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'Cut down to quit' with nicotine replacement therapies in smoking cessation: a systematic review of effectiveness and economic analysis

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The research reported in this issue of the journal was commissioned by the HTA Programme as project number 06/09/01. The contractual start date was in May 2006. The draft report began editorial review in March 2007 and was accepted for publication in June 2007. 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

'Cut down to quit' with nicotine replacement therapies in smoking cessation: a systematic review of effectiveness and economic analysis

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Objectives: To examine the effectiveness and cost-effectiveness of nicotine replacement therapy (NRT) for 'cut down to quit' (CDTQ) smoking.

Data sources: Major electronic databases were searched up to July 2006.

Review methods: Data from studies meeting the criteria were reviewed and analysed. A decision analytical model was constructed to estimate the cost-effectiveness of CDTQ from the NHS perspective.

Results: No systematic reviews of the effectiveness of CDTQ and no randomised controlled trials (RCTs) specifically addressing CDTQ were identified. Seven randomised placebo-controlled trials satisfied the inclusion criteria; six of these were industry sponsored. However, sustained smoking cessation was only reported as a secondary outcome in these trials and required commencement of cessation within the first 6 weeks of treatment. Meta-analyses of the study level results demonstrated statistically significant superiority of NRT compared with placebo. Individual patient data from unpublished reports of five RCTs were used to calculate sustained abstinence of at least 6 months starting at any time during the treatment period (generally 12 months). From this the meta-analysis indicated statistically significant superiority of NRT versus placebo [relative risk 2.06, 95% confidence interval (CI) 1.34 to 3.15]. The proportions achieving this outcome across all five RCTs were 6.75% of participants in receipt of NRT and 3.29% of those receiving placebo. The number-needed-to-treat was 29. This measure of sustained abstinence was used for economic modelling. No existing economic analyses of CDTQ were identified. A *de novo* decision analytic model was constructed to estimate the cost-effectiveness of making CDTQ with NRT available for smokers unwilling or unable to attempt an abrupt quit. The outcome measure was expected quality-adjusted life-years (QALYs). The model results suggest that CDTQ with NRT delivers incremental cost-effectiveness ratios (ICERs) ranging from around £1500/QALY to £7700/QALY depending on the age at which smoking cessation was achieved and the modes of CDTQ delivery. Assuming applicability to a single population, CDTQ was not cost-effective compared with abrupt quitting. If CDTQ with NRT were to be offered on the NHS as a matter of policy, the base-case results suggest that it would only be effective and cost-effective if a substantial majority of the people attempting CDTQ with NRT were those who would otherwise make no attempt to quit. This result is robust to considerable variation in the forms of CDTQ with NRT offered, and to the assumptions about QALY gained per quit success.

on reasonable assumptions about costs, benefits and success rates, suggests that CDTQ is highly cost-effective compared with no quit attempt. CDTQ remains cost-effective if dilution from abrupt quitting forms a small proportion of CDTQ attempts. In an alternative analysis in which smokers who switch from an abrupt quit to CDTQ retain the success rate of abrupt quitters, all forms of CDTQ appear cost-effective. Randomised trials in recalcitrant smokers allowing head-to-head comparison of CDTQ delivered with various modalities would be informative.

Contents

Glossary and list of abbreviations

Technical terms and abbreviations are used throughout this report. The meaning is usually clear from the context, but a glossary is provided for the non-specialist reader. In some cases, usage differs in the literature, but the term has a constant meaning throughout this review.

Glossary

Adverse effect An abnormal or harmful effect caused by and attributable to exposure to a chemical (e.g. a drug), which is indicated by some result such as death, a physical symptom or visible illness. An effect may be classed as adverse if it causes functional or anatomical damage, causes irreversible change in the homeostasis of the organism or increases the susceptibility of the organism to other chemical or biological stress.

Confidence interval (CI) A measure of the precision of a statistical estimate; quantifies the uncertainty in measurement. Usually reported as 95% CI, i.e. the range of values within which one can be 95% sure that the true values for the whole population lie.

Cytochrome P450 2A6 (CYP2A6) The enzyme primarily responsible for the oxidation of nicotine and cotinine.

Discounting Refers to the process of adjusting the value of costs or benefits that occur at different points of time in the future so that they may all be compared as if they had occurred at the same time.

Intention-to-treat (ITT) An ITT analysis is one in which all the participants in a trial are analysed according to the intervention to which they were allocated, whether they received it or not. ITT analyses are favoured in assessments of effectiveness as they mirror the non-compliance and treatment changes that are likely to occur when the intervention is used in practice, and because of the risk of attrition bias when participants are excluded from the analysis.

Incremental cost-effectiveness ratio An expression of the additional cost of health gain associated with an intervention relative to an appropriate comparator. Expressed as the difference in mean costs (relative to the comparator) divided by the difference in mean health gain.

Major histocompatibility complex (MHC) A set of genes whose products on all cells are primarily responsible for determining tissue compatibility between individuals (especially important in organ and tissue transplantation procedures).

Meta-analysis The statistical pooling of the results of a collection of related individual studies, to increase statistical power and synthesise their findings.

Odds A ratio of the number of people incurring an event to the number of people who do not have an event.

Odds ratio Ratio of odds of a specified characteristic in the treated group to the odds in the control group.

Point prevalence Proportion or percentage of individuals with a characteristic (e.g. abstinence from smoking or smoking reduction) at a specific time.

Quality of life A concept incorporating all the factors that might impact on an individual's life, including factors such as the absence of disease or infirmity and also other factors that might affect their physical, mental and social well-being.

continued

Glossary *continued*

Quality-adjusted life-year (QALY) An index of health gain where survival duration is weighted or adjusted by the patient's quality of life during the survival period. QALYs have the advantage of incorporating changes in both quantity (mortality) and quality (morbidity) of life.

Risk ratio The ratio of risk in the treated group to the risk in the control group.

Sustained abstinence Continuous abstinence from smoking of specified duration.

List of abbreviations

ASH	Action on Smoking and Health
CDTQ	cut down to quit
CI	confidence interval
CO	exhaled carbon monoxide
CRD	Centre for Reviews and Dissemination
CYP2A6	cytochrome P450 2A6
DARE	Database of Abstracts of Reviews of Effects
DOH	Department of Health
EED	Economic Evaluation Database
GHS	General Household Survey
HEED	Health Economic Evaluation Database
HR	hazard ratio
HRQoL	health-related quality of life
ICER	incremental cost-effectiveness ratio
IPD	individual patient data
ITT	intention-to-treat
LCI	lower limit of 95% confidence interval
LYG	life-year gained
MHC	major histocompatibility complex
MHRA	Medicines and Healthcare products Regulatory Agency
NNT	number-needed-to-treat
NRT	nicotine replacement therapy
ONS	Office for National Statistics
OR	odds ratio
OTC	over-the-counter
PSS	Personal Social Services
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
RR	relative risk
SF-36	Short Form with 36 Items
UCI	upper limit of 95% confidence interval

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

Background

Approximately 25% of adults in the UK are smokers. Smoking is associated with numerous diseases, including cancer and heart disease, and smokers have reduced life expectancy. Nicotine in cigarettes renders them addictive so that smokers generally find it extremely difficult to give up their habit. Most smokers (around 70%) say they would like to stop but some express an unwillingness or inability to do so in the near future. Nicotine replacement therapy (NRT) attempts to substitute the nicotine obtained from smoking with that derived from gum, inhaler or patch, so that smokers are enabled to quit smoking and then gradually become independent of nicotine.

Some nicotine replacement therapies that were previously licensed in the UK for abrupt quitting from smoking have recently been granted a new licensed indication called 'cut down to stop' or 'cut down to quit' (CDTQ). This aims at smokers who express unwillingness or inability to stop smoking in the short term by enabling them gradually to cut down their smoking over an extended period while supported by NRT so that they may eventually become able and willing to attempt to quit altogether. Thus the CDTQ stratagem involves more prolonged support with NRT than the previously licensed indication for an abrupt quit attempt and by definition targets a different population of smokers.

Objective

The primary objective of this assessment report was to examine the effectiveness and cost-effectiveness of NRT for CDTQ smoking.

Method

Searches of bibliographic databases and contact with experts and industry were undertaken in order to identify relevant systematic reviews, randomised controlled trials (RCTs) and existing economic analyses of CDTQ. Searches were carried out in July 2006. Evidence from RCTs was included in the report if the population consisted of smokers who declared an inability or unwillingness to attempt to quit smoking in the short term, if the intervention encompassed a cut-down smoking programme supported by NRT and if the comparator was a cut-down programme with placebo or other support.

Systematic reviews were included if at least one electronic database had been searched and if RCTs documenting quit rates in smoking reduction programmes with NRT were reviewed. Economic studies were included if they encompassed cost-effectiveness or cost–utility analysis of CDTQ programme(s).

A systematic review of RCTs was performed that included meta-analyses of smoking outcomes and analyses of individual patient data.

The outcome taken as an indicator of success was the proportion of smokers who sustained continuous abstinence from smoking. Various measures for this outcome have been used, and these encompass different durations of continuous abstinence. The measures reviewed were:
(1) a defined period of sustained abstinence that starts within the first 6 weeks of NRT treatment (the measure used in most RCTs); and (2) at least 6 months' continuous abstinence that starts at any time within the NRT treatment period (a measure that can be calculated from individual patient data in the RCTs).

A decision analytical model was constructed to estimate the cost-effectiveness of CDTQ from the NHS perspective. CDTQ was considered as a choice option for individual smokers and also as a policy option.

Results

Effectiveness

No systematic reviews of the effectiveness of CDTQ were identified. No RCTs specifically addressing CDTQ were identified. Seven randomised placebo-controlled trials satisfied the inclusion criteria; six of these were industry sponsored. The RCTs were primarily designed to investigate the effectiveness of a smoking

reduction programme. Sustained smoking cessation was only reported as a secondary outcome in these trials and required commencement of cessation within the first 6 weeks of treatment.

In four RCTs smokers received NRT gum or placebo, in two NRT inhalator or placebo and in one placebo-controlled RCT smokers exercised free choice of the type of NRT they received.

Meta-analyses of the study level results for sustained abstinence from smoking, point prevalence of smoking abstinence, sustained smoking reduction and point prevalence of smoking reduction demonstrated statistically significant superiority of NRT compared with placebo for all four outcomes. The proportion of participants who achieved sustained abstinence commencing within the first 6 weeks of treatment was meagre (about 2% of those in receipt of NRT). This is not surprising given that it is inherently unlikely that smokers who had expressed unwillingness or inability to quit in the short term would stop within 6 weeks. Therefore, individual patient data from unpublished reports of five RCTs were used to calculate sustained abstinence of at least 6 months starting at any time during the treatment period (generally 12 months). Using this more realistic criterion for sustained abstinence, meta-analysis indicated statistically significant superiority of NRT versus placebo [relative risk 2.06, 95% confidence interval (CI) 1.34 to 3.15]. The proportions achieving this outcome across all five RCTs were 6.75% (95% CI 5.3 to 8.56%) of participants in receipt of NRT and 3.29% (95% CI 2.56 to 4.21%) of those receiving placebo. The number-needed-to-treat was 29. This measure of sustained abstinence was used for economic modelling.

No significant treatment-related adverse events were reported in the trials and minor events were similar in frequency and type to those in previously reported studies of NRT. None of the included studies reported health-related quality of life measures for abstainers from smoking.

Cost-effectiveness analysis

No existing economic analyses of CDTQ were identified. A *de novo* decision analytic model was constructed to estimate the cost-effectiveness of making CDTQ with NRT available for smokers unwilling or unable to attempt an abrupt quit. The outcome measure was expected quality-adjusted life-years (QALYs). The model also took account of the possibility that some smokers willing to attempt abrupt quitting might instead switch to CDTQ. Smokers leaking from abrupt quit to CDTQ were assumed either to experience a 'CDTQ-success rate' or to retain the abstinence success rate of abrupt quitters.

The model compared three CDTQ NRT options (over-the-counter NRT; brief advice + NRT repeat prescriptions; smokers' clinic with individual or group counselling + repeat NRT prescriptions) with no quit attempt, attempt without NRT, abrupt quit attempt with NRT in any of three options (over-the-counter NRT; brief advice + NRT repeat prescriptions; smokers' clinic with individual or group counselling + NRT repeat prescriptions). A smoker may thus switch to any one of three CDTQ modes from any of five other behaviours (no quit attempt, quit attempt without NRT, abrupt quit attempt with NRT in any of three available modes). Further analyses compared each CDTQ option with a mix of no quit attempt and corresponding abrupt quit option. Lastly, a 'full analysis' compared a range of CDTQ options with the full mix of non-CDTQ options.

CDTQ success rate was based on trials in which behavioural support was variously described as minimal or moderate (at least eight scheduled clinic visits). In a real-world setting this corresponds more closely to 'smokers' clinic' than to 'brief advice plus repeat prescription'.

Model results suggest that CDTQ with NRT delivers incremental cost-effectiveness ratios (ICERs) ranging from approximately £1500/QALY to approximately £7700/QALY depending on the age at which smoking cessation was achieved and the modes of CDTQ delivery.

Assuming applicability to a single population, CDTQ was not cost-effective compared with abrupt quitting.

If CDTQ with NRT were to be offered on the NHS as a matter of policy, the base-case results suggest that it would only be effective and cost-effective if a substantial majority of the people attempting CDTQ with NRT were those who would otherwise make no attempt to quit. This result is robust to considerable variation in the forms of CDTQ with NRT offered, and to the assumptions about QALY gained per quit success.

However, incremental cost-effectiveness ratio values are sensitive to assumptions about success

rates for different methods of attempting to quit smoking. The base case assumes that willing abrupt quitters who switch to CDTQ have the same success rate in CDTQ as smokers who are unwilling to try abrupt quit. If it is assumed that smokers who might otherwise try abrupt quitting and undertake CDTQ instead retain a fixed success rate (i.e. the same success rate in CDTQ as in abrupt quit), then all forms of CDTQ provision appear to be cost-effective. This assumes that success rate is more strongly related to characteristics of smokers than to the particular nature of the NRT intervention.

Conclusion

Meta-analysis of RCT evidence of quit rates in NRT-supported smoking reduction studies indicates that NRT is an effective intervention in achieving sustained smoking abstinence for smokers who declare unwillingness or inability to attempt an abrupt quit. The 12-month sustained abstinence success rate in this population (approximately 5.3% with NRT versus approximately 2.6% with placebo) is considerably less than that documented for an abrupt quit NRT regime in smokers willing to attempt an abrupt quit with NRT (which according to other systematic reviews is approximately 16% with NRT versus 10% with placebo).

Most of the evidence of effectiveness of CDTQ in this report came from trials that required considerable patient–investigator contact. Therefore, for CDTQ with NRT to generate similar abstinence rates for this recalcitrant population in a real-world setting would probably require a similar mode of delivery.

Decision analytic modelling based on reasonable assumptions about costs, benefits and success rates suggests that CDTQ is highly cost-effective compared with no quit attempt. CDTQ remains cost-effective if dilution from abrupt quitting forms a small proportion of CDTQ attempts. In an alternative analysis in which smokers who switch from an abrupt quit to CDTQ retain the success rate of abrupt quitters, all forms of CDTQ appear cost-effective.

Recommendations for further research

Randomised trials in recalcitrant smokers allowing head-to-head comparison of CDTQ delivered with various NRT modalities (e.g. inhalator, nasal spray, lozenge, gum, patch) would be informative. Research is also needed into the best ways of implementing a CDTQ strategy and integrating this with abrupt quit options in the context of all UK smoking services.

Chapter 1

Aim of the review

The aim of this review was twofold. First, to undertake a systematic review of the clinical effectiveness of 'cut down to quit' (CDTQ) with nicotine replacement therapy in smoking cessation. Second, to review published economic evaluations and undertake a *de novo* cost-effectiveness analysis of CDTQ with nicotine replacement therapy in smoking cessation.

Chapter 2

Background

Description of underlying health problem

Smoking is one of the greatest causes of illness and premature death in the UK. It causes a wide range of diseases, including cancers, breathing problems, heart attacks and other arterial disease that in extreme cases may require limb amputation. Giving up reduces the health hazards of smoking. Exposure to second-hand smoke increases the risk of disease in non-smokers. Children are especially exposed to secondary smoke. Environmental tobacco smoke has been linked with lung cancer in non-smokers.

The nicotine in tobacco causes addiction. After inhaling cigarette smoke, nicotine reaches the brain, where it brings about changes responsible for the craving of tobacco that make it very difficult for people to stop smoking. About 70% of smokers say they would like to stop. Currently around half of smokers attempt to quit in any given year.[1] If smokers who wish to stop managed to do so, the public health impact and individual benefits would be enormous. Therefore, it is crucial that the people who want to stop smoking continue to be encouraged to stop and are offered a means of doing so.

