.2010	0.4672	0.6554

Males aged 40–79 years (10% treatment effect on progression from precancer to cancer)

Strategy	Screen option	Screener	Cost (£)	QALY	ICER (£)	Probability cost-effective for maximum WTP[a]		
						£20,000	£30,000	£40,000
A	No screen	NA	41.28	12.3661	NA	0.5118	0.2466	0.1270
C	Invitational screen	GDP	60.79	12.3670	ED	0.0000	0.0000	0.0000
B	Invitational screen	GP	92.11	12.3684	ED	0.0000	0.0000	0.0000
G	Opportunistic high-risk screen	GDP	104.35	12.3694	19,171	0.0262	0.0138	0.0092
H	Invitational screen	Spec	119.71	12.3687	D	0.0000	0.0000	0.0000
E	Opportunistic screen	GDP	121.33	12.3702	ED	0.0278	0.0146	0.0060
F	Opportunistic high-risk screen	GP	161.84	12.3722	20,240	0.1070	0.1042	0.0772
D	Opportunistic screen	GP	194.72	12.3737	21,405	0.3272	0.6208	0.7806

Males aged 40–79 years (20% treatment effect on progression from precancer to cancer)

Strategy	Screen option	Screener	Cost (£)	QALY	ICER (£)	Probability cost-effective for maximum WTP[a]		
						£20,000	£30,000	£40,000
A	No screen	NA	41.16	12.3675	NA	0.3838	0.1714	0.0840
C	Invitational screen	GDP	60.56	12.3686	ED	0.0000	0.0000	0.0000
B	Invitational screen	GP	91.72	12.3703	ED	0.0000	0.0000	0.0000
G	Opportunistic high-risk screen	GDP	103.94	12.3714	16,220	0.0236	0.0098	0.0044
H	Invitational screen	Spec.	119.29	12.3707	D	0.0000	0.0000	0.0000
E	Opportunistic screen	GDP	120.75	12.3724	ED	0.0208	0.0116	0.0048
F	Opportunistic high-risk screen	GP	161.16	12.3747	17,108	0.1084	0.0824	0.0544
D	Opportunistic screen	GP	193.71	12.3766	17,964	0.4634	0.7248	0.8524

Females aged 40–79 years (no treatment effect on progression from pre-cancer to cancer)

Strategy	Screen option	Screener	Cost (£)	QALY	ICER (£)	Probability cost-effective for maximum WTP[a]		
						£20,000	£30,000	£40,000
A	No screen	NA	18.97	13.3498	NA	0.5986	0.3250	0.1818
C	Invitational screen	GDP	27.98	13.3501	ED	0.0000	0.0000	0.0000
B	Invitational screen	GP	43.49	13.3506	ED	0.0000	0.0000	0.0000
G	Opportunistic high-risk screen	GDP	45.02	13.3510	21,407	0.0216	0.0110	0.0084
E	Opportunistic screen	GDP	52.67	13.3513	ED	0.0112	0.0066	0.0048
H	Invitational screen	Spec.	67.33	13.3508	D	0.0000	0.0000	0.0000
F	Opportunistic high-risk screen	GP	76.09	13.3524	22,080	0.1448	0.1712	0.1368
D	Opportunistic screen	GP	93.28	13.3531	25,849	0.2238	0.4862	0.6682

Females aged 40–79 years (10% treatment effect on progression from precancer to cancer)

Strategy	Screen option	Screener	Cost (£)	QALY	ICER (£)	Probability cost-effective for maximum WTP[a]		
						£20,000	£30,000	£40,000
A	No screen	NA	18.96	13.3506	NA	0.4580	0.2204	0.1070
C	Invitational screen	GDP	28.21	13.3510	ED	0.0000	0.0000	0.0000
B	Invitational screen	GP	44.06	13.3516	ED	0.0000	0.0000	0.0000
G	Opportunistic high-risk screen	GDP	45.91	13.3520	18,388	0.0194	0.0110	0.0050
E	Opportunistic screen	GDP	53.72	13.3524	ED	0.0098	0.0040	0.0030
H	Invitational screen	Spec.	67.98	13.3518	D	0.0000	0.0000	0.0000
F	Opportunistic high-risk screen	GP	77.88	13.3537	18,861	0.1710	0.1448	0.1014
D	Opportunistic screen	GP	95.40	13.3545	22,018	0.3418	0.6198	0.7836

Females aged 40–79 years (20% treatment effect on progression from precancer to cancer)

Strategy	Screen option	Screener	Cost (£)	QALY	ICER (£)	Probability cost-effective for maximum WTP[a]		
						£20,000	£30,000	£40,000
A	No screen	NA	18.95	13.3499	NA	0.3408	0.1318	0.0592
C	Invitational screen	GDP	27.91	13.3504	ED	0.0000	0.0000	0.0000
B	Invitational screen	GP	43.35	13.3512	ED	0.0000	0.0000	0.0000
G	Opportunistic high-risk screen	GDP	44.90	13.3517	14,896	0.0138	0.0076	0.0032
E	Opportunistic screen	GDP	52.46	13.3521	ED	0.0100	0.0056	0.0018
H	Invitational screen	Spec.	67.18	13.3513	D	0.0000	0.0000	0.0000
F	Opportunistic high-risk screen	GP	75.85	13.3537	15,404	0.1846	0.1292	0.0802
D	Opportunistic screen	GP	92.84	13.3546	18,196	0.4508	0.7258	0.8556

D, option ruled out by dominance (more expensive and less effective); ED, option ruled out by extended dominance; NA, not applicable; Spec. hospital specialist.
[a] The probability that each strategy is more cost-effective than the others conditional on different maximum willingness to pay (WTP) for an additional QALY.