Some smokers are willing to try to cut down but do not intend to quit and may not make a quit attempt. Several trials have been completed recently that enrolled people who did not want to stop smoking in the short term.[2] These trials showed that people who try to cut down aided by nicotine replacement therapy (NRT) are more likely to do so than those unaided. A secondary outcome in these trials was quitting and, on the basis of positive results in some of the trials, Pfizer, a manufacturer of NRT, applied for and obtained a licence in the UK for use of nicotine gum and nicotine inhalator for a new indication called 'cut down then stop'[3] (referred to as CDTQ throughout this report). Although smoking reduction, not quitting, was the aim of these trials, it is ethical that patients are advised to quit and many individuals attempted to stop smoking even though they were initially unwilling to do so. Some of these succeeded. A variety of mechanisms could be advanced to explain this success.

Cut-down smoking guidance for health providers and others has been prepared by Action on Smoking and Health (ASH)[4] and was published approximately concurrently with the granting of the new licensed indication for NRT. This particular set of guidance discussed NRT-assisted reduction in the context of a private activity entered into by smokers with input of professional advice only to initiate the strategy. However, clinical trials generally do not work in this way so that evidence relevant to effectiveness of this approach is unlikely to exist. The ASH publication stated that, should CDTQ be supported on the NHS, then patients should prove a 50% reduction in intake by week six of NRT or no further NHS prescriptions should be issued. Neither the evidence base nor the rationale for this stricture was stated.

This report assesses the scientific research on how well CDTQ works, whether there are any associated harms and whether it provides good value for money from the NHS perspective.

Nicotine replacement therapy

When smokers are repeatedly exposed to nicotine, the number of nicotinic receptors in the brain increase and tolerance to the effects of nicotine develops. Smokers develop tolerance to some of the behavioural and sympathomimetic effects of nicotine over time, a process called neuroadaptation.[5] When nicotine is stopped abruptly, withdrawal symptoms occur as a consequence of neuroadaptation. Most withdrawal symptoms associated with tobacco dependence are clinically and/or psychologically significant and include the following: aggressiveness, anxiety, confusion, impatience, inability to concentrate, irritability, nicotine craving, restlessness, constipation, dizziness, headache, sweating and difficulty sleeping.[6] Most withdrawal symptoms reach maximum intensity within 24 hours of cessation and diminish in intensity over 2–4 weeks.[6] Some symptoms such as desire to smoke can persist for months or even years after cessation. Many smokers consider there to be benefits from smoking, such as control over weight gain and relief from stress, so that while the

attempt to stop smoking persists there is a perceived loss of benefits.[6]

The pronounced withdrawal symptoms and tobacco craving that occur on trying to quit smoking may be offset by various therapies, including several modes of NRT. A previous Health Technology Assessment[6] found that NRT is a more effective intervention for smoking cessation than many other healthcare interventions, that it is associated with a low level of adverse events and that it is cost-effective in terms of life-years saved. However, some patients fail to quit despite the availability of NRT and others are not attracted to an intervention that aims to achieve quitting smoking immediately or in the very short term. For these reasons, an additional strategy has been proposed that has been called 'cut down to quit' (CDTQ), also known as 'cut down then stop' and 'nicotine-assisted reduction to stop'. This aims at a structured gradual reduction in tobacco consumption while the patient is supported with NRT, eventually leading to an increased probability of complete cessation from smoking.

Place of the intervention in the treatment pathway(s)

NRT can assist smokers in reducing smoking by replacing some of the nicotine formerly obtained from tobacco. Nicorette® gum and Nicorette® inhalator (Pfizer) are licensed for CDTQ in the UK. The licensed indication is specifically targeted at so-called 'recalcitrant smokers', that is, those who are unwilling or feel unable to stop smoking in the near future but nevertheless, from whatever motivation, are willing to try to cut down the volume of their smoking. The proportion of the smoking population that is encompassed in this category is thought to be considerable.

A structured schedule for CDTQ was not linked directly to granting of the newly licensed indication. An illustrative example of one possible structure for a CDTQ is as follows:[4]

- *Step 1*: (0–6 weeks) – START CUTTING DOWN. Smoker sets target for both the number of cigarettes per day to cut down and a date to achieve it by. (Recommend at least a 50% reduction for best results). Smoker advised to use Nicorette gum or inhalator (currently only Nicorette products are covered by the UK licence) as required to manage cravings. Smoker advised to return if not cut down within 6 weeks.
- *Step 2*: (6 weeks up to 6 months) – CONTINUE CUTTING DOWN. Smoker continues to cut down cigarettes using Nicorette gum or inhalator. Goal should be to completely stop by 6 months. Smoker advised to return if not managed to stop smoking within 9 months.
- *Step 3*: (within 9 months) – STOP SMOKING. Smoker stops all cigarettes and continues to use Nicorette gum or inhalator to relieve cravings.
- *Step 4*: (within 12 months) – STOP NICORETTE.

After successful quitting, the use of NRT gum or inhalator is gradually cut down, then stopped completely (within 3 months of stopping smoking).

The CDTQ programme might help smokers to gain confidence in their ability to do without cigarettes and be able to choose a stop date that is achievable for them.

CDTQ with NRT may be used as a stand-alone intervention or with an adjunct such as motivational support.

Aetiology, pathology and prognosis

The aetiology of smoking is uncertain. Dependence on nicotine is a complex trait that is associated with genetic and environmental factors.

Studies of twins and families who smoke showed that inherited factors account for about 50% of the variability in smoking initiation and about 70% of the variance in liability to nicotine dependence.[7,8] Cytochrome P450 enzymes are the main candidate genes that are associated with nicotine metabolism. Sib-pair linkage analysis has shown a significant association between the ever–never smoking trait and four genomic regions, including two adjacent markers on chromosome 6. A recent study has shown a highly significant association between ever-smoking and specific major histocompatibility complex (MHC) haplotype. This implied a potential role of the MHC-linked olfactory receptor genes in the initiation of smoking.[9]

Smoking behaviour may be influenced by genetic variations. Smokers who possess a particular variant of a gene that seems to be associated with

a craving for tobacco are more likely to relapse after a treatment programme than smokers without the variant. The effect of cytochrome P450 2A6 (CYP2A6)-reduced-activity polymorphisms on smoking cessation and cigarette consumption has been noted.[10] Discovery of genes which are associated with smoking may lead to improved smoking cessation treatment options.

Social factors are also strongly related to the initiation, maintenance and cessation of smoking. For example, people who grow up in lower social class households are more likely to become smokers than those in more affluent households and maintain this disadvantage into adulthood independently of their current social class.[11,12] Smoking in adolescence is strongly related to the smoking habits of friends and peers,[13,14] with some authors proposing a contagion model of smoking, and others emphasising the selection of like-minded individuals as an explanation for the homogeneity of friendship groups' smoking status.[15–19] Furthermore, having a partner who disapproves of smoking is an incentive to attempt to give up,[20] and having a non-smoking partner is a good prognostic factor in maintaining abstinence.[21] On the other hand, social class is strongly related to the prevalence of smoking in the UK and people from relatively disadvantaged backgrounds are less likely to succeed when they do stop smoking.[22,23]

Epidemiology

The estimated number of adult smokers in the UK is about 11.6 million.[1,24] Information on the national prevalence of cigarette smoking in the adult population is available from several sources, including the General Household Survey (GHS)[22] and the Omnibus Survey.[1] The GHS found that 26% of men, 23% of women and 25% of the whole adult population smoke and the Omnibus Survey[1] found that 25% of men, 23% of women and 24% of the whole adult population smoke.

The prevalence of adult smoking has been reduced by about 3% in one decade; the present prevalence is about 25% compared with 28% amongst 13 million adults aged 16 years or over in the UK in 1996.[25] Smoking trends in the UK projected to 2020 are illustrated in *Figure 1*.[26]

In December 1998, the Department of Health (DOH) published a White Paper entitled "Smoking Kills – a White Paper on Tobacco".[25] This document described the serious health consequences of smoking and proposed targets and practical measures to make inroads into the prevalence of smoking. The aim was to reduce adult smoking from 28% in 1996 to 24% by 2010.

Although smoking has decreased in prevalence since 1996, the smoking rates among the poorest

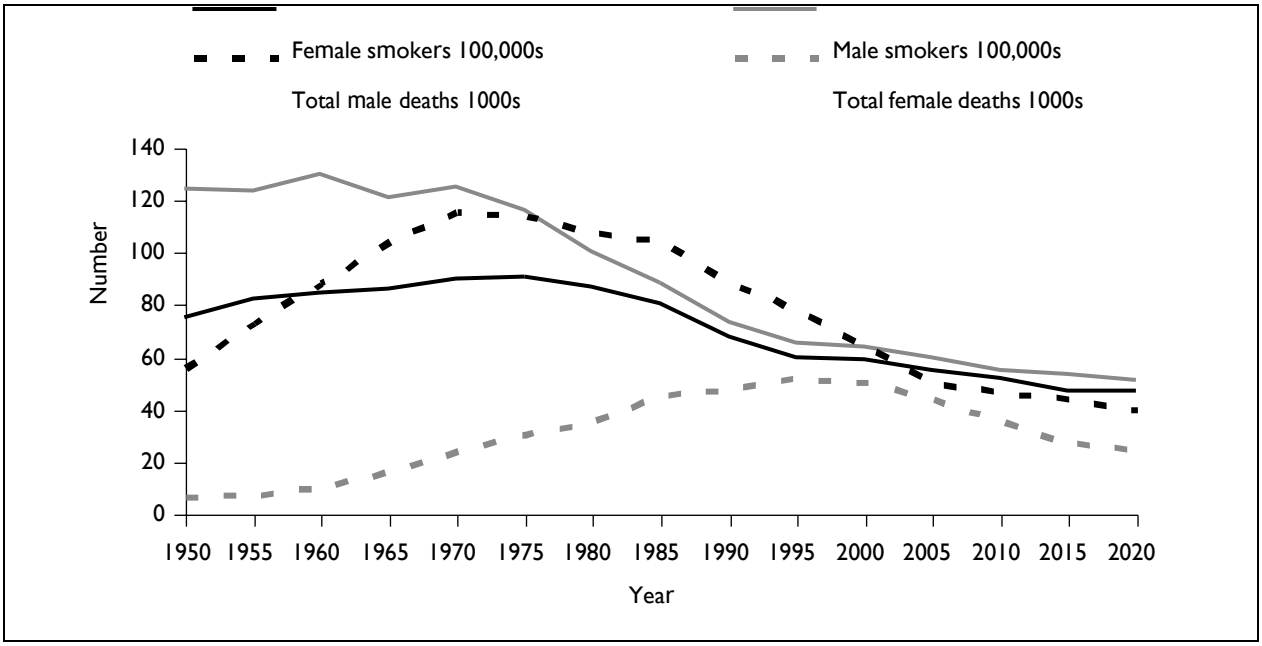

FIGURE 1 *Smoking and mortality trends: UK 1950 to 2020. Redrawn from ASH publication "Nicotine assisted reduction to stop*

(NARS) guidance for health professionals on this new indication for nicotine replacement therapy".[26]

in Britain have remained unchanged for more than a decade.[27] In September 2000, the first ever smoking inequalities target was set out in the Cancer Plan, and was repeated in the Public Service Agreement in 2004.[28,29] These aimed to reduce smoking rates among manual groups from 32% in 1998 to 26% by 2010.

Impact of health problem

Smoking is the biggest single threat to health faced by large sections of the population.[25] Considerable harms associated with smoking include increased mortality, risk of disease due to passive smoking and high cost.

Increased mortality

Smoking has become the single greatest cause of preventable illness and premature death in the UK. In 2000, there were about 114,000 UK deaths attributable to smoking, 22% and 16% of all male and female deaths, respectively.[3]

Smoking causes or is strongly associated with many types of cancers, including lung, larynx, pharynx, oesophagus, bladder, kidney and pancreas cancers. Overall, smoking causes 46,500 deaths from cancer per year in the UK, which accounts for one-third of cancer deaths.[25]

Smoking is an important cause of cardiovascular disease. The British doctors' cohort study found that mortality from coronary heart disease was 50% higher in smokers than in non-smokers.[30] Around 40,300 deaths a year in the UK from all circulatory diseases are attributable to smoking. It accounts for one out of every seven deaths from heart disease.

Smoking is the main cause of chronic obstructive lung disease, a cause of pneumonia and also causes or aggravates a wide variety of illnesses including asthma, osteoporosis, peptic ulcer, erectile dysfunction, chronic rhinitis and multiple sclerosis.[3] Smoking causes 83% of deaths from chronic obstructive lung disease, including bronchitis.[31]

Passive smoking

Although the risk of diseases for non-smokers from passive smoking is small compared with that for the active smokers, the overall impact is probably large because the diseases induced are common.[3] It has been estimated that several hundred people a year in the UK die from lung cancer brought about by passive smoking. Passive smoking may also contribute to deaths from heart disease.[25]

Asthma sufferers are especially sensitive to passive smoking. Children are usually at particular risk of bronchitis and pneumonia and other lower respiratory tract infections as they have little choice over their exposure to tobacco smoke. Almost half of all children in the UK are exposed to tobacco smoke at home.[3] It has been estimated that around 17,000 hospital admissions per year of children under 5 years old are attributable to parental smoking and that mothers' smoking could account for one-quarter of cot deaths.[25] Smoking during pregnancy is linked to low birth-weight and may be associated with increased ill-health of babies.[25]

The cost of smoking

The cost of smoking is high not only for the NHS but also for families. It is estimated that smoking costs the NHS up to £1.7 billion every year.[25] In 1996, about 55% of lone parents on Income Support smoked an average of five packs of cigarettes per week, suggesting that lone parent families spent over £357 million on cigarettes during that year.

Current service provision

The UK has well-established smoking treatment services to help smokers to quit smoking. The UK government White Paper on tobacco published in 1998 set out development plans for smoking cessation treatment services as part of the English NHS.[32] Between April 1999 and March 2000, smoking cessation services were established in only 26 Health Action Zones (HAZs) with funding provided by the central government. Between April 2003 and March 2006, central government provided £138 million for the smoking cessation services.[33] Services were set directed at smokers motivated to quit and prioritised for the young, the pregnant and the disadvantaged.[33] It suggested that smokers need to be strongly motivated and able to deal with the inevitable cravings for nicotine with the help of NRT, which is available over-the-counter (OTC) in pharmacies.

NRT and bupropion (Zyban) are the only pharmacological products that have been licensed in the UK to help smokers quit. Six different NRT delivery systems are available: patches, gum, inhalators, tablets, lozenges and nasal sprays. A typical course of NRT lasts approximately 10 weeks. Originally smoking cessation treatment was licensed for adult smokers. Recent licence extensions for NRT have encompassed new populations of smokers, including adolescents aged

12–18 years, pregnant and breastfeeding women, cardiovascular disease patients, diabetes mellitus patients and renal or hepatic impaired patients.

Previously NRT was only authorised for abrupt quitting in the UK. However, smokers who want to stop immediately may represent only a very small proportion of smokers. The Medicines and Healthcare products Regulatory Agency (MHRA) recently considered seven double-blinded randomised placebo-controlled trials carried out in smokers not motivated to stop in the short term. An abstinence rate of 8.6% across these studies was achieved for NRT recipients compared with 4.5% for placebo recipients. The adverse events recorded in the studies did not indicate any issues for concern. Consequently, in September 2005, Nicorette® gums (2 and 4 mg) and Nicorette® inhalator (10 mg) were licensed for CDTQ in the UK.[26] It was suggested that gums and inhalators should be used between smoking episodes to reduce smoking. Smokers should make a quit attempt once they feel ready to do so. Professional advice should be sought if no reduction occurs in 6 weeks or no quit attempt in 9 months.

Current usage in the NHS

The very recent licensing of CDTQ means that there is little information about current usage of this intervention strategy. About 70% of smokers currently report that they would like to stop smoking, but only about 49% of smokers attempt to quit in any given year.[1] An unpublished household survey (IPSOS[34]) interrogated a representative sample of smokers and ex-smokers and found that amongst ex-smokers 18% had cut down prior to quitting successfully.

Anticipated costs associated with intervention

An estimate of the additional cost of the new CDTQ indication has been made in the ASH guidance for CDTQ published in October 2005.[28] A figure of £55 million per annum for England was calculated. This estimate assumed that the main cost burden to the NHS would come from prescribing NRT for cutting down and that there are about 10 million smokers in England. It was conceded that the estimate was grounded in 'educated guesswork'. The authors estimated the cost per life-year gained (LYG) by the additional smokers who would stop by CDTQ as approximately £5000. This was based on an estimate of £1000 for treatment by NRT-supported abrupt cessation, the assumption that on average about 2–3 times more NRT would be used for CDTQ than for an abrupt quit treatment and an estimated effect size for CDTQ of half that observed for the abrupt quit intervention.

Chapter 3

Clinical effectiveness

The aim of this section is to review systematically the published and unpublished evidence relating to the effectiveness of CDTQ using NRT. A further objective is to ascertain if effectiveness varies amongst subgroups of patients.

Methods

Search strategy

An established search protocol was used to identify systematic reviews of CDTQ with NRT. Comprehensive searches for primary studies of the effectiveness of CDTQ with NRT were conducted using bibliographic databases, bibliographies of relevant reviews and primary studies and contact with authors and industry. Searches were carried out in July 2006 without language restrictions and included a combination of index and text words. The search strategy is described in detail in Appendix 1 and is summarised below:

1. Bibliographic databases:
   (a) Cochrane Library (Wiley) 2006 Issue 2
   (b) MEDLINE (Ovid) 1992–July 2006
   (c) MEDLINE In-Process (Ovid) 12 July 2006
   (d) EMBASE (Ovid) 1992–week 27 2006
   (e) CINAHL (Ovid) 1992–July 2006
   (f) PsycINFO (Ovid) 1992–July 2006
   (g) Science Citation Index (Web of Science) 1992–July 2006.
2. Research registries of ongoing trials: National Research Register 2006 Issue 2, Current Controlled Trials *meta*-Register and Clinical Trials.gov.
3. Citations of relevant studies and reviews.
4. Further information was sought from contacts with experts and industry.
5. Information in licensing authority and industry documents.

All titles and abstracts were screened for relevance by two reviewers and discrepancies resolved by discussion. Full paper copies of any titles or abstracts judged of potential relevance were obtained. Two reviewers judged the relevance of each full text according to predefined criteria (see below). Studies that failed to satisfy all criteria were excluded and the reason for their exclusion was recorded. Any discrepancies were resolved by discussion and with the involvement of a third reviewer where necessary.

Inclusion criteria

Inclusion criteria for systematic reviews of CDTQ for smoking cessation were:

- At least one electronic database (e.g. MEDLINE) was scrutinised using a stated search strategy.
- RCT studies of CDTQ were reviewed.
- Quit rates were quantitatively reviewed and/or meta-analysed.

The inclusion criteria for primary studies of CDTQ for smoking cessation were:

- Population: smokers who are currently unable or unwilling to quit abruptly.
- Intervention: NRT with gum or inhalator alone or as part of combination therapy (e.g. motivational support).
- Comparator: placebo or no treatment, non-NRT drugs for smoking cessation, psychological interventions (e.g. motivational support) for quitting. Where the intervention embraced an adjunct therapy so also will the comparator.
- Outcome measures: quit rates must be provided.
- Study design: randomised controlled trials (RCTs).

The main clinical outcome of interest was the number of participants who sustained abstinence from smoking for substantial periods of time, for example 6, 12 or more months. Where studies did not report sustained abstinence, authors were contacted to obtain these data. Other outcomes of interest were health-related quality of life (HRQoL), reduction in smoking and adverse events.

The protocol inclusion criteria for primary studies specified the intervention as gum or inhalator. In practice, some studies allowed choice of NRT mode for the intervention group; these studies therefore consider NRT as a generic intervention. We modified application of the inclusion criteria so as to capture such studies irrespective of whether data could be disaggregated for the different forms of NRT.

Outcomes

Primary outcomes

- sustained abstinence
- point prevalence abstinence
- sustained reduction
- point prevalence reduction.

Secondary outcomes

- serious adverse events
- NRT usage
- HRQoL.

Data extraction

Data were extracted by one reviewer using a standard data extraction form and independently checked for accuracy by a second reviewer. Disagreements were resolved by discussion and with involvement of a third reviewer when necessary. Where information was missing it was sought from authors or sponsors of trials. Data from studies with multiple reports (published and/or unpublished) was extracted and reported as a single study; in the case of reported discrepancies, information from the fullest study report was utilised.

Quality assessment

The quality of the individual studies was assessed by one reviewer and independently checked for agreement by a second reviewer. Disagreements were resolved by consensus and if necessary a third reviewer was consulted. The quality of included studies was assessed according to guidelines proposed in NHS Centre for Reviews and Dissemination (CRD) Report No. 4.[35]

Data synthesis and analysis

The main results were placed in tables. Studies were grouped according to outcome and comparison groups. Where possible, the results were summarised by calculating relative risks (RRs) [including hazard ratios (HRs) if appropriate] or odds ratios (ORs) with 95% confidence intervals (CIs). Meta-analysis was carried out where appropriate.

Where possible, data from different durations of follow-up were examined separately and continued abstinence rather than point prevalence was preferred to assess levels of smoking cessation. Where judged possible, subgroup analyses were conducted to assess differences in effectiveness between different participant groups or interventions. Depending on availability of data, the following subgroups were to be examined with regard to response to CDTQ with NRT: age (including adolescents), sex, ethnicity, occupation, employment status, extent of social support, cardiovascular disease, pregnancy, length of smoking, intensity of smoking and social class, type of NRT and its setting, and combination therapies.

Any individual patient data (IPD) made available were employed to explore time-related rates of quitting.

Developing a measure of sustained abstinence

In most smoking cessation studies, all individuals begin attempts to stop smoking at commencement of the study. If they relapse, they are counted for ever as a sustained abstinence failure, even if subsequently they make a renewed quit attempt and succeed. For this report, abstinence sustained for at least 6 or 12 months was the preferred outcome measure as it can be reliably converted into lifetime abstinence, which in turn can be reliably converted into LYGs or quality-adjusted life-years (QALYs).

In CDTQ, participants have the opportunity to use NRT for a prolonged period (usually 9–12 months), during which time they may make several quit attempts. Unlike normal cessation studies, where the index quit attempt is the first, in CDTQ studies, treatment continues whether or not a person attempts to stop and fails. Thus, only the last sustained attempt is the critical measure of success and prior failures do not nullify any later success (as they would in a typical abrupt-cessation trial). Participants could also start a quit attempt late in the period of treatment with NRT and continue abstinence to the end of follow-up. Some such participants may not have achieved 6 months of sustained abstinence (because of lack of follow-up time). It would be inappropriate to count such individuals as treatment failures, therefore a method to reflect the fact that follow-up was censored was developed using IPD. This was the outcome used for cost-effectiveness modelling and was a primary outcome in the analysis of effectiveness.

For studies where IPD was available, the rate of sustained abstinence for at least 6 months was estimated using the following procedure. The potential number of smokers who sustained abstinence for at least 6 months measured from any time point during the treatment period (N_6) was estimated. N_6 was calculated in two steps: first, the uncorrected number of smokers (N_6^u) who had sustained abstinence for at least 6 months within the study period (starting at any time within treatment period) was counted. Thus N_6^u was simply calculated from the IPD as the number of smokers who sustained abstinence for at least

6 months starting from any time point within the treatment period to the end of follow-up. Second, the censored number of smokers (N^c_6) who would have sustained abstinence for at least 6 months if the follow-up had been sufficiently extended was calculated. This censored estimate is the product of the numbers abstinent for less than 6 months [j (<6) months (N_j)] but still abstinent at end of study multiplied by the probability (P_j) that they would have gone on to remain abstinent for at least 6 months

$$N^c_6 = \sum_{j=1}^{5} N_j P_j.$$

P_j was obtained from the number of smokers who sustained abstinence for at least 6 months (N^u_6) divided by the number of smokers who sustained at least j months abstinence to the end of the follow-up period, excluding those who were censored (n_j)

$$P_j = N^u_6/n_j.$$

The detailed procedure to estimate of the potential number of smokers who sustained abstinence for at least 6 months starting from any time point during the treatment period is summarised as follows:

1. For the NRT group:
   (a) Calculate N^u_6, the number of smokers who sustained abstinence of at least 6 months starting from any time point within the treatment period to the end of follow-up.
   (b) Calculate N_j, j = 1, 2, 3, 4, 5, the number of smokers who sustained abstinence at least j months starting from any time point within the treatment period, but who were censored at the end of study follow-up.
   (c) Calculate P_j, j = 1, 2, 3, 4, 5, the probability that smokers would sustain abstinence for at least 6 months given that they sustained at least j months by the end of the follow-up period.
   (d) Estimate N_6, the potential number of smokers who sustained abstinence at least 6 months starting from any time point within the treatment period using:

$$N_6 = N^u_6 + N^c_6 = N^u_6 + \sum_{j=1}^{5} N_j P_j.$$

4. Obtain the pooled OR (NRT versus placebo) of sustained abstinence for at least 6 months across all studies.

The study duration in typical smoking trials is commonly about 12 months. Estimation of 6 months rather than 12 months sustained abstinence was chosen in this report because in order to calculate the latter a value for N_{12} would be required based on actual (i.e. non-censored) 12 months sustained abstinence. For a typical smoking trial of approximately 12 months, this would necessitate abstinence from day one and would represent an unrealistic target for most smokers, especially for those expressing unwillingness to quit in the short term (as is the case in CDTQ populations). Therefore, analyses based on 6 months duration, rather than 12 months, was judged a more reliable estimate of sustained abstinence.

Results

Quantity and quality of research

The search strategy yielded a large number of hits from each of the electronic bibliographic data bases that were searched (see *Figure 2*). Contact with experts and industry and searching reference lists of published papers yielded further studies. A total of 131 full texts of peer-reviewed published papers were obtained together with seven unpublished full trial reports supplied by Pfizer.

Several reviews that briefly touched on smoking reduction or CDTQ strategies for smoking cessation were amongst the full texts obtained; however none were systematic reviews so they were excluded.

Application of inclusion criteria for RCTs yielded seven trials, one represented by two full publications, three represented each by a peer-reviewed publication and an unpublished full trial report supplied by an industry sponsor, and three represented by unpublished full trial reports from industry. Various brief abstracts describing trials were also identified but did not meet the inclusion criteria.

Description of included studies

The main characteristics of the included studies are summarised in *Table 1*.

2. Repeat the above steps for the placebo group.
3. Calculate the OR of sustained abstinence for at least 6 months for each individual study (steps 1–2 above).

Sponsorship, type of study and country of origin

Of the seven included RCTs, six were industry sponsored. Three industry-sponsored trials remain

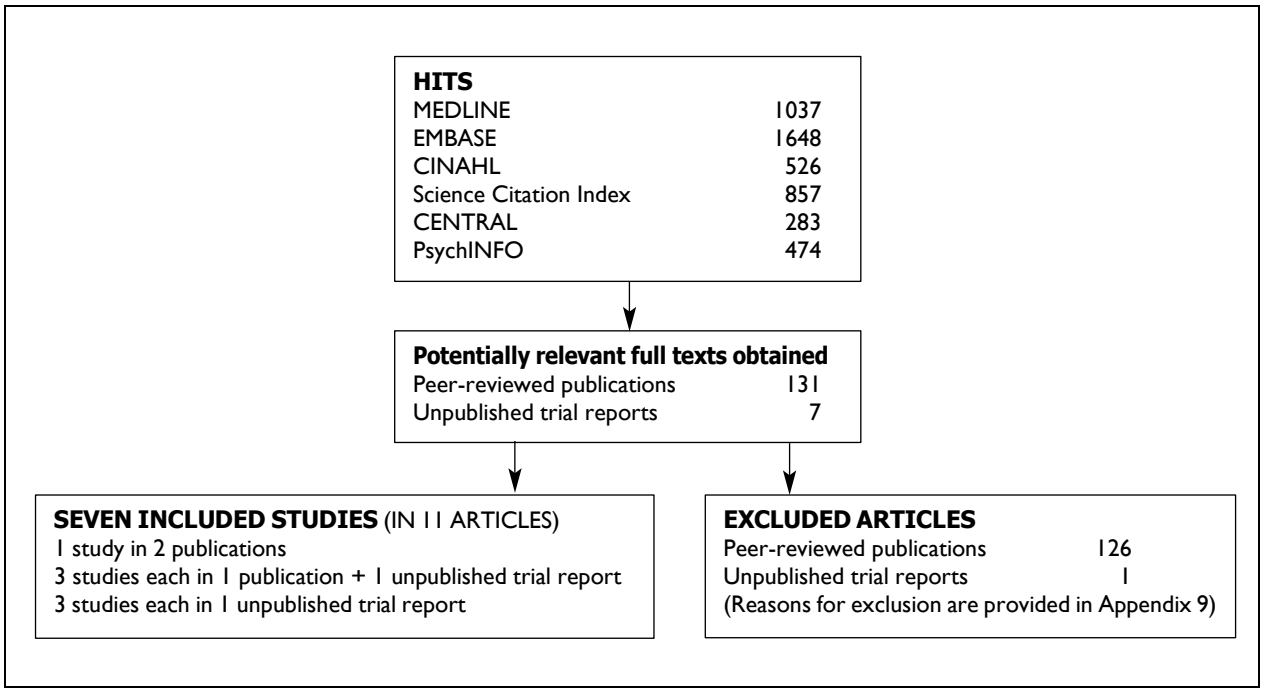

FIGURE 2 *Number of studies identified and included for effectiveness review*

unpublished as full papers (Rennard study 98-NNIN-027,[36] Haustein study 980-CHC-9021-0013[37] and Wood-Baker study 98-NNCG-017[38]), but details were made available by the industry sponsor (Pfizer) as full trial reports that included IPD. The Rennard study was published as a peer-reviewed article after the close of our searches. Similarly, for the three published industry-sponsored trials (Bolliger and colleagues,[39] study 96-NNIN 016;[40] Wennike and colleagues,[41] study 98-NNCG-014;[42] and Batra and colleagues,[43] study 980-CHC-1013-028[44]), Pfizer made available trial reports, two of which contained IPD (Wennike study 98-NNCG-014[42] and Batra study 980-CHC-1013-028[44]). These industry trial reports contained substantial information not detailed in the published papers of these trials. The seventh included trial (Etter), sponsored by the Swiss government, was published as two peer-reviewed full papers covering 6 months[45] and 26 months[46] follow-up, respectively. Contact with the author yielded additional unpublished information.

The studies all predated the approval of the newly licensed indication of NRT for CDTQ. Although all the studies fulfilled the inclusion criteria, in particular that the smokers recruited were unwilling or unable to quit in the near future, none were ostensibly designed as a CDTQ study. Furthermore, in no study was smoking cessation declared a primary outcome. All studies specified smoking reduction as the primary outcome and therefore probably they should be viewed as smoking reduction studies that exclusively recruited a recalcitrant population of smokers. Measures of smoking cessation were reported as secondary outcomes. Thus a legitimate view is that these trials are relevant to a CDTQ stratagem by default only.

None of the studies were conducted in the UK. Five were completed elsewhere in Europe (Germany, Batra and colleagues[43] and Haustein study 980-CHC-9021-0013;[37] Switzerland, Etter and colleagues[45,46] and Bolliger and colleagues;[39] Denmark, Wennike and colleagues[41]), one in Australia (Wood-Baker study 98-NNCG-017[38]) and one in the USA (Rennard study 98-NNIN-027[36]).

Trial design

The information provided in reports of industry-sponsored trials indicates that they were similar in design and execution, differing mainly in regard to the type of NRT (gum or inhalator) and duration of follow-up.