Appendix 13

Results of the probabilistic analysis by age and sex subgroups (Chapter 6)

Males: aged 40–49 years (no treatment effect on progression from precancer to cancer)

Strategy	Screen option	Screener	Cost (£)	QALY	ICER (£)	Probability cost-effective for maximum WTP[a]		
						£20,000	£30,000	£40,000
A	No screen	NA	48.23	16.2521	NA	0.5844	0.4442	0.3526
C	Invitational screen	GDP	69.07	16.2531	ED	0.0000	0.0000	0.0000
B	Invitational screen	GP	99.70	16.2545	ED	0.0000	0.0000	0.0000
G	Opportunistic high-risk screen	GDP	115.95	16.2556	19,259	0.0030	0.0020	0.0036
H	Invitational screen	Spec.	127.57	16.2548	D	0.0000	0.0000	0.0000
E	Opportunistic screen	GDP	133.76	16.2565	ED	0.0000	0.0000	0.0000
F	Opportunistic high-risk screen	GP	162.80	16.2581	19,384	0.0470	0.0440	0.0400
D	Opportunistic screen	GP	193.24	16.2595	20,930	0.3656	0.5098	0.6038

Males aged 50–59 years (no treatment effect on progression from precancer to cancer)

Strategy	Screen option	Screener	Cost (£)	QALY	ICER (£)	Probability cost-effective for maximum WTP[a]		
						£20,000	£30,000	£40,000
A	No screen	NA	49.96	13.0323	NA	0.6664	0.5154	0.4132
C	Invitational screen	GDP	72.18	13.0332	ED	0.0000	0.0000	0.0000
B	Invitational screen	GP	109.24	13.0346	ED	0.0000	0.0000	0.0000
G	Opportunistic high-risk screen	GDP	122.59	13.0354	23,387	0.0024	0.0032	0.0010
H	Invitational screen	Spec.	138.20	13.0350	D	0.0000	0.0000	0.0000
E	Opportunistic screen	GDP	142.13	13.0362	ED	0.0000	0.0000	0.0000
F	Opportunistic high-risk screen	GP	190.86	13.0384	23,496	0.0400	0.0416	0.0370
D	Opportunistic screen	GP	229.09	13.0399	24,716	0.2912	0.4398	0.5488

Males: aged 60–69 years (no treatment effect on progression from precancer to cancer)

Strategy	Screen option	Screener	Cost (£)	QALY	ICER (£)	Probability cost-effective for maximum WTP[a]		
						£20,000	£30,000	£40,000
A	No screen	NA	36.57	9.8189	NA	0.7516	0.5990	0.4894
C	Invitational screen	GDP	56.32	9.8195	ED	0.0000	0.0000	0.0000
B	Invitational screen	GP	87.34	9.8205	ED	0.0000	0.0000	0.0000
G	Opportunistic high-risk screen	GDP	100.54	9.8211	29,058	0.0026	0.0018	0.0026
H	Invitational screen	Spec.	114.88	9.8207	D	0.0000	0.0000	0.0000
E	Opportunistic screen	GDP	117.58	9.8217	ED	0.0000	0.0000	0.0000
F	Opportunistic high-risk screen	GP	165.30	9.8233	29,215	0.0474	0.0496	0.0476
D	Opportunistic screen	GP	199.96	9.8244	31,488	0.1984	0.3496	0.4604

Males aged 70+ years (no treatment effect on progression from precancer to cancer)

Strategy	Screen option	Screener	Cost (£)	QALY	ICER (£)	Probability cost-effective for maximum WTP[a]		
						£20,000	£30,000	£40,000
A	No screen	NA	17.48	6.6315	NA	0.8746	0.7580	0.6518
C	Invitational screen	GDP	28.46	6.6318	ED	0.0000	0.0000	0.0000
B	Invitational screen	GP	£50.25	6.6322	ED	0.0000	0.0000	0.0000
G	Opportunistic high-risk screen	GDP	51.28	6.6323	42,582	0.0020	0.0028	0.0028
E	Opportunistic screen	GDP	60.66	6.6325	ED	0.0000	0.0000	0.0000
H	Invitational screen	Spec.	74.70	6.6323	D	0.0000	0.0000	0.0000
F	Opportunistic high-risk screen	GP	99.98	6.6335	42,906	0.0412	0.0640	0.0760
D	Opportunistic screen	GP	123.25	6.6339	48,468	0.0822	0.1752	0.2694

Males aged 40–49 years (10% treatment effect on progression from precancer to cancer)

Strategy	Screen option	Screener	Cost (£)	QALY	ICER (£)	Probability cost-effective for maximum WTP[a]		
						£20,000	£30,000	£40,000
A	No screen	NA	48.21	16.2528	NA	0.4926	0.3378	0.2620
C	Invitational screen	GDP	69.02	16.2541	ED	0.0000	0.0000	0.0000
B	Invitational screen	GP	99.61	16.2558	ED	0.0000	0.0000	0.0000
G	Opportunistic high-risk screen	GDP	115.82	16.2572	15,460	0.0016	0.0016	0.0016
H	Invitational screen	Spec.	127.47	16.2562	D	0.0000	0.0000	0.0000
E	Opportunistic screen	GDP	133.63	16.2583	ED	0.0000	0.0002	0.0000
F	Opportunistic high-risk screen	GP	162.58	16.2602	15,560	0.0472	0.0422	0.0314
D	Opportunistic screen	GP	193.05	16.2620	16,678	0.4586	0.6182	0.7050

Males aged 50–59 years (10% treatment effect on progression from precancer to cancer)

Strategy	Screen option	Screener	Cost (£)	QALY	ICER (£)	Probability cost-effective for maximum WTP[a]		
						£20,000	£30,000	£40,000
A	No screen	NA	49.77	13.0332	NA	0.5788	0.4318	0.3402
C	Invitational screen	GDP	72.07	13.0343	ED	0.0000	0.0000	0.0000
B	Invitational screen	GP	109.25	13.0361	ED	0.0000	0.0000	0.0000
G	Opportunistic high-risk screen	GDP	122.47	13.0371	18,938	0.0018	0.0018	0.0014
H	Invitational screen	Spec.	138.24	13.0365	D	0.0000	0.0000	0.0000
E	Opportunistic screen	GDP	142.24	13.0380	ED	0.0000	0.0000	0.0000
F	Opportunistic high-risk screen	GP	190.80	13.0407	19,028	0.0426	0.0346	0.0324
D	Opportunistic screen	GP	229.49	13.0425	19,605	0.3768	0.5318	0.6260