All studies were randomised parallel group trials with NRT and placebo arms. The Haustein trial (study 980-CHC-9021-0013[37]) had four parallel

TABLE 1 *Main characteristics of included studies*

Author, year Country *Trial dates*	Treatment duration (months) Follow-up (*months*)	Indication	Sample size (*NRT/control*) Mean age (years) % F/M	Baseline NRT/control CPD CO (ppm) FS	NRT[j] intervention (mg nicotine content)	Comparator	Other treatment components	Main outcomes measured	Funding trial code
Batra, 2005[43] Germany and Switzerland *Not reported*	12 *13*	Not intending to quit in next month, willing to change behaviour	364 (*184/180*) 42.6/43.5 45.9/35.2	27.9/29.6 29.1/28.2 5.7/5.9	Gum (4 mg) as desired up to 12 months	Placebo gum as desired up to 12 months	Clinic visits (9) Telephone: counselling Additional clinic visits as necessary	1. Smoking reduction 2. Abstinence (CO < 10 ppm)[e] 3. NRT use (SR and records) 4. Serum cotinine and SCN 5. Adverse events 6. Haematological risk factors[f]	Industry 980-CHC 1013-028[44]
Bolliger, 2000[39] Sweden and Switzerland *02/97 to 05/99*	18 *24*	Unwilling or unable to quit, wanted to reduce	400 (*200/200*) 46.4/45.8 57/48	28.2/30.3 27.1/27.1 5.5/5.6	Inhalator (10 mg)[k] as required to recommended maximum for up to 18 months	Placebo inhalator as required	Clinic visits (9) with counselling at each visit	1. Smoking reduction 2. Abstinence (CO < 10 ppm)[e] 3. NRT use (SR), acceptability 4. Plasma cotinine and SCN 5. QoL[g] and adverse events 6) Haematological risk factors[f]	Industry 96-NNIN-016[40]
Wennike, 2003[41] Denmark *02/99 to 05/00*	12 *24*	Not intending to quit within next month, wanted to reduce	411 (*205/206*) 45/44 65/59	24/24 29/27 6.4/6.4	Gum (2 or 4 mg; depending on FS) for up to 12 months	Placebo gum for up to 12 months	Clinic visits (9) with counselling at each visit	1. Smoking reduction 2. Abstinence (CO < 10 ppm)[e] 3. NRT use (SR) and compliance 4. Plasma cotinine and SCN 5. QoL[g] and adverse events 6. Haematological risk factors[f]	Industry 98-NNCG-014[42]
Wood-Baker, Unpublished Australia *06/99 to 03/01*	12 *15*	Not intending to quit within next month, wanted to reduce	436 (*218/218*) 42.9/45.3 54/55	29.0/27.4 25.8/25.9 6.6/6.4	Gum (2 or 4 mg; depending on FS) for up to 12 months as desired	Placebo gum for up to 12 months as desired	Clinic visits (9) Literature only on ways to achieve reduction	1. Smoking reduction 2. Abstinence (CO < 10 ppm)[e] 3. NRT use and compliance 4. Plasma cotinine and SCN 5. QoL[g] and adverse events 6. Haematological risk factors[f]	Industry 98-NNCG-017[38]

continued

TABLE 1 *Main characteristics of included studies (cont'd)*

Author, year Country ***Trial dates***	**Treatment duration (months) Follow-up (*months*)**	**Indication**	**Sample size (*NRT/control*) Mean age (years) % F/M**	**Baseline NRT/control CPD CO (ppm) FS**	**NRT intervention (mg nicotine content)**	**Comparator**	**Other treatment components**	**Main outcomes measured**	**Funding trial code**
Rennard, Unpublished USA *02/00 to 04/01*	12 *15*	Not intending to quit within next month, wanted to reduce	429 (*215/214*) 45.9/44.8 59/51	29.3/30.4 29.7/29.5 6.5/6.6	Inhalator (10 mg) as required to a recommended maximum for up to 12 months	Placebo inhalator as required	Clinic visits (9) Behavioural reduction information	1. Smoking reduction 2. Abstinence (CO < 10 ppm)[e] 3. NRT use (SR), acceptability 4. Plasma cotinine and SCN 5. QoL[h] and adverse events 6. Haematological risk factors[f]	Industry 98-NNIN-027[36]
Etter, 2004[45,46a] Switzerland *1999 to 2002*	6[c] *26*	Not intending to quit within next 6 months, wanted to reduce	923 (*265/269/389*) 43.2/41.7/42.9 46/51/56	29.8/29.4/30.2 Not reported 6.0/5.9/6.2	Free choice:[d] Inhalator (10 mg), gum (4 mg), patch (25 mg) for 6 months	Placebo NRT or no intervention	Literature only	1. Smoking reduction 2. Abstinence[i] 3. Product use 4. Change in FS 5. Adverse events	Government and industry, no trial code
Haustein, Unpublished[b] Germany *03/00 to 11/01*	9 *12*	Not intending to quit in next month, wanting to reduce	193 (*97/96*) 42.3/41.7 50/50	24.3/24.4 27.5/28.9 5.4/5.5	Gum (4 mg) *ad libitum* for 9 months	Placebo gum *ad libitum* for 9 months	Clinic visits (8) with verbal advice information at visits	1. Smoking reduction 2. Abstinence (CO < 10 ppm) 3. Product use 4. Change in FS 5. Adverse events	Industry 980-CHC-9021-0013[37]

CO, exhaled carbon monoxide; CPD, cigarettes smoked per day; FS, Fagerström test for nicotine dependence; QoL, quality of life; SCN, thiocyanate; SR, self-reported.
[a] This study had a third arm in which subjects received no treatment.
[b] This study had two further arms comparing short-term quit intervention with gum to placebo.
[c] Quitters continued to receive NRT after 6 months.
[d] Switching between products allowed.
[e] 7 day point prevalence.
[f] E.g. C-reactive protein, fibrinogen, white blood cell count.
[g] Short-form 36.
[h] Revised RAND 36-item Health Survey 1.0.
[i] 7 day and 1 month point prevalence.
[j] Gum and inhalator are Nicorette® products.
[k] Total available nicotine 4–5 mg.

arms, but two of these received intervention or placebo within an essentially abrupt quit design called 'short-term reduction' with the reduction phase lasting 4 weeks prior to a quit attempt. Only the 'long-term reduction' (CDTQ) NRT and placebo arms have been included in this report. The Etter study encompassed a 'no treatment' arm in addition to placebo and NRT arms (see below).[45,46]

Population

All studies recruited similarly aged men and women (mean age in the forties), with average cigarette consumption and Fagerström scores indicative of heavy smokers. Potential participants with overt heart disease, who were in receipt of psychiatric medications, who were pregnant or lactating, or had drug problems additional to nicotine, were generally excluded. Trials typically recruited approximately 400 smokers with about 200 randomised to each study arm. However, in the Haustein trial the number in each arm was approximately 100 (because four arms were compared), and the Etter trial recruited about 265 participants each to placebo and NRT arms. Recruitment was generally from smokers responding to advertisements.

Intervention

The trials compared NRT with placebo. NRT consisted of gum in four trials (Haustein, study 980-CHC-9021-0013;[37] Batra;[43] Wennike;[41] Wood-Baker, study 98-NNCG-017[38]) and inhalator in two trials (Rennard, study 98-NNIN-027;[36] Bolliger[39]). The Etter trial[45,46] differed from the other studies in that patients chose the NRT aid (gum, inhalator or patch) that suited them and were allowed to switch type of NRT during the trial. Prior to randomisation in two trials (Wennike, study 98-NNCG-014[42] and Wood-Baker, study 98-NNCG-017[38]), smokers were stratified into two groups according to their score in the Fagerström test for nicotine dependence; the less dependent group were administered 2 mg nicotine-strength gum whereas the more dependent group received 4 mg nicotine-strength gum; 4 mg nicotine-strength gum was used in the other gum trials.

NRT was available for only 6 months in the Etter trial[45,46] (except for quitters, who were allowed extended use of NRT) but in the other trials NRT availability was variously 9 months (Haustein, study 980-CHC-9021-0013[37]), 12 months (four trials: Batra;[43] Wennike;[41] Rennard, study 98-NNIN-027;[36] Wood-Baker, study 98-NNCG-017[38]) or 18 months (Bolliger[39]).

Comparator

The trials all provided placebo that was essentially indistinguishable in appearance and taste/smell from the NRT intervention.

The Etter study[45,46] included a third arm variously termed 'no treatment' and 'control' arm. Smokers in this arm, like the NRT and placebo arms, received a baseline 20-page booklet that described methods to reduce smoking and provided addresses of cessation clinics. All three arms received a mailed questionnaire follow-up at 3, 6 and 26 months. After baseline, only placebo and NRT groups were sent NRT or placebo every 2 weeks, together with further information about NRT products. Methods of reduction mentioned in the booklet presumably included use of NRT so that 'no treatment' group participants might be expected also to use these products. After the 6-months treatment period, use of NRT in the 'no treatment' arm was in fact greater than in the placebo arm (27.4% versus 17.1% of participants) and was similar to that in the NRT arm (28.5%).[45] This diffusion of NRT into the 'no treatment' and also placebo arms means that analyses up to 6 months are of greatest relevance for this report.

Additional elements of intervention/comparator

In the six industry-sponsored trials, treatment components over and above the receipt of NRT or placebo involved clinic visits. Between baseline and final follow-up, a further six or seven visits were scheduled. Clinic visits allowed investigators to gather outcome data and necessarily involved contact between participants and potential advisors. The Etter trial differed in that no clinic visits were involved and all contact with study participants was by post (or telephone for non-respondents). Participants in this trial received a 20-page booklet covering reasons for reducing cigarette consumption. As mentioned above, after 6 months smokers in the 'no treatment' arm used NRT products at about the same frequency as in the NRT arm. As all the trials were intended as smoking reduction trials, the main emphasis in verbal advice or in provision of written information material appears to have been smoking reduction rather than cessation; however, because failure to mention cessation is unethical, all trials involved advice to quit. The extent of behavioural support supplied at clinic visits in these trials was variously described as 'minimal' or 'moderate' and is difficult to gauge because reporting was not sufficiently explicit. It is likely that the support provided in the industry trials approximates to a counselling package offered in a real-world setting.[6]

Outcomes

Smoking status was monitored at various follow-up times during the studies; typically six to eight follow-up time points were used in the six industry-sponsored trials (e.g. 2 and 6 weeks and 4, 6, 9 and 12 months) and beyond 1 year in five studies: Batra;[43] Bolliger;[39] Wennike;[41] Rennard, study 98-NNIN-027;[36] Wood-Baker, study 98-NNCG-017.[38] The primary outcomes in all studies were smoking reduction measures, either point prevalence of reduction or sustained reduction. Smoking cessation was the outcome of greatest relevance to this report but, as previously mentioned, was only a secondary outcome in all seven included studies.

Smoking reduction required self-reported decrease in cigarette consumption of ?:50% relative to baseline. In all trials except the Etter study this was 'validated' as a measured carbon monoxide (CO) level in exhaled breath that was lower than that recorded at baseline. If cigarette consumption continued at baseline levels (no reduction), then there would be about an even chance that exhaled CO concentration would be recorded as lower than baseline. This potential weakness of the validation instrument would be felt mostly in the point prevalence measure of reduction. For sustained smoking reduction validation as measured CO levels reduced from baseline is more convincing since reduced levels would need to be recorded at consecutive measuring times and the probability of consecutive decreases in CO from baseline in absence of real reduction in smoking would be low.

The smoking cessation measures reported were point prevalence of abstinence and/or sustained abstinence. These measures depended on self-reporting in all studies, and in the six industry-sponsored studies required validation by an exhaled CO concentration of <10 ppm. Sustained abstinence recorded in the six industry-sponsored trials required continued abstinence at each scheduled follow-up starting before week six of the trial (Batra;[43] Bolliger;[39] Wennike;[41] Rennard, study 98-NNIN-027;[36] Wood-Baker, study 98-NNCG-017;[38] Haustein, study 980-CHC-9021-0013[37]). In the Etter study abstinence equated to no puff of tobacco in the last 7 days or no puff in the last 4 weeks.[45,46]

In some trials, additional smoking-related outcomes were reported such as percentage reduction from baseline in the number of cigarettes smoked, the CO level in exhaled breath and serum or plasma concentrations of cotinine, nicotine (or other nicotine-like or derived alkaloids) and thiocyanate (SCN). The biochemical analyses may be regarded as surrogate markers of smoking and/or NRT status. Thiocyanate measures were undertaken because these would be expected to reflect cigarette consumption irrespective of NRT usage.

In most studies, attitudes to smoking and HRQoL were measured by means of variously designed questionnaires. In some studies, haematological risk factors for disease were recorded.[36,38,39,41,43]

Quality of included studies

Guidelines proposed in NHS CRD Report No. 4 were used to assess the quality of the included RCTs.[35] *Table 2* summarises the results. According to these criteria, the studies were of high quality.

The full trial reports supplied by Pfizer indicated that the six industry-sponsored trials (Batra 980-CHC 1013-028,[44] Bollinger 96-NNIN 016,[40] Haustein 980 CHC-9021-0013,[37] Rennard 98-NNIN-027,[36] Wennike 98-NNCG-014[42] and Wood-Baker 98-NNCG-017[38]) were conducted according to very similar procedures. These were all placebo-controlled randomised double-blind studies with adequate randomisation and allocation concealment (although this was not explicit in Rennard study 98-NNIN-027). The Etter trial was single-blind by design and a method for allocation concealment was not explicitly stated.[45,46]

The effectiveness of participant blinding was not tested in the six industry-sponsored trials and it was possible that smokers who reduced their cigarette consumption in the placebo arms may have surmised they were not in the NRT arms because of the nicotine-withdrawal symptoms they experienced. Participants in the NRT arms may be less likely to guess their allocation. At 6 months into the Etter trial participants were asked to guess which product they had received (NRT or placebo) and a statistically significant greater proportion guessed correctly in the placebo group; this analysis was not intention-to-treat (ITT). It is possible that full double-blinding may be difficult to attain in placebo-controlled trials of NRT.

All studies employed power calculations.

Results for smoking outcomes

Four major smoking outcomes were reported in the included trials (Appendix 2): sustained abstinence from smoking, point prevalence of smoking abstinence, sustained reduction of

TABLE 2 *Summary of quality assessment of included RCTs*[a]

Study	Was assignment of treatment really random?	Was allocation concealed and concealment method described?	Were groups similar at baseline?	Were eligibility criteria specified?	Who was blinded to treatment allocation?	Was ITT analysis used and were dropouts accounted for?
Batra[43] 980-CHC 1013-028[44]	Yes. Computer-generated list	Yes. Sealed envelopes	Yes[b]	Yes	Participants and Investigators	Yes Yes
Bolliger[39] 96-NNIN 016[40]	Yes. Computer-generated list	Yes. Sealed envelopes	Yes[b]	Yes	Participants and Investigators	Yes Yes
Etter[45,46]	Yes. Computer-generated list	Unclear	Yes	Yes	Participants	Most outcomes[c] Yes
Haustein 980 CHC-9021-0013[37]	Yes. Computer-generated list	Yes. Sealed envelopes	Yes	Yes	Participants and Investigators	Yes Yes
Rennard 98-NNIN-027[36]	Likely, but method not described	Likely, but method not reported	Yes	Yes	Participants and Investigators	Yes Yes
Wennike[41] 98-NNCG-014[42]	Yes (stratified by Fagerström score). Computer-generated list	Yes. Sealed code list	Yes[b]	Yes	Participants and Investigators	Yes Yes
Wood-Baker 98-NNCG-017[38]	Yes (stratified by Fagerström score). Computer-generated list	Yes. Sealed envelopes	Yes	Yes	Participants and Investigators	Yes Yes

ITT, intention-to-treat.
[a] When extensive unpublished study reports were available, they were used for quality analysis.
[b] Except for small imbalance in gender distribution.
[c] Not ITT for product usage and for completeness of blinding of participants (determined at 6 months).

TABLE 3 *Numbers of subjects sustaining abstinence for at least 6 months*

Study[a]	Nicotine active group			Nicotine placebo group		
	Total number	Number of subjects sustained abstinence	%	Total number	Number of subjects sustained abstinence	%
Rennard (inhalator) 98-NNIN-027[36]	215	10	4.65	214	10	4.67
Batra[43] (gum) 980-CHC-1013-028[44]	184	16	8.70	180	2	1.11
Haustein (gum) 980 CHC-9021-0013[37]	97	8	8.25	96	3	3.13
Wennike[41] (gum) 98-NNCG-014[42]	205	21	10.24	206	8	3.88
Wood-Baker (gum) 98-NNCG-017[38]	218	7	3.21	218	7	3.21
Total (RR = 2.06)	919	62	6.75	914	30	3.28

[a] Unpublished study reports used for data.

cigarettes smoked per day to :s;50% of the number smoked at baseline, and point prevalence of reduction in smoking to :s;50% of the number of cigarettes smoked at baseline. In all the trials abstinence and number of cigarettes smoked were self-reported in response to structured questionnaires. In all trials except the Etter study[45,46] self-reported smoking status was validated by measures of the concentration of CO in exhaled breath; for abstinence to be confirmed, this concentration was required to be <10 ppm and for validation of smoking reduction CO concentration was required to be lower than that at baseline.

Data for the four major smoking outcomes described above were analysed in detail. In the analyses NRT was regarded as a generic intervention so that where meta-analysis was conducted data from both nicotine inhalator and nicotine gum trials were combined. For comparative purposes, analyses distinguishing inhalator and gum trials were undertaken and are provided in Appendix 7. Any comparison of the two interventions should be viewed with caution since no head-to-head trials were identified.

The outcome taken as an indicator for success of NRT was the proportion of smokers who sustained continuous abstinence from smoking. Various measures for this outcome can be used, and they may encompass different durations of continuous abstinence. The measures reviewed were (1) a defined period of sustained abstinence that starts within the first 6 weeks of NRT treatment (outcome reported in trial reports) and (2) at least 6 months' continuous abstinence that starts at any time within the NRT treatment period. The latter was calculated using IPD data from unpublished study reports supplied by Pfizer (for details, see the section 'Developing a measure of sustained abstinence', p. 10).

Sustained abstinence outcomes based on IPD

The included studies only reported the sustained abstinence outcomes measured beginning week six after start of treatment up to various monthly time points. Any sustained abstinence measured from later than week six was not considered at all. This may underestimate the sustained abstinence rate of interest as treatment was continued for many months. The trials only included people who did not want to stop smoking in the near future, so to expect people to have done so 6 weeks later is surprising but presumably reflects the fact that these trials primarily aimed to investigate smoking reduction. We re-analysed the IPD and estimated the sustained abstinence outcomes measured from any time point during the treatment period to at least 6 months for the five studies where IPD were available. The estimated numbers of subjects who sustained abstinence of at least 6 months are summarised in *Table 3*.

Sustained abstinence outcomes were meta-analysed using the data shown in *Table 3*. The forest plots of RRs are shown in *Figure 3* for inhalator and gum together and in *Figure 4* for gum alone. The pooled ORs and RRs for sustained abstinence for at least 6 months and the

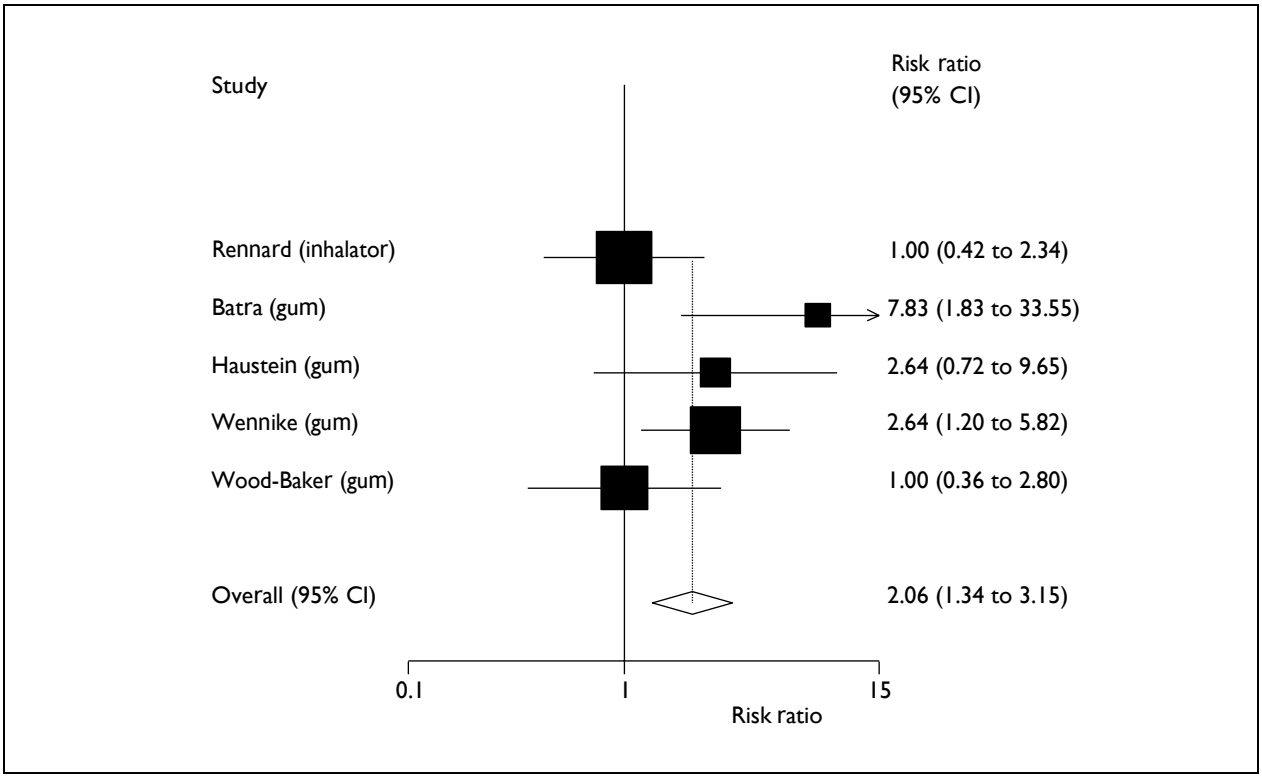

FIGURE 3 *Relative risk for at least 6 months' sustained abstinence (gum and inhaled NRT) IPD. Data from unpublished study reports where available; Batra = study 980-CHC-1013-028,[44] Haustein = study 980-CHC-9021-0013,[37] Rennard = study 98-NNIN-027,[36] Wennike = study 98-NNCG-014,[42] Wood-Baker = study 98-NNCG-017.[38]*

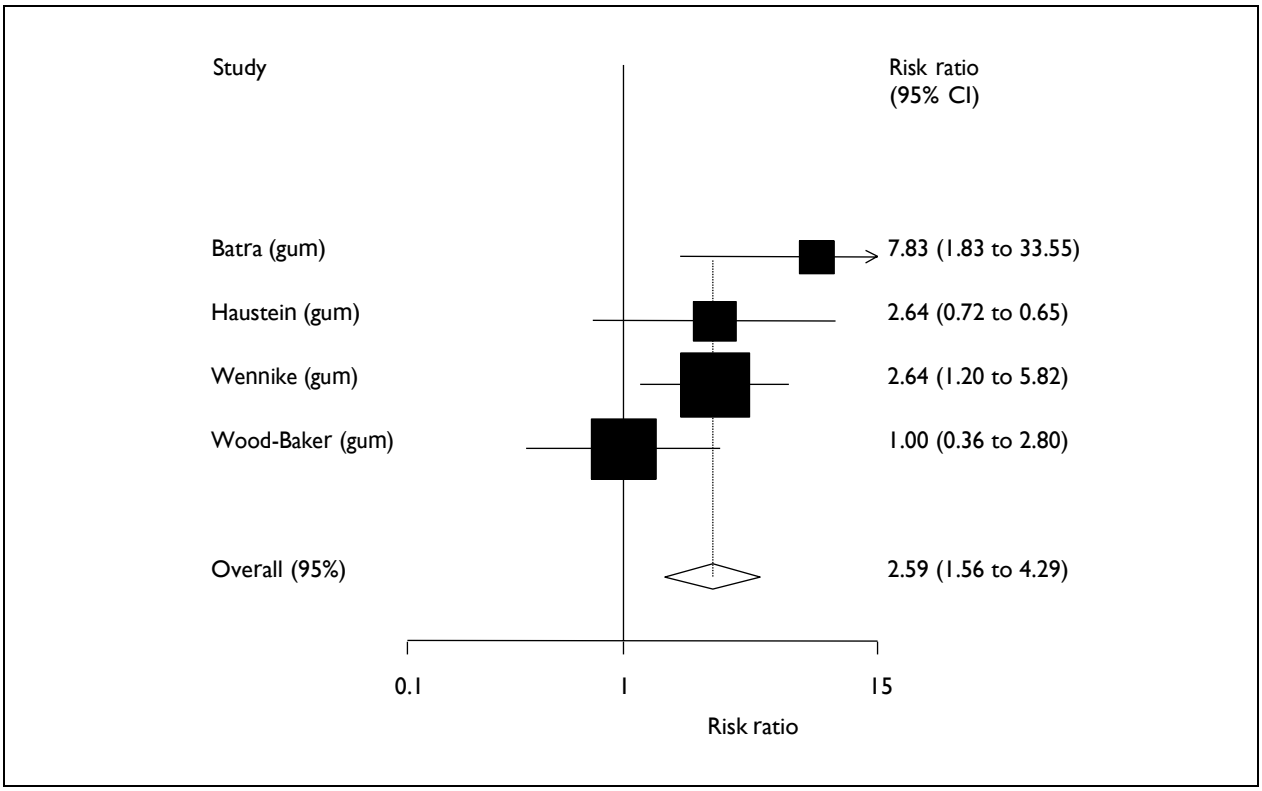

FIGURE 4 *Relative risk for at least 6 months' sustained abstinence (gum NRT) IPD. Data from unpublished study reports where available; Batra = study 980-CHC-1013-028,[44] Haustein = study 980-CHC-9021-0013,[37] Wennike = study 98-NNCG-014,[42] Wood-Baker = study 98-NNCG-017.[38]*

TABLE 4 *Sustained abstinence for at least 6 months (IPD) meta-analysis*

Intervention	Number of studies	Risk ratio	95% LCI	95% UCI	Odds ratio	95% LCI	95% UCI	Statistical heterogeneity: x^2 (degrees of freedom), *p*	Test of OR = 1 *z*, *p*
Inhalator	1	1.00	0.42	2.34	1.00	0.41	2.44	NA	$z = 0.01$, $p = 0.991$
Gum	4	2.59	1.56	4.29	2.72	1.60	4.60	5.65 (*d.f.* = 3), $p = 0.130$	$z = 3.72$, $p = 0.000$
Inhalator + gum	5	2.06	1.34	3.15	2.13	1.36	3.33	8.61 (*d.f.* = 4), $p = 0.072$	$z = 3.33$, $p = 0.001$

LCI, lower limit of 95% CI; NA, not applicable; UCI, upper limit of 95% CI.

TABLE 5 *Rates of sustained abstinence for at least 6 months (IPD)*

Intervention	Number of studies	Active nicotine group			Placebo nicotine group		
		Percentage of sustained abstinence at least 6 months	95% LCI	95% UCI	Percentage of sustained abstinence at least 6 months	95% LCI	95% UCI
Inhalator	1	4.65	2.57	8.35	4.67	2.58	8.39
Gum	4	7.39	5.68	9.56	2.85	2.17	3.74
Inhalator + gum	5	6.75	5.30	8.56	3.29	2.56	4.21

corresponding heterogeneity tests are given in *Table 4*. The percentages and 95% CIs of sustained abstinence for at least 6 months for both nicotine and placebo groups are listed in *Table 5*.

The meta-analysis demonstrated statistically significant superiority of NRT over placebo; RR 2.06, 95% CI 1.34 to 3.15 (OR 2.13, 95% CI 1.36 to 3.33), although for the single trial of inhalator for which IPD were available NRT and placebo were equivalent (RR 1.00, 95% CI 0.42 to 2.34; OR 1.0, 95% CI 0.41 to 2.44).

The proportion of patients in the NRT arms who sustained abstinence for at least 6 months was 6.75% (with range in different studies 3.2–10.2%) and in the placebo arms 3.29% (range 1.1–4.7%). Taking the difference between NRT and placebo of 3.46% gives a number-needed-to-treat (NNT) of 29.

Study level sustained abstinence

Of the seven included studies, four of gum and two of inhalator reported data on sustained abstinence from smoking. This outcome was measured as duration of sustained abstinence from a particular starting time early in the study (e.g. usually the first 6 weeks of study) up to various time points including end of follow-up. In five studies, the early starting time was 6 weeks (Bolliger,[39] Wennike,[41] Rennard study 98-NNIN-027,[36] Haustein study 980-CHC-9021-0013,[37] Wood-Baker study 98-NNCG-017[38]) and in the sixth study (Batra[43]) it was 2 weeks. Smoking cessation was self-reported (e.g. by responding 'yes' to the question 'have you stopped smoking?') but had to be validated by a CO concentration of <10 ppm detected in exhaled breath. Proportions of patients who sustained abstinence were low. The greatest proportion of subjects attaining sustained abstinence for any duration measured in the NRT arm of any study was 4.3% (*Table 47*). At 6 months, 24 of 1119 (2.1%) NRT-treated patients and two of 1114 (0.2%) placebo patients had sustained their abstinence. As these rates were low and there was good balance between the study arms, Peto's OR was used as a measure of effectiveness of NRT relative to placebo (OR > 1 favours NRT). *Figure 5* provides a forest plot of the results of this analysis for each time point in each study.

The OR was reasonably consistent between studies and also through time within each study and indicated (1) a tendency for NRT superiority relative to placebo and (2) that early cessation of smoking (within 6 weeks of study commencement) was associated with prolonged abstinence.

At many time points the OR did not reach statistical significance (95% CI included 1.0).

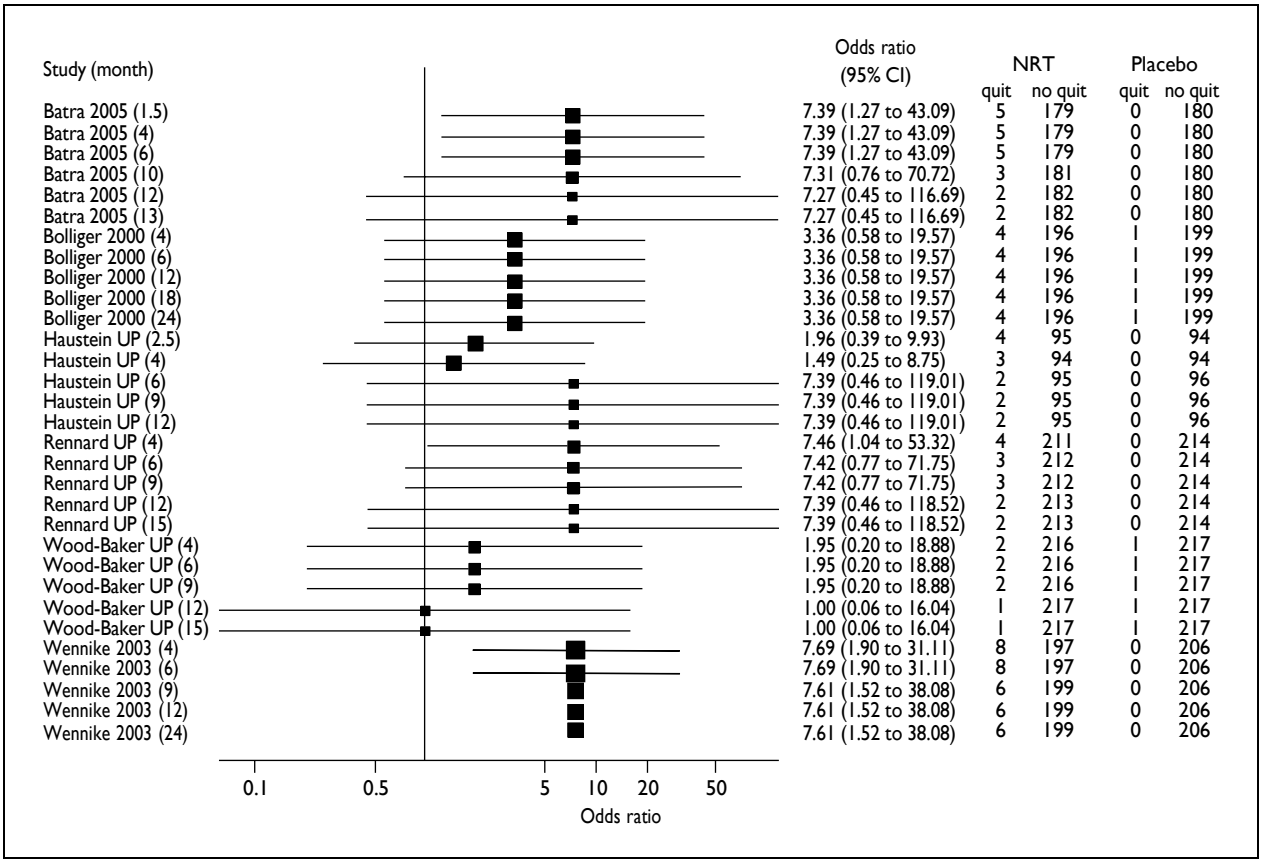

FIGURE 5 *Sustained smoking abstinence from 6 weeks; Peto's odds ratio at monthly time points by study. Batra reported abstinence at 6 weeks as sustained abstinence and this is included in the forest plot. Dates refer to publication of studies. Data from unpublished study reports where available; Batra = study 980-CHC-1013-028,[44] Bolliger = study 96-NNIN-016,[40] Haustein = study 980-CHC-9021-0013,[37] Rennard = study 98-NNIN-027,[36] Wennike = study 98-NNCG-014,[42] Wood-Baker = study 98-NNCG-017.[38] UP, unpublished.*

To add power to the analysis, results for time points common between studies were combined in meta-analysis. The results are summarised in *Figure 6* and *Table 6* and full data are available in Appendix 3. At all time points the OR favoured NRT. Appendix 7 provides the results for gum and inhalator separately.

This meta-analysis demonstrated statistically significant superiority of NRT over placebo (95% CI OR >1.0; log OR >0) at all time points for which results were available from more than two trials.

This outcome required sustained abstinence from an 'early' time point (e.g. 6 weeks) onwards. This means that only 'early quitters' could be classified as sustained abstainers. Unfortunately, any patients who became abstinent at a later time and managed to sustain their abstinence to the end of follow-up or for a substantial period are not taken into account. Hence the low proportion of subjects (never greater than 4.3% in any of the trials) who achieved sustained abstinence as defined by this outcome might be an underestimate of abstinence. In order to explore this further, we examined IPD that were available from five trial reports made available by Pfizer, the sponsor of these trials (Batra,[43] Wennike,[41] Rennard study 98-NNIN-027,[36] Haustein study 980-CHC-9021-0013,[37] Wood-Baker study 98-NNCG-017[38]). The results of IPD analysis are provided in the section 'Sustained abstinence outcomes based on IPD' (p. 18).