Males aged 60–69 years (10% for treatment effect on progression from precancer to cancer)

Strategy	Screen option	Screener	Cost (£)	QALY	ICER (£)	Probability cost-effective for maximum WTP[a]		
						£20,000	£30,000	£40,000
A	No screen	NA	36.55	9.8121	NA	0.6846	0.5304	0.4240
C	Invitational screen	GDP	56.44	9.8129	ED	0.0000	0.0000	0.0000
B	Invitational screen	GP	87.66	9.8140	ED	0.0000	0.0000	0.0000
G	Opportunistic high-risk screen	GDP	100.81	9.8147	24,569	0.0018	0.0016	0.0016
H	Invitational screen	Spec.	115.26	9.8142	D	0.0000	0.0000	0.0000
E	Opportunistic screen	GDP	118.19	9.8154	ED	0.0000	0.0000	0.0000
F	Opportunistic high-risk screen	GP	165.86	9.8174	24,700	0.0484	0.0426	0.0398
D	Opportunistic screen	GP	201.21	9.8187	26,247	0.2652	0.4254	0.5346

Males aged 70+ years (10% treatment effect on progression from precancer to cancer)

Strategy	Screen option	Screener	Cost (£)	QALY	ICER (£)	Probability cost-effective for maximum WTP[a]		
						£20,000	£30,000	£40,000
A	No screen	NA	17.17	6.6350	NA	0.8322	0.6908	0.5758
C	Invitational screen	GDP	28.03	6.6352	ED	0.0000	0.0000	0.0000
B	Invitational screen	GP	49.58	6.6357	ED	0.0000	0.0000	0.0000
G	Opportunistic high-risk screen	GDP	50.46	6.6359	35,711	0.0024	0.0030	0.0038
E	Opportunistic screen	GDP	59.77	6.6361	ED	0.0000	0.0000	0.0000
H	Invitational screen	Spec.	74.00	6.6358	D	0.0000	0.0000	0.0000
F	Opportunistic high-risk screen	GP	98.43	6.6372	35,981	0.0516	0.0686	0.0858
D	Opportunistic screen	GP	121.55	6.6378	41,415	0.1138	0.2376	0.3346

Males aged 40–49 years (20% treatment effect on progression from precancer to cancer)

Strategy	Screen option	Screener	Cost (£)	QALY	ICER (£)	Probability cost-effective for maximum WTP[a]		
						£20,000	£30,000	£40,000
A	No screen	NA	46.58	16.2557	NA	0.4232	0.2984	0.2354
C	Invitational screen	GDP	67.31	16.2572	ED	0.0000	0.0000	0.0000
B	Invitational screen	GP	97.79	16.2592	ED	0.0000	0.0000	0.0000
G	Opportunistic high-risk screen	GDP	113.81	16.2608	13,285	0.0024	0.0014	0.0018
H	Invitational screen	Spec.	125.61	16.2597	D	0.0000	0.0000	0.0000
E	Opportunistic screen	GDP	131.69	16.2621	ED	0.0000	0.0000	0.0000
F	Opportunistic high-risk screen	GP	160.32	16.2643	13,371	0.0458	0.0366	0.0286
D	Opportunistic screen	GP	190.88	16.2664	14,468	0.5286	0.6636	0.7342

Males aged 50–59 years (20% treatment effect on progression from precancer to cancer)

Strategy	Screen option	Screener	Cost (£)	QALY	ICER (£)	Probability cost-effective for maximum WTP[a]		
						£20,000	£30,000	£40,000
A	No screen	NA	50.88	13.0333	NA	0.4986	0.3610	0.2774
C	Invitational screen	GDP	73.09	13.0346	ED	0.0000	0.0000	0.0000
B	Invitational screen	GP	110.14	13.0367	ED	0.0000	0.0000	0.0000
G	Opportunistic high-risk screen	GDP	123.66	13.0380	15,755	0.0006	0.0008	0.0014
H	Invitational screen	Spec.	139.11	13.0372	D	0.0000	0.0000	0.0000
E	Opportunistic screen	GDP	142.94	13.0391	ED	0.0000	0.0000	0.0000
F	Opportunistic high-risk screen	GP	192.06	13.0423	15,829	0.0444	0.0342	0.0256
D	Opportunistic screen	GP	229.81	13.0445	16,772	0.4564	0.6040	0.6956

Males aged 60–69 years (20% treatment effect on progression from precancer to cancer)

Strategy	Screen option	Screener	Cost (£)	QALY	ICER (£)	Probability cost-effective for maximum WTP[a]		
						£20,000	£30,000	£40,000
A	No screen	NA	37.06	9.8153	NA	0.6042	0.4484	0.3538
C	Invitational screen	GDP	56.70	9.8162	ED	0.0000	0.0000	0.0000
B	Invitational screen	GP	87.56	9.8175	ED	0.0000	0.0000	0.0000
G	Opportunistic high-risk screen	GDP	100.49	9.8184	20,502	0.0026	0.0020	0.0018
H	Invitational screen	Spec.	115.06	9.8178	D	0.0000	0.0000	0.0000
E	Opportunistic screen	GDP	117.62	9.8192	ED	0.0000	0.0000	0.0002
F	Opportunistic high-risk screen	GP	164.72	9.8215	20,613	0.0458	0.0488	0.0426
D	Opportunistic screen	GP	199.54	9.8231	21,853	0.3474	0.5008	0.6016

Males aged 70–79 years (20% treatment effect on progression from precancer to cancer)

Strategy	Screen option	Screener	Cost (£)	QALY	ICER (£)	Probability cost-effective for maximum WTP[a]		
						£20,000	£30,000	£40,000
A	No screen	NA	16.88	6.6336	NA	0.7844	0.6338	0.5230
C	Invitational screen	GDP	27.74	6.6339	ED	0.0000	0.0000	0.0000
B	Invitational screen	GP	49.31	6.6344	ED	0.0000	0.0000	0.0000
G	Opportunistic high-risk screen	GDP	50.10	6.6346	31,703	0.0026	0.0034	0.0042
E	Opportunistic screen	GDP	59.51	6.6349	ED	0.0000	0.0000	0.0000
H	Invitational screen	Spec.	73.72	6.6346	D	0.0000	0.0000	0.0000
F	Opportunistic high-risk screen	GP	97.97	6.6361	31,947	0.0656	0.0784	0.0814
D	Opportunistic screen	GP	121.33	6.6368	36,145	0.1474	0.2844	0.3914

Females aged 40–49 years (no treatment effect on progression from precancer to cancer)

Strategy	Screen option	Screener	Cost (£)	QALY	ICER (£)	Probability cost-effective for maximum WTP[a]		
						£20,000	£30,000	£40,000
A	No screen	NA	21.75	17.3883	NA	0.5416	0.4058	0.3184
C	Invitational screen	GDP	31.19	17.3887	ED	0.0000	0.0000	0.0000
B	Invitational screen	GP	46.03	17.3893	ED	0.0000	0.0000	0.0000
G	Opportunistic high-risk screen	GDP	48.91	17.3898	17,307	0.0060	0.0040	0.0024
E	Opportunistic screen	GDP	56.97	17.3902	ED	0.0002	0.0000	0.0000
H	Invitational screen	Spec.	69.94	17.3895	D	0.0000	0.0000	0.0000
F	Opportunistic high-risk screen	GP	77.10	17.3915	17,528	0.1100	0.0970	0.0874
D	Opportunistic screen	GP	93.92	17.3923	21,027	0.3422	0.4932	0.5918

Females aged 50–59 years (no treatment effect on progression from precancer to cancer)

Strategy	Screen option	Screener	Cost (£)	QALY	ICER (£)	Probability cost-effective for maximum WTP[a]		
						£20,000	£30,000	£40,000
A	No screen	NA	23.09	14.4038	NA	0.6244	0.4678	0.3778
C	Invitational screen	GDP	33.31	14.4042	ED	0.0000	0.0000	0.0000
B	Invitational screen	GP	51.30	14.4048	ED	0.0000	0.0000	0.0000
G	Opportunistic high-risk screen	GDP	53.46	14.4052	20,980	0.0048	0.0032	0.0032
E	Opportunistic screen	GDP	62.20	14.4056	ED	0.0000	0.0000	0.0000
H	Invitational screen	Spec.	75.78	14.4050	D	0.0000	0.0000	0.0000
F	Opportunistic high-risk screen	GP	91.76	14.4070	21,183	0.0846	0.0852	0.0748
D	Opportunistic screen	GP	111.93	14.4079	24,039	0.2862	0.4438	0.5442

Females aged 60–69 years (no treatment effect on progression from precancer to cancer)

Strategy	Screen option	Screener	Cost (£)	QALY	ICER (£)	Probability cost-effective for maximum WTP[a]		
						£20,000	£30,000	£40,000
A	No screen	NA	18.20	11.1555	NA	0.7080	0.5544	0.4516
C	Invitational screen	GDP	27.79	11.1558	ED	0.0000	0.0000	0.0000
B	Invitational screen	GP	43.75	11.1563	ED	0.0000	0.0000	0.0000
G	Opportunistic high-risk screen	GDP	46.26	11.1566	25,740	0.0048	0.0044	0.0044
E	Opportunistic screen	GDP	54.35	11.1569	ED	0.0000	0.0000	0.0000
H	Invitational screen	Spec.	67.72	11.1564	D	0.0000	0.0000	0.0000
F	Opportunistic high-risk screen	GP	79.11	11.1578	26,028	0.0840	0.0974	0.0982
D	Opportunistic screen	GP	97.07	11.1584	30,574	0.2032	0.3438	0.4458

Females aged 70–79 years (no treatment effect on progression from precancer to cancer)

Strategy	Screen option	Screener	Cost (£)	QALY	ICER (£)	Probability cost-effective for maximum WTP[a]		
						£20,000	£30,000	£40,000
A	No screen	NA	8.95	7.6510	NA	0.8192	0.6832	0.5802
C	Invitational screen	GDP	14.71	7.6511	ED	0.0000	0.0000	0.0000
G	Opportunistic high-risk screen	GDP	24.17	7.6514	35,415	0.0052	0.0080	0.0068
B	Invitational screen	GP	26.96	7.6513	D	0.0000	0.0000	0.0000
E	Opportunistic screen	GDP	28.98	7.6515	ED	0.0002	0.0000	0.0000
F	Opportunistic high-risk screen	GP	46.73	7.6520	35,997	0.0910	0.1208	0.1328
H	Invitational screen	Spec.	49.57	7.6514	D	0.0000	0.0000	0.0000
D	Opportunistic screen	GP	59.06	7.6523	46,294	0.0844	0.1880	0.2802

Females aged 40–49 years (10% treatment effect on progression from precancer to cancer)

Strategy	Screen option	Screener	Cost (£)	QALY	ICER (£)	Probability cost-effective for maximum WTP[a]		
						£20,000	£30,000	£40,000
A	No screen	NA	21.30	17.3903	NA	0.4648	0.3340	0.2554
C	Invitational screen	GDP	31.67	17.3908	ED	0.0000	0.0000	0.0000
B	Invitational screen	GP	47.79	17.3916	ED	0.0000	0.0000	0.0000
G	Opportunistic high-risk screen	GDP	51.72	17.3922	16,230	0.0056	0.0044	0.0038
E	Opportunistic screen	GDP	60.50	17.3926	ED	0.0002	0.0000	0.0000
H	Invitational screen	Spec.	72.02	17.3917	D	0.0000	0.0000	0.0000
F	Opportunistic high-risk screen	GP	83.25	17.3941	16,416	0.0934	0.0888	0.0802
D	Opportunistic screen	GP	101.53	17.3951	18,758	0.4360	0.5728	0.6606