Point prevalence of abstinence from smoking

The seven included studies all reported point prevalence of abstinence from smoking at various time points during the study. Except for the Etter study,[45] self-reported abstinence was confirmed by reduction in exhaled CO relative to baseline (in the Etter study 'no puff in last 7 days'). The results are tabulated in Appendix 4 and illustrated in the forest plot in *Figure 7*.

The proportion of patients abstinent at different time points during the studies varied from less than 1% to 12%. The RR of abstinence was used as

TABLE 6 *Meta-analysis of sustained abstinence by month of study (NRT versus placebo)*

Month	Number of studies	Peto's odds ratio	95% LCI	95% UCI	Statistical heterogeneity: x^2 (degrees of freedom), *p*
2.5	1	1.96	0.39	9.93	NA
4	6	4.40	2.14	9.04	3.24 (*d.f.* = 5), *p* = 0.663
6	6	5.51	2.54	11.94	1.54 (*d.f.* = 5), *p* = 0.909
9	4	5.63	2.00	16.11	1.06 (*d.f.* = 3), *p* = 0.786
10	1	7.31	0.76	70.72	NA
12	6	4.90	1.99	12.08	1.97 (*d.f.* = 5), *p* = 0.853
13	1	7.30	0.45	116.69	NA
15	2	2.72	0.38	19.34	1.00 (*d.f.* = 1), *p* = 0.318
18	1	3.36	0.58	19.57	NA
24	2	5.25	1.60	17.22	0.45 (*d.f.* = 1), *p* = 0.502

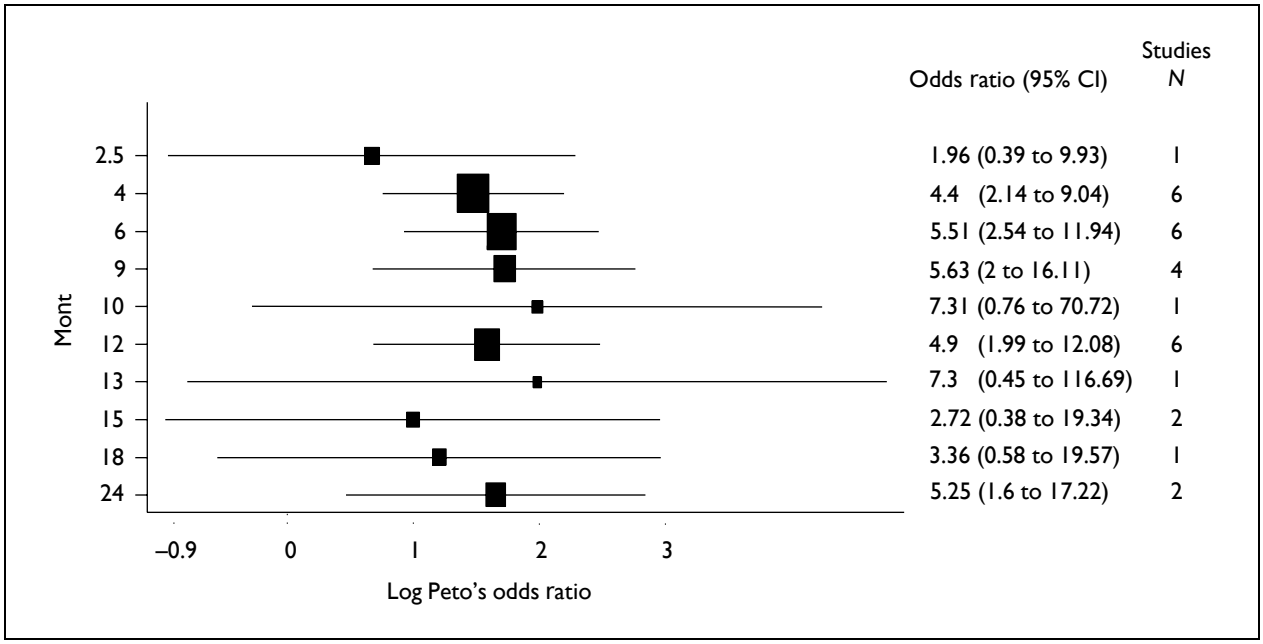

FIGURE 6 *Sustained abstinence meta-analysis by month (log scale)*

a measure of effectiveness of NRT relative to placebo (RR > 1 favours NRT).

The RR of point prevalence of abstinence favoured NRT in all instances except one. There was a trend for 95% CIs to narrow as months after start of treatment increased and also for the RR to decrease; thus at later times in the study there appeared to be a trend towards less effectiveness of NRT relative to placebo.

The existence of such a trend was examined by regressing log RR upon month from start of treatment for each study and the findings are shown in *Figure 8*. In these plots, a log RR of zero represents no effect of one treatment over another (analogous to an RR of 1).

All studies, apart from Rennard study 98-NNIN-027,[36] exhibit a trend to reduced effectiveness of NRT compared with placebo over time.

The slope coefficients and their standard errors calculated by weighted and unweighted regression are shown in *Table 7*.

The resulting coefficients were meta-analysed and the results are also shown in *Table 7*. When the Etter trial,[45,46] which differed from the other trials with respect to NRT choice and CO validation of smoking, was included in the meta-analysis, the regression coefficients were statistically significant and negative (fixed and random effects models). When this trial was omitted, only the unweighted regression coefficient reached statistical

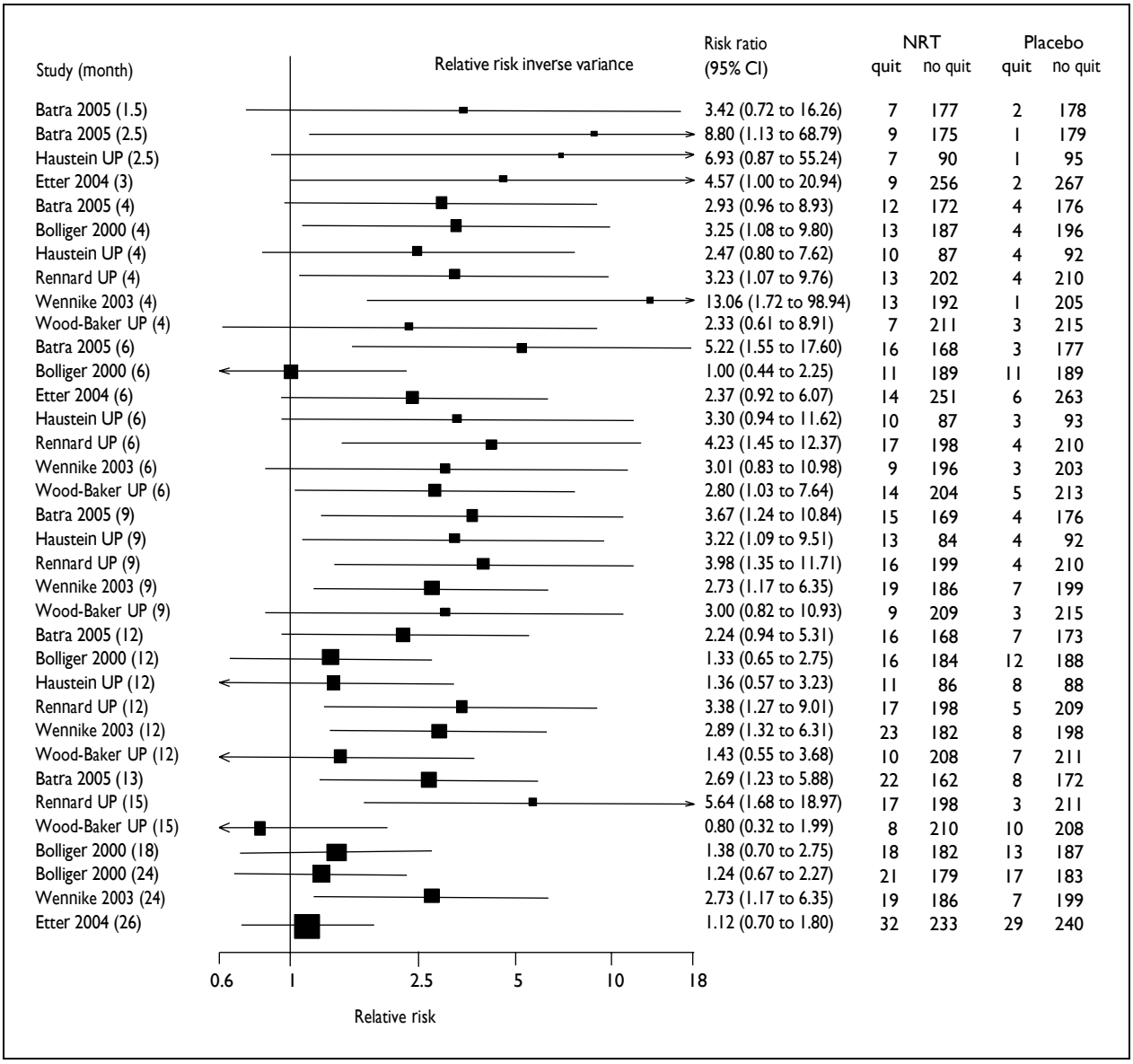

FIGURE 7 *Point prevalence of abstinence at different times after start of treatment. Seven-day point prevalence was reported in the Etter study;[45] other studies reported 1-day point prevalence or this was assumed when reports were not explicit. Data from unpublished study reports where available; Batra = study 980-CHC-1013-028,[44] Bolliger = study 96-NNIN-016,[40] Haustein = study 980-CHC-9021-0013,[37] Rennard = study 98-NNIN-027,[36] Wennike = study 98-NNCG-014,[42] Wood-Baker = study 98-NNCG-017.[38]*

significance (fixed effects model). As suspected from cursory inspection of results displayed in *Figure 7*, these results suggest a strong trend for the effectiveness of NRT compared with placebo to diminish over time.

To add power to the comparison, results for point prevalence of abstinence for time points common between studies were combined. The results are summarised in *Table 8* and *Figure 9* and further details are available in Appendix 4.

This meta-analysis shows statistically significant superiority of NRT over placebo at time points up to 1 year (except at those time points where only a single study was available). Again, a trend was evident toward reduced effectiveness of NRT relative to placebo as the time from start of study increased. When results from the Etter mixed-NRT study[45,46] were omitted, this trend became slightly less pronounced.

These results may reflect a catch-up in frequency of quit attempts in the placebo arm relative to the intervention arm as study duration extends.

Sustained smoking reduction

Six trials (Batra,[43] Bolliger,[39] Haustein study 980-CHC-9021-0013,[37] Rennard study 98-NNIN-027,[36] Wennike[41] and Wood-Baker study

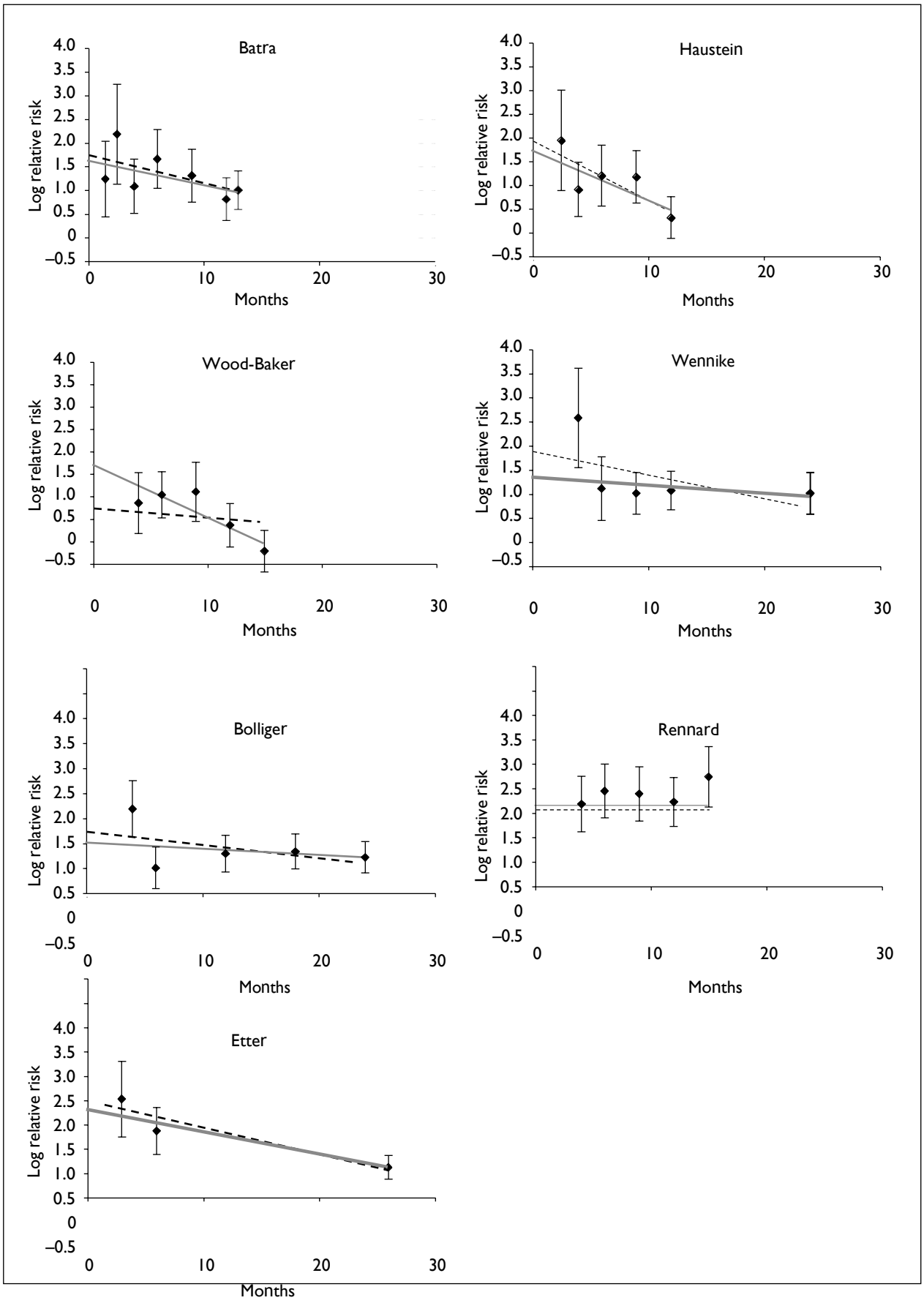

FIGURE 8 *Log RR (point prevalence of abstinence) regressed on month of study. Dashed lines unweighted and solid lines weighted (inverse variance) regression. Error bars = standard error.*

TABLE 7 *Results for log RR of point prevalence of abstinence regressed upon month of study*

Study[a]	Slope coefficient (SE)	
	Unweight regression	**Weight regression**
Batra[43]	–0.060 (0.036)	–0.051 (0.052)
Bolliger[39]	–0.024 (0.028)	–0.012 (0.023)
Rennard[36]	0.031 (0.022)	0.026 (0.065)
Wennike[41]	–0.046 (0.043)	–0.017 (0.033)
Wood-Baker[38]	–0.016 (0.010)	–0.117 (0.060)
Haustein[37]	–0.121 (0.054)	–0.104 (0.077)
Etter[45]	–0.053 (0.020)	–0.046 (0.023)

	Meta-analysis			
	Fixed effects		**Random effects**	
	Coefficient (95% CI)	***p***	**Coefficient (95% CI)**	***p***
Unweighted with Etter	–0.021 (–0.036 to –0.007)	0.004	–0.028 (–0.056 to –0.001)	0.042
Weighted with Etter	–0.033 (–0.059 to –0.007)	0.013	–0.033 (–0.059 to –0.007)	0.013
Unweighted Etter omitted	–0.016 (–0.032 to –0.001)	0.042[b]	–0.023 (–0.054 to 0.008)	0.143
Weighted Etter omitted	–0.026 (–0.058 to 0.005)	0.103	–0.026 (–0.058 to 0.005)	0.103

[a] Data from unpublished study reports where available, Batra = study 980-CHC-1013-028,[44] Bolliger = study 96-NNIN-016,[40] Haustein = study 980-CHC-9021-0013,[37] Rennard = study 98-NNIN-027,[36] Wennike = study 98-NNCG-014,[42] Wood-Baker = study 98-NNCG-017.[38] It should be borne in mind that by 26 months' follow-up in the Etter study the use of NRT in the placebo arm was reported to be 17.1% and approached the rate of use in the NRT arm (28.5%). Similarly in the 'no treatment' arm, after the first 6 months of the study, NRT use (27%) was similar to that in the intervention arm. The leakage of NRT use in these arms means that effectiveness comparisons with the NRT arm at 26 months will not reliably reflect the influence of NRT.

[b] Test for heterogeneity: $Q = 10.203$ on five degrees of freedom ($p = 0.070$). Study weighting by inverse variance.