Females aged 50–59 years (10% treatment effect on progression from precancer to cancer)

Strategy	Screen option	Screener	Cost (£)	QALY	ICER (£)	Probability cost-effective for maximum WTP[a]		
						£20,000	£30,000	£40,000
A	No screen	NA	24.00	14.4031	NA	0.5278	0.3788	0.2924
C	Invitational screen	GDP	34.15	14.4036	ED	0.0000	0.0000	0.0000
B	Invitational screen	GP	52.02	14.4044	ED	0.0000	0.0000	0.0000
G	Opportunistic high-risk screen	GDP	54.21	14.4049	16,586	0.0026	0.0044	0.0036
E	Opportunistic screen	GDP	62.83	14.4054	ED	0.0000	0.0000	0.0000
H	Invitational screen	Spec.	76.45	14.4046	D	0.0000	0.0000	0.0000
F	Opportunistic high-risk screen	GP	92.31	14.4072	16,748	0.0930	0.0882	0.0760
D	Opportunistic screen	GP	112.21	14.4082	19,590	0.3766	0.5286	0.6280

Females aged 60–69 years (10% treatment effect on progression from precancer to cancer)

Strategy	Screen option	Screener	Cost (£)	QALY	ICER (£)	Probability cost-effective for maximum WTP[a]		
						£20,000	£30,000	£40,000
A	No screen	NA	17.84	11.1571	NA	0.6398	0.4826	0.3794
C	Invitational screen	GDP	27.36	11.1575	ED	0.0000	0.0000	0.0000
B	Invitational screen	GP	43.24	11.1580	ED	0.0000	0.0000	0.0000
G	Opportunistic high-risk screen	GDP	45.67	11.1584	21,992	0.0054	0.0056	0.0040
E	Opportunistic screen	GDP	53.69	11.1587	ED	0.0000	0.0000	0.0000
H	Invitational screen	Spec.	67.19	11.1581	D	0.0000	0.0000	0.0000
F	Opportunistic high-risk screen	GP	78.25	11.1598	22,242	0.0994	0.1054	0.0960
D	Opportunistic screen	GP	96.07	11.1605	26,226	0.2554	0.4064	0.5206

Females aged 70–79 years (10% treatment effect on progression from precancer to cancer)

Strategy	Screen option	Screener	Cost (£)	QALY	ICER (£)	Probability cost-effective for maximum WTP[a]		
						£20,000	£30,000	£40,000
A	No screen	NA	8.64	7.6511	NA	0.7894	0.6318	0.5232
C	Invitational screen	GDP	14.38	7.6513	ED	0.0000	0.0000	0.0000
G	Opportunistic high-risk screen	GDP	23.84	7.6516	31,786	0.0056	0.0096	0.0086
B	Invitational screen	GP	26.60	7.6515	D	0.0000	0.0000	0.0000
E	Opportunistic screen	GDP	28.62	7.6517	ED	0.0000	0.0002	0.0000
F	Opportunistic high-risk screen	GP	46.37	7.6523	32,306	0.0974	0.1400	0.1464
H	Invitational screen	Spec.	49.19	7.6516	D	0.0000	0.0000	0.0000
D	Opportunistic screen	GP	58.63	7.6526	41,118	0.1076	0.2184	0.3218

Females aged 40–49 years (20% treatment effect on progression from precancer to cancer)

Strategy	Screen option	Screener	Cost (£)	QALY	ICER (£)	Probability cost-effective for maximum WTP[a]		
						£20,000	£30,000	£40,000
A	No screen	NA	22.00	17.3909	NA	0.3818	0.2708	0.2034
C	Invitational screen	GDP	31.41	17.3916	ED	0.0000	0.0000	0.0000
B	Invitational screen	GP	46.20	17.3925	ED	0.0000	0.0000	0.0000
G	Opportunistic high-risk screen	GDP	49.18	17.3933	11,730	0.0048	0.0030	0.0028
E	Opportunistic screen	GDP	57.06	17.3938	ED	0.0000	0.0000	0.0000
H	Invitational screen	Spec.	70.11	17.3927	D	0.0000	0.0000	0.0000
F	Opportunistic high-risk screen	GP	77.38	17.3956	11,879	0.1050	0.0806	0.0668
D	Opportunistic screen	GP	93.84	17.3968	14,137	0.5084	0.6456	0.7270

Females aged 50–59 years (20% treatment effect on progression from precancer to cancer)

Strategy	Screen option	Screener	Cost (£)	QALY	ICER (£)	Probability cost-effective for maximum WTP[a]		
						£20,000	£30,000	£40,000
A	No screen	NA	23.03	14.4026	NA	0.4686	0.3408	0.2616
C	Invitational screen	GDP	33.24	14.4032	ED	0.0000	0.0000	0.0000
B	Invitational screen	GP	51.22	14.4042	ED	0.0000	0.0000	0.0000
G	Opportunistic high-risk screen	GDP	53.48	14.4047	14,589	0.0026	0.0036	0.0018
E	Opportunistic screen	GDP	62.13	14.4053	ED	0.0000	0.0000	0.0000
H	Invitational screen	Spec.	75.68	14.4044	D	0.0000	0.0000	0.0000
F	Opportunistic high-risk screen	GP	91.89	14.4073	14,729	0.0938	0.0766	0.0682
D	Opportunistic screen	GP	111.85	14.4085	17,037	0.4350	0.5790	0.6684

Females aged 60–69 years (20% treatment effect on progression from precancer to cancer)

Strategy	Screen option	Screener	Cost (£)	QALY	ICER (£)	Probability cost-effective for maximum WTP[a]		
						£20,000	£30,000	£40,000
A	No screen	NA	18.05	11.1547	NA	0.5584	0.4142	0.3346
C	Invitational screen	GDP	27.53	11.1551	ED	0.0000	0.0000	0.0000
B	Invitational screen	GP	43.34	11.1558	ED	0.0000	0.0000	0.0000
G	Opportunistic high-risk screen	GDP	45.73	11.1562	18,546	0.0072	0.0036	0.0030
E	Opportunistic screen	GDP	53.76	11.1566	ED	0.0002	0.0000	0.0000
H	Invitational screen	Spec.	67.27	11.1559	D	0.0000	0.0000	0.0000
F	Opportunistic high-risk screen	GP	78.13	11.1579	18,758	0.1064	0.0988	0.0804
D	Opportunistic screen	GP	95.97	11.1587	22,246	0.3278	0.4834	0.5820

Females aged 70–79 years (20%) treatment effect on progression from precancer to cancer)

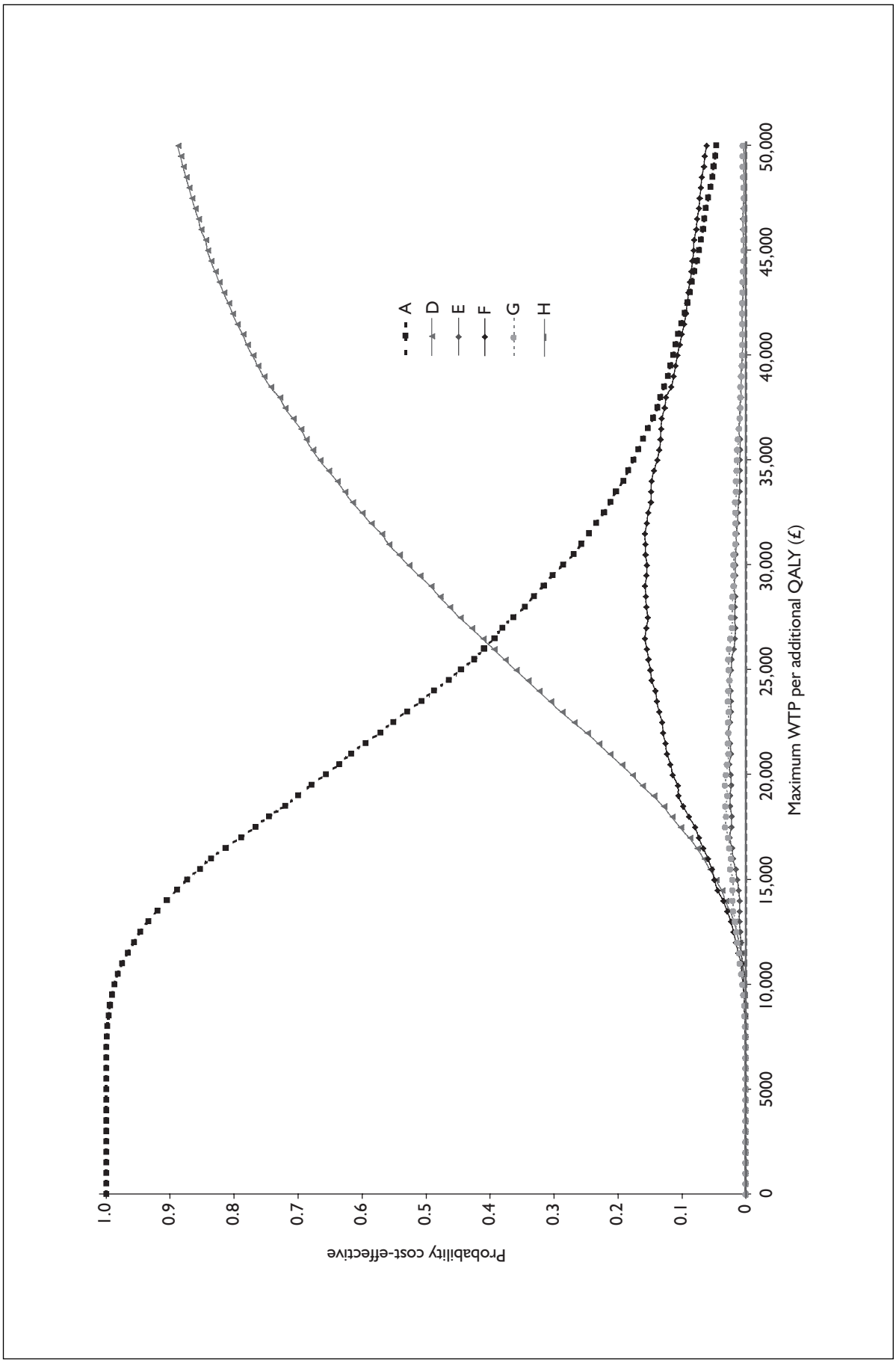
Strategy	Screen option	Screener	Cost (£)	QALY	ICER (£)	Probability cost-effective for maximum WTP[a]		
						£20,000	£30,000	£40,000
A	No screen	NA	8.70	7.6501	NA	0.7264	0.5696	0.4618
C	Invitational screen	GDP	14.41	7.6503	ED	0.0000	0.0000	0.0000
G	Opportunistic high-risk screen	GDP	23.72	7.6507	26,883	0.0082	0.0080	0.0060
B	Invitational screen	GP	26.57	7.6506	D	0.0000	0.0000	0.0000
E	Opportunistic screen	GDP	28.50	7.6508	ED	0.0000	0.0000	0.0000
F	Opportunistic high-risk screen	GP	45.98	7.6515	27,330	0.1264	0.1426	0.1526
H	Invitational screen	Spec.	49.15	7.6506	D	0.0000	0.0000	0.0000
D	Opportunistic screen	GP	58.25	7.6518	36,041	0.1390	0.2798	0.3796

D, option ruled out by dominance (more expensive and less effective); ED, option ruled out by extended dominance; NA, not applicable; Spec. hospital specialist.
[a] The probability that each strategy is more cost-effective than the others conditional on different maximum willingness to pay (WTP) for an additional QALY.