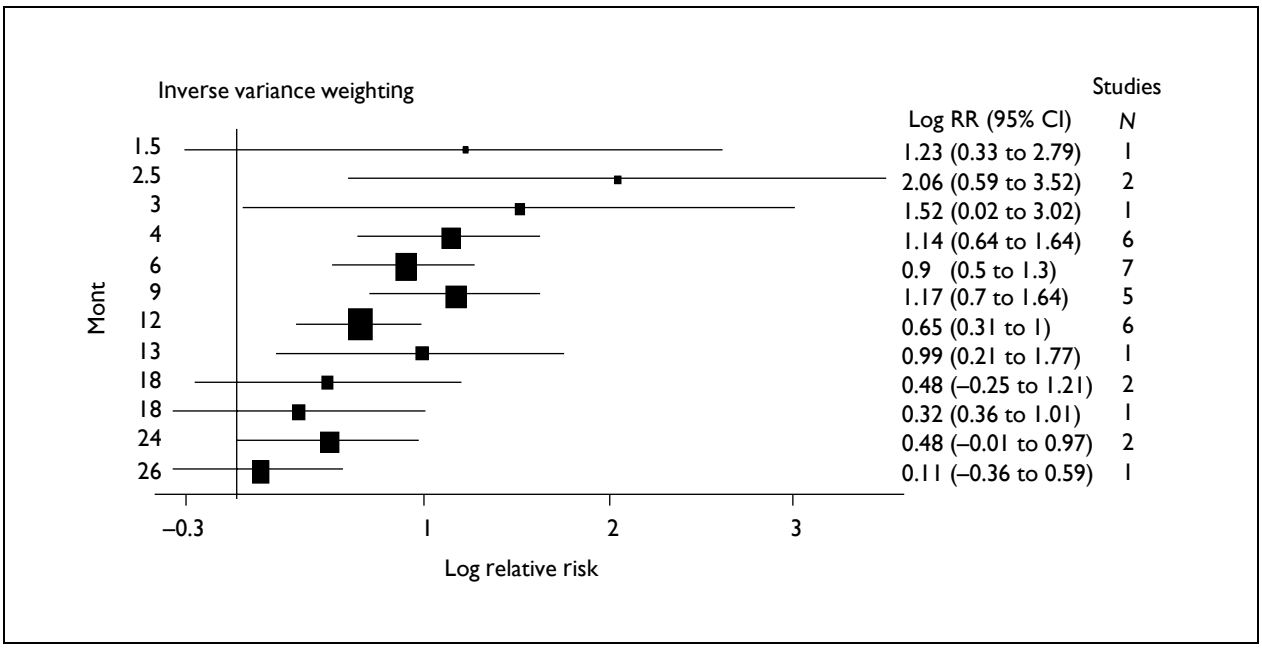

FIGURE 9 *Meta-analysis of point prevalence of abstinence according to month of study*

TABLE 8 *Meta-analysis of point prevalence abstinence by month of study*

Month	Number of studies	Relative risk	95% LCI	95% UCI	Statistical heterogeneity: x^2 (degrees of freedom), *p*
1.5	1	3.42	0.72	16.26	NA
2.5	2	7.82	1.81	33.69	0.03 (*d.f.* = 1), *p* = 0.872
3	1	4.57	1.00	20.10	NA
4	6	3.13	1.90	5.15	2.29 (*d.f.* = 5), *p* = 0.808
6	7	2.46	1.66	3.66	7.54 (*d.f.* = 6), *p* = 0.274
9	5	3.23	2.02	5.16	0.36 (*d.f.* = 4), *p* = 0.985
12	6	1.92	1.36	2.70	4.42 (*d.f.* = 5), *p* = 0.491
13	1	2.69	1.23	5.88	NA
15	2	1.62	0.78	3.35	6.37 (*d.f.* = 1), *p* = 0.012
18	1	1.38	0.70	2.75	NA
24	2	1.62	0.99	2.65	2.22 (*d.f.* = 1), *p* = 0.136
26	1	1.12	0.70	1.80	NA

TABLE 9 *Meta-analysis results: sustained smoking reduction by month of study*

Month	Number of studies	Relative risk	95% LCI	95% UCI	Statistical heterogeneity: x^2 (degrees of freedom), *p*
2.5	2	2.04	1.31	3.19	1.02 (*d.f.* = 1), *p* = 0.313
4	6	2.30	1.77	3.00	7.00 (*d.f.* = 5), *p* = 0.221
6	6	3.32	2.33	4.75	3.35 (*d.f.* = 5), *p* = 0.646
9	4	3.27	1.85	5.76	2.99 (*d.f.* = 3), *p* = 0.394
10	1	3.33	1.25	8.82	NA
12	6	3.64	2.30	5.77	2.62 (*d.f.* = 5), *p* = 0.758
13	1	2.93	1.09	7.91	NA
15	2	2.91	1.15	7.37	0.73 (*d.f.* = 1), *p* = 0.391
18	1	2.71	1.17	6.31	NA
24	2	3.99	1.76	9.07	1.57 (*d.f.* = 1), *p* = 0.210

98-NNCG-017[38]) reported numbers of patients who sustained self-reported ?:50% reduction in cigarettes smoked per day from an early time point (6 weeks) in the study (see Appendix 6). This was determined by self-report confirmed by a reduction of any size in exhaled CO relative to baseline. We used the RR of sustained reduction as an indicator of the effectiveness of NRT relative to placebo. These results are shown in *Figure 10*.

In all studies, with increasing months into study there was a reduction in the numbers of patients able to sustain reduction from week six. To add power to the comparison of NRT versus placebo we combined results for sustained reduction for time points common between studies. The results are shown in *Table 9* and *Figure 11*.

This meta-analysis demonstrates that statistically significant superiority of NRT over placebo is maintained up to 24 months of study despite diminishing numbers of subjects sustaining their smoking reduction.

Point prevalence of smoking reduction

Six trials (Batra,[43] study 980-CHC-1013-028;[44] Bolliger,[39] study 96-NNIN 016;[40] Haustein study 980 CHC-9021-0013;[37] Rennard study 98-NNIN-027;[36] Wennike,[41] study 98-NNCG-014;[42] Wood-Baker, study 98-NNCG-017[38]) reported point prevalence of smoking reduction according to month of study (see Appendix 5). The numbers of patients who reduced cigarettes smoked per day by ?:50% was determined by self-reporting, confirmed by a reduction of any size in exhaled CO relative to baseline. The RR of smoking reduction was used as an indicator of the effectiveness of NRT relative to placebo. The results are shown in *Figure 12*.

At most time points in most of the studies NRT was superior to placebo, but this did not reach statistical significance in several instances. To add power to the comparison of NRT versus placebo, the RRs of reduced smoking for time points common between studies were combined. The results are summarised in *Table 10* and in *Figure 13*.

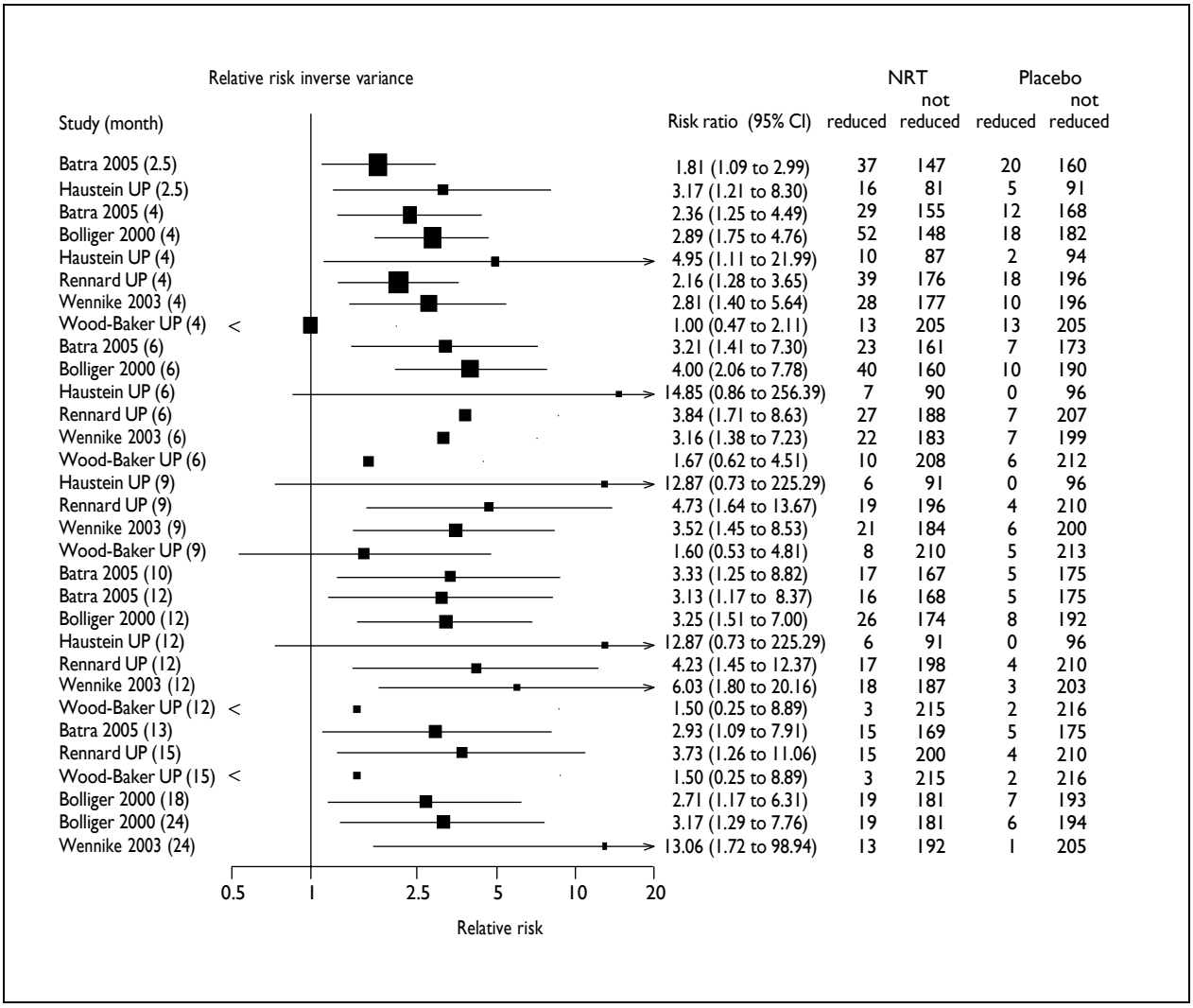

FIGURE 10 *Relative risk of sustained smoking reduction by month of study. Data from unpublished study reports where available. Batra = study 980-CHC-1013-028,[44] Bolliger = study 96-NNIN-016,[40] Haustein = study 980-CHC-9021-0013,[37] Rennard = study 98-NNIN-027,[36] Wennike = study 98-NNCG-014,[42] Wood-Baker = study 98-NNCG-017.[38]*

TABLE 10 *Meta-analysis of point prevalence for smoking reduction by month of study*

Month	Number of studies	Relative risk[a]	95% LCI	95% UCI	Statistical heterogeneity: x^2 (degrees of freedom), *p*
1.5	1	1.52	1.04	2.23	NA
2.5	2	1.64	1.17	2.29	0.71 (*d.f.* = 1), *p* = 0.399
4	6	1.64	1.40	1.93	7.42 (*d.f.* = 5), *p* = 0.191
6	6	1.73	1.44	2.07	5.38 (*d.f.* = 5), *p* = 0.371
9	5	1.65	1.33	2.06	5.38 (*d.f.* = 4), *p* = 0.250
12	6	1.43	1.20	1.71	5.61 (*d.f.* = 5), *p* = 0.346
13	1	1.63	1.12	2.38	NA
15	2	1.05	0.74	1.49	5.63 (*d.f.* = 1), *p* = 0.018
18	1	1.53	1.03	2.28	NA
24	2	1.28	0.96	1.70	0.52 (*d.f.* = 1), *p* = 0.472

[a] Fixed effects, inverse variance.

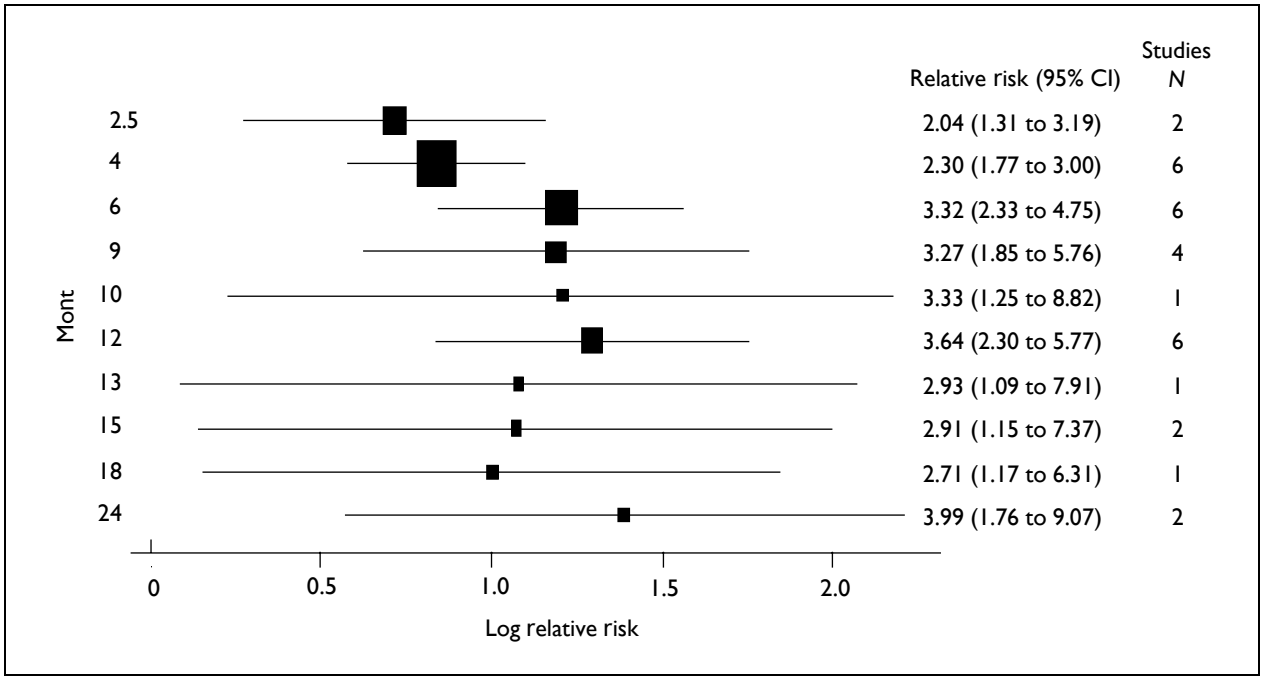

FIGURE 11 *Meta-analysis of relative risk of sustained smoking reduction by month of study*

The meta-analysis demonstrates statistically significant superiority of NRT over placebo at all time points up to 13 months into study. At later time points, the effectiveness of NRT relative to placebo appears to diminish but the analyses are associated with considerable statistical uncertainty.

Other outcomes

Adverse events

Adverse events were monitored throughout the included trials. At each visit, subjects were asked an open-ended general question to elicit information regarding adverse events. Treatment-emergent adverse events, serious adverse events and deaths reported in the included studies are summarised in Appendix 8.

Adverse events relating to symptoms of possible nicotine overdose (nausea, nausea/vomiting, vomiting and palpitation) were not significantly different between the NRT group and placebo group for five out of seven studies (Rennard study 98-NNIN-027,[36] Wood-Baker study 98-NNCG-017,[38] Wennike study 98-NNCG-014,[42] Batra study 980-CHC-1013-028[44] and Bolliger study 96- NNIN-016[40]), with ORs of 2.05 (95% CI 0.75 to 5.56), 1.31 (95% CI 0.69 to 2.50), 1.52 (95% CI 0.42 to 5.48), 1.87 (95% CI 0.87 to 4.03) and 1.00 (95% CI 0.41 to 2.46). Adverse events relating to symptoms of possible nicotine overdose (nausea, nausea/vomiting, vomiting and palpitation) were significantly different between the NRT group and placebo group for the Haustein 980-CHC-9021-0013 study[37] (OR 4.74, 95% CI 2.46 to 9.17).

The death rates were not significantly different between the NRT group and the placebo group. The numbers of serious adverse events were only significantly different between two groups for the Haustein study,[37] with an OR of 2.90 (95% CI 1.15 to 7.30), but it was reported that none of the serious adverse events were considered to be related to study treatment.

NRT usage

For cost-effectiveness analysis, it is necessary to have an estimate of the actual amount of NRT consumed by smokers undertaking a CDTQ programme. Average patient usage of NRT was calculated from trial report data of five studies (one using an inhalator and four using gum). The data are summarised in *Table 11*.