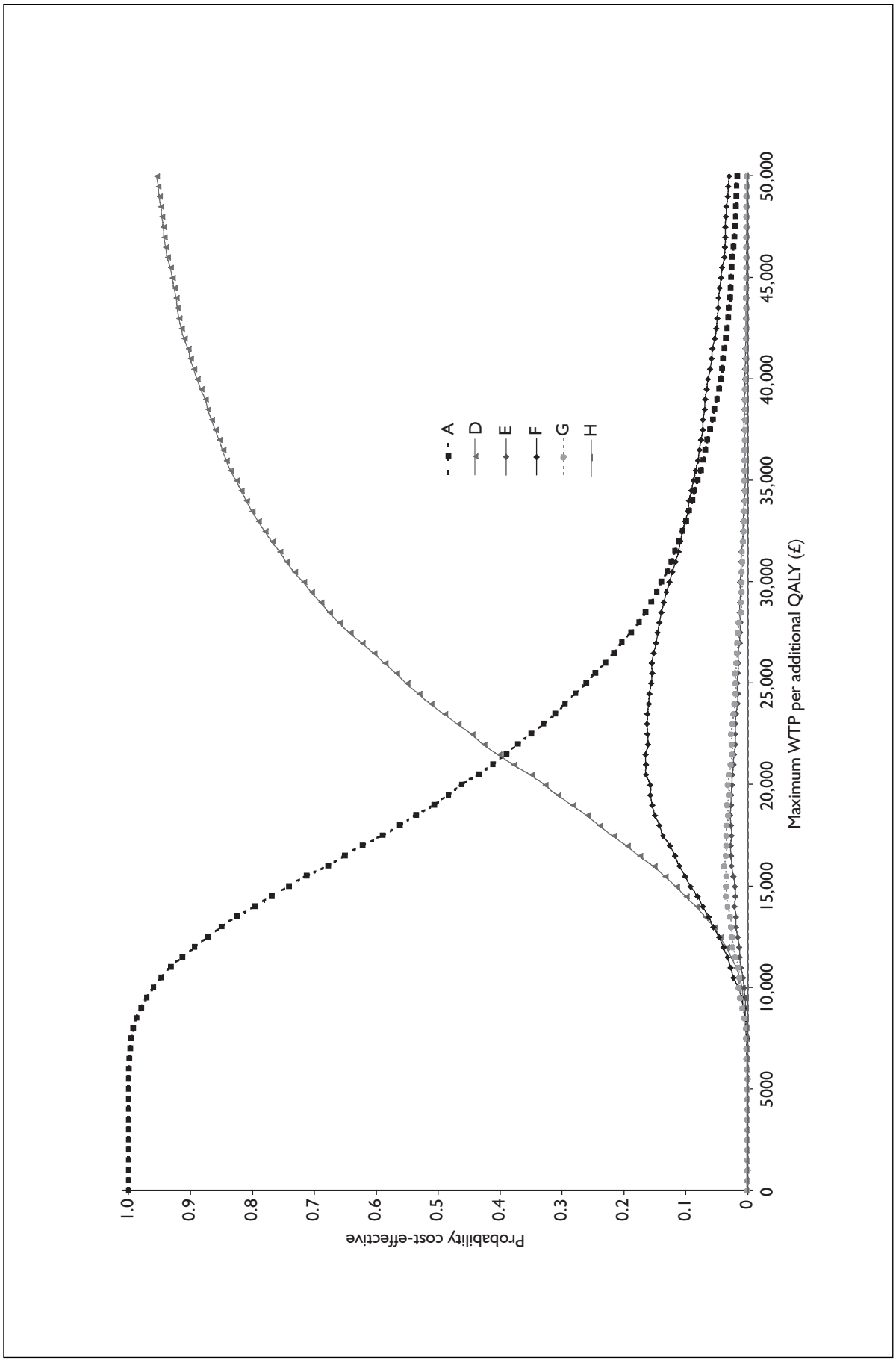
Appendix 14

Cost-effectiveness acceptability curves (Chapter 6)

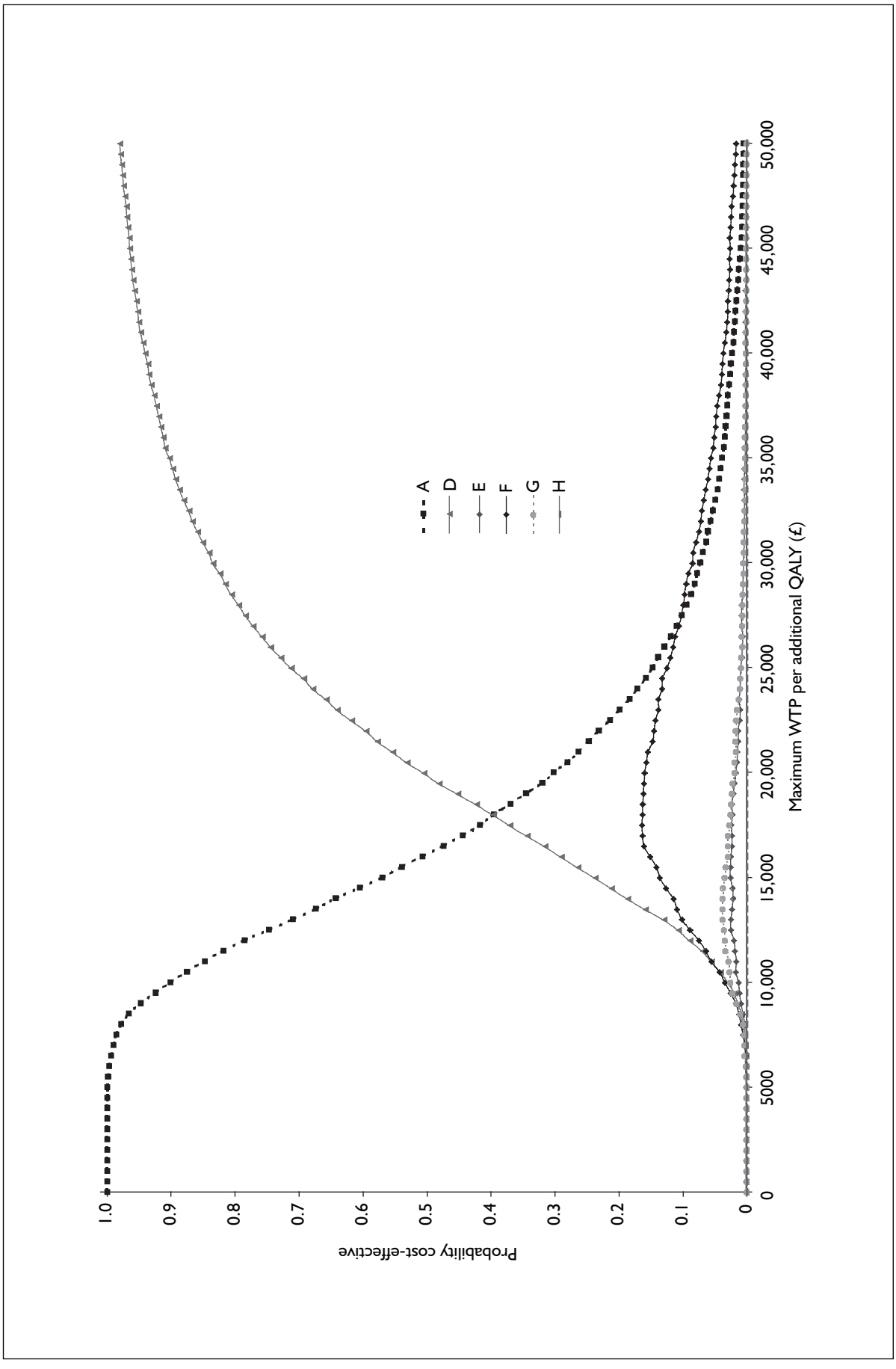
Males and females (aged 40–79 years): no reduction in annual malignancy transformation rate



Males and females (aged 40–79 years): 10% reduction in annual malignancy transformation rate



Males and females (aged 40–79 years): 20% reduction in annual malignancy transformation rates



Appendix 15

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

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

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

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

The condition

1. *The condition should be an important health problem*.
   The project has not addressed this issue.
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, or disease marker and a latent period or early symptomatic stage*.
   The project did not directly address this issue. However, there was considerable variability in the parameters used to populate the model. VoI analysis (Chapter 7) indicates that the EVPI for research into oral cancer screening is high. Specifically, partial EVPI analysis (*Table 40*) suggests that the greatest benefit would be derived from research relating to the natural history of the disease – MTR of premalignant lesions and rate of progression through different stages of oral cancer. This indicates that the natural history of the disease is not adequately understood.
3. *All the cost-effective primary prevention interventions should have been implemented as far as practicable*.
   The project has not addressed this issue

The test

4. *There should be a simple, safe, precise and validated screening test*.
   This issue was addressed in a systematic review (Chapter 2), which indicates that an oral examination has sufficient sensitivity and specificity and predictive values to be a feasible screening test. However, because of uncertainty about the natural history of lesions detected, the criteria for a positive result need to be refined.
5. *The distribution of test values in the target population should be known and a suitable cut-off level defined and agreed*.
   The project has not addressed this issue.
6. *The test should be acceptable to the population*.
   The project has not addressed this issue.
7. *There should be an agreed policy on the further diagnostic investigation of individuals with a positive test result and on the choices available to those individuals*.
   The project has not addressed this issue.

The treatment

8. *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*.
   The project has not addressed this issue.
9. *There should be agreed evidence-based policies covering which individuals should be offered treatment and the appropriate treatment to be offered*.
   The project has not addressed this issue.

10. Clinical management of the condition and patient outcomes should be optimised by all health care providers prior to participation in a screening programme.
    The project has not addressed this issue

The screening programme

11. There must be evidence from high-quality RCTs 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.
    This issue was partly addressed in a systematic review of effectiveness of screening programmes (Chapter 3). It was concluded that there are insufficient available data at present to determine the effectiveness of oral cancer screening programmes.
12. *There should be evidence that the complete screening programme (test, diagnostic procedures, treatment/intervention) is clinically, socially and ethically acceptable to health professionals and the public.*
    The project has not addressed this issue.
13. *The benefit from the screening programme should outweigh the physical and psychological harm (caused by the test, diagnostic procedures and treatment).*
    The project has not addressed this issue.
14. *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).*
    This study has shown that opportunistic screening for oral cancer may be cost-effective. In particular, that opportunistic high-risk screening in a primary care environment (particularly by GDPs) may be a practical proposition.
15. *There must be a plan for managing and monitoring the screening programme and an agreed set of quality assurance standards.*
    The project has not addressed this issue.
16. *Adequate staffing and facilities for testing, diagnosis, treatment and programme management should be made available prior to the commencement of the screening programme*
    The project has not addressed this issue.
17. *All other options for managing the condition should have been considered (e.g. improving treatment, providing other services), to ensure that no more cost-effective intervention could be introduced or current interventions increased within the resources available.*
    The project has not addressed this issue.
18. *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.*
    The project has not addressed this issue.
19. *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.*
    The project has not addressed this issue.

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We look forward to hearing from you.

The National Coordinating Centre for Health Technology Assessment,
Mailpoint 728, Boldrewood,
University of Southampton,
Southampton, SO16 7PX, UK.
Fax: +44 (0) 23 8059 5639 Email: hta@hta.ac.uk
http://www.hta.ac.uk

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