The average consumption of NRT product per day reflects the non-attendance at clinic and non-uptake of intervention that is evident in the trials; thus if all participants had attended all clinics and had sustained their NRT-aided attempt to reduce smoking, the average daily consumption would have been higher.

Health-related quality of life

Five trial reports made available contained study-level HRQoL data determined using the validated

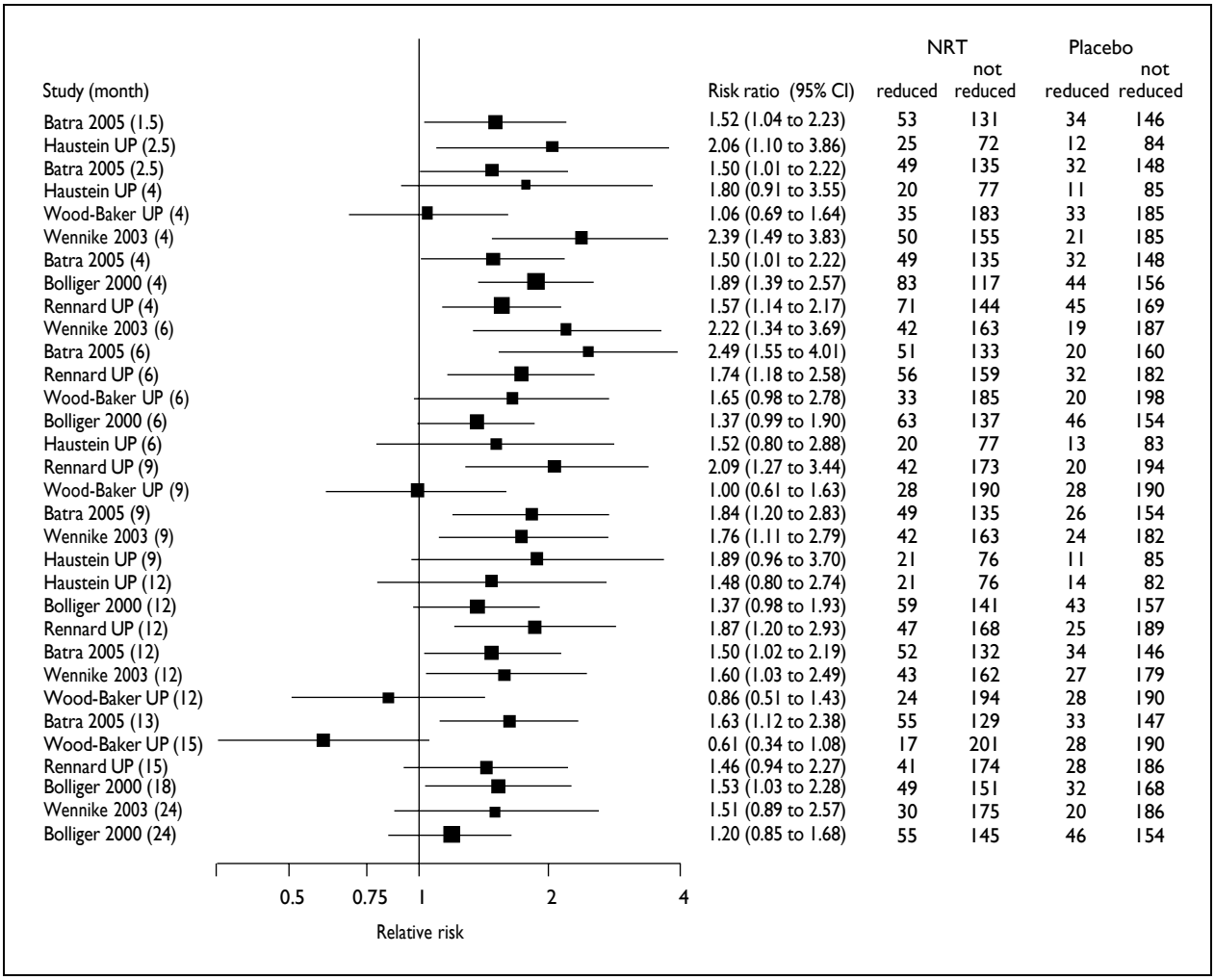

FIGURE 12 *Relative risk of point prevalence of reduction in smoking. Data from unpublished study reports where available. Batra = study 980-CHC-1013-028,[44] Bolliger = study 96-NNIN-016,[40] Haustein = study 980-CHC-9021-0013,[37] Rennard = study 98-NNIN-027,[36] Wennike = study 98-NNCG-014,[42] Wood-Baker = study 98-NNCG-017.[38]*

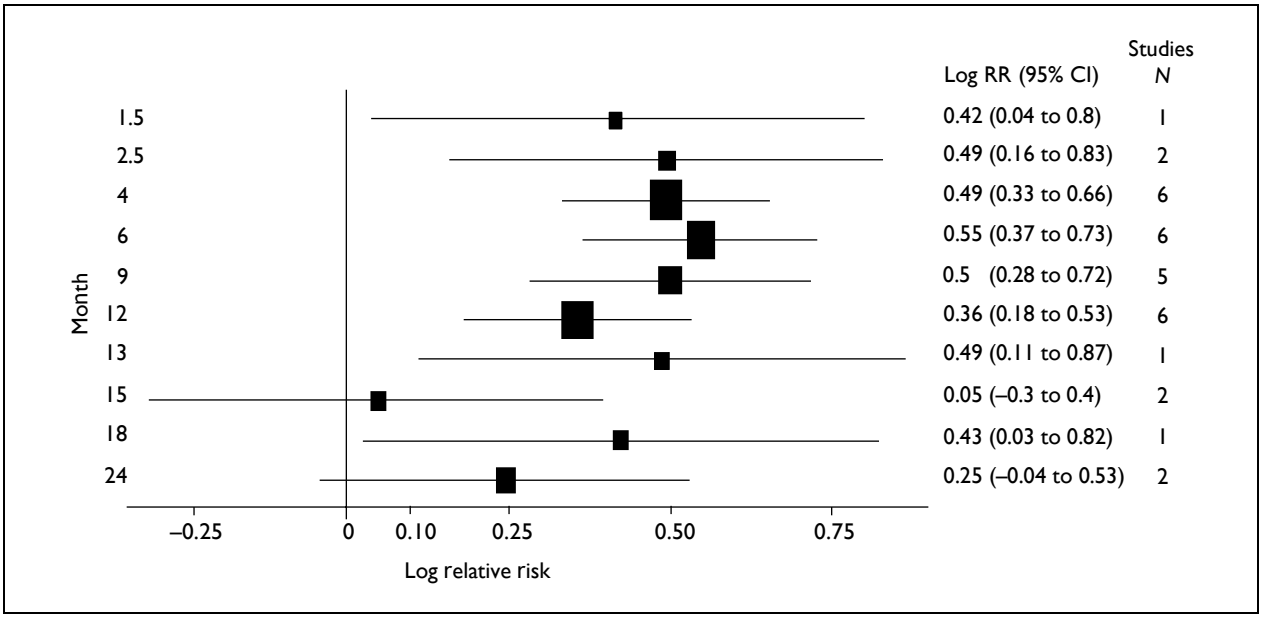

FIGURE 13 *Meta-analysis of point prevalence for reduction in smoking by month of study*

TABLE 11 *Average usage of NRT units during study*

Study (NRT type[a])	Number of smokers	Duration of treatment (months)	Average (gum or inhaler)/treatment	Average (gum or inhaler)/day
Rennard (inhalator), 98-NNIN-027[36]	215	12	800.07	2.19
Wennike[41] (gum), 98-NNCG-014[42]	215	12	1250.92	3.42
Haustein (gum), 980-CHC-9021-0013[37]	97	9	322.16	1.17
Batra[43] (gum), 980-CHC-1013-028[44]	184	13	524.52	1.44
Wood-Baker (gum), 98-NNCG-017[38]	218	12	683.91	1.87
Weighted average (gum)			774.42	2.15

[a] A unit of gum is one piece and a unit of inhalator is one cartridge.

Short Form with 36 Items (SF-36) instrument. Study-level baseline scores in eight domains (physical functioning, role limitations due to physical health, role limitations due to emotional health, energy/fatigue, emotional well-being, social functioning, pain and general health) were reported and compared with scores at various times thereafter. In all studies investigators provided SF-36 domain scores for patient groups defined as 'sustained reducers' or 'non-reducers' irrespective of the trial arm (NRT or placebo) to which they belonged. Although these comparisons are capable of indicating whether smoking reduction is associated with detectable improvements in HRQoL, they have little relevance to the primary objectives of this report, which requires information regarding any incremental change in quality of life (QoL) utility scores associated with sustained smoking abstinence versus non-abstinence and NRT treatment versus placebo.

The SF-36 scores reported in these five trials are summarised in Appendix 10. The direction of this evidence lends support to the suggestion that involvement in trials is associated with small improvements in several domain scores (e.g. physical functioning) and that these improvements tend to be greater for sustained reducers than non-reducers of the number of cigarettes smoked. The proportion of individuals who achieved sustained reduction was small in most trials, so the power of the analyses for this group was far less than that for non-reducers.

Discussion of effectiveness results

The smokers who participated in the included studies all expressed an initial inability or unwillingness to quit smoking abruptly, hence we can assume that many had no plans to stop. The newly licensed indication for NRT is called 'cut down then stop'. However, no RCTs were found that were conducted to ascertain the effectiveness of NRT for this indication. All the included studies declared that their primary aim was to estimate NRT effectiveness for smoking reduction.

The included studies were remarkably similar in the baseline demographic characteristics of the study populations: typically average age 42–46 years, average number of cigarettes smoked per day 24–30, average exhaled CO concentration 26–30 ppm, average Fagerström score 5.4–6.6, proportion female 45–65%. Within this population, we were unable to identify studies that examined specific subgroups.

For the main analyses undertaken for this report, NRT was considered a generic intervention. No direct comparisons of nicotine gum versus nicotine inhalator were identified and because of the paucity of trials it was not judged appropriate to conduct indirect comparisons.

Meta-analyses of reported study-level results revealed that NRT was superior to placebo for all four smoking outcomes: point prevalence of abstinence and sustained abstinence, sustained and point prevalence of smoking reduction.

Greater numbers of smokers were able to achieve and sustain 50% smoking reduction than were able to quit smoking. Meta-analyses of study-level smoking reduction outcomes (point prevalence and sustained reduction) demonstrated statistically significant superiority of NRT versus placebo.

The RR (NRT versus placebo) for point prevalence of abstinence from smoking reflects the frequency of both quit attempts and of sustained smoking cessation. Meta-analysis demonstrated statistically significant superiority of NRT compared with placebo for this outcome but there was a trend for this superiority to decrease with length of follow-up, probably reflecting a catch-up in quit attempts in the placebo arms. The

TABLE 12 *Numbers of smokers abstinent at 12 months*

		Active arm		Placebo arm	
NRT	**Study**	**Stopped**	**Not stopped**	**Stopped**	**Not stopped**
Gum	Batra,[43] 980-CHC 1013-028[44]	16	168	7	173
Inhalator	Bolliger, 96-NNIN 016[40]	16	184	12	188
Gum	Haustein, 980 CHC-9021-0013[37]	11	86	8	88
Inhalator	Rennard, 98-NNIN-027[36]	17	198	5	209
Gum	Wennike,[41] 98-NNCG-014[42]	23	182	8	198
Gum	Wood Baker, 98-NNCG-017[38]	10	208	7	211
	All	93	1026	47	1067
	All (%)	8.31		4.22	
	MHRA (%)	8.6		4.5	

combined estimate for RR of point prevalence at 4 months was 3.1 in favour of NRT, but this had declined to 1.9 by month 12.

Only low levels of sustained abstinence were reported in the trials due to the arguably inappropriate criterion that a quit attempt had to commence within the first 6 weeks of treatment. For this outcome, the OR for NRT versus placebo at 6 months was 5.5 (95% CI 2.5 to 11.9), but this represented only approximately 2.1% of the NRT-treated participants and approximately 0.2% of those receiving placebo.

The MHRA working group report concerning the extension of the licensed indication of NRT to encompass CDTQ considered data from several 'good quality' RCTs.[3] The identity of these studies was not revealed but is likely to correspond closely to the six industry-sponsored RCTs included here. The MHRA report quotes an abstinence success rate of 8.6% (105/1215) across all studies for NRT and 4.5% (54/1209) for placebo.

This success rate was based on measures of the point prevalence of abstinence at 12 months into studies and not on measures of sustained abstinence. The corresponding estimates for point prevalence at 12 months from analysis of the RCTs included in the present review are very slightly lower for both arms than those quoted in the MHRA report (see *Table 12*; details taken from full data set shown in *Table 49*, in Appendix 4).

As studies included in this report measured sustained abstinence from smoking when started within the first 6 weeks of treatment, this may arguably be considered an unrealistic target for a population recruited on the basis of an expressed inability or unwillingness to quit smoking at least in the short term. Therefore, we used the available IPD from these studies to calculate sustained abstinence according to a more realistic criterion with the starting point of cessation occurring before the end of treatment.

IPD from five trials (Rennard study 98-NNIN-027,[36] Wennike study 98-NNCG-014,[42] Wood-Baker study 98-NNCG-017,[38] Batra study 980-CHC-1013-028[44] and Haustein study 980-CHC-9021-0013[37]) were used to estimate proportions of smokers who sustained 6 months of abstinence that started at any time during NRT treatment. Meta-analysis of available IPD indicated that NRT was significantly superior to placebo (Peto's OR 2.13, 95% CI 1.36 to 3.33). The crude quit rates for 6 months of sustained abstinence were much higher when the criterion was abstinence starting any time during treatment period rather than a start within the first 6 weeks of treatment: NRT versus placebo 6.75% and 3.29% compared with 2.14% and 0.18%, respectively. Thus, using the more realistic criterion for sustained abstinence (and the available IPD from five studies), an extra 4.6% of smokers could be judged to sustain 6 months of abstinence in the NRT group and an extra 3.1% in the comparator group. The overall gain yielded from the realistic criterion of sustained abstinence was 1.5% of smokers using NRT rather than placebo.

The IPD made available for five of the included studies were characterised by a large amount of missing data, a phenomenon also found for studies of interventions to treat other more addictive drugs such as opiates (e.g. heroin).[47] Missing data occurred for both self-reported smoking status and measures of CO in exhaled breath used as a validation tool for self-reported smoking status. When more than approximately 10% of data are missing, simple study-level assumptions regarding the distributions of missing

data are likely to introduce bias in results and such situations are best addressed by more complex modelling. Complex modelling of data missing from the studies considered here was beyond the scope of this review. In the case of smoking studies, the simple assumption that missing data represent a return to baseline smoking behaviour (failure of treatment) is intuitively reasonable and is unlikely to lead to an overestimate of the effectiveness of NRT.

Whichever success rate for CDTQ is adopted (8.6% based on 12-month point prevalence, MHRA, approximately 2% based on 6 months of sustained abstinence commencing within 6 weeks of starting treatment or 6.75% based on 6 months of sustained abstinence started within treatment period), it will be considerably less than the success rates reported for abrupt quit with NRT (approximately 15%). This may not be surprising in view of the differences in populations of smokers that have been investigated using these interventions. It is a moot point whether a head-to-head comparison of the effectiveness of abrupt quit and CDTQ makes sense, because randomising smokers who declare unwillingness or inability to quit in the short term to an abrupt quit programme would not appear to be a rational intervention. The alternative approach of randomising smokers willing or able to attempt an abrupt quit to either an abrupt or CDTQ regime does not appear to have been attempted, but would indicate whether early motivation of willing abrupt attempters changed (subsided or increased) with prolonged treatment.

In the included studies, NRT was made available for longer than is customary in abrupt quit regimes. Thus smokers undertaking a reduction strategy are likely to be exposed to nicotine for longer than those pursuing an abrupt quit stratagem and additionally they will be exposed simultaneously to both cigarette and NRT-derived nicotine. Despite these considerations, there was no evidence from these trials that these exposures were related to greater frequency or seriousness of adverse events previously reported to be associated with NRT. The MHRA working group remarked, "… smoking reduction indication had been authorised in ten other European countries, the first in 1997, and that post-marketing surveillance did not indicate a different profile of adverse events that could be related to the smoking reduction indication," and "when considering those who had not significantly reduced the number of cigarettes smoked while using gum or inhaler, the working group were satisfied that the majority of smokers titrated nicotine to their individual preferred level regardless of source" and further "even if higher than usual plasma levels were attained, this was not likely to be associated with an increased risk of adverse events".[3]

Summary of effectiveness

No systematic reviews of the effectiveness of CDTQ were found. Seven placebo-controlled RCTs, of which six were sponsored by industry, were identified that examined the effectiveness of smoking reduction with NRT versus placebo in populations unwilling or unable to quit smoking in the short term. Sustained abstinence from smoking was a secondary outcome in all studies and so none were specifically designed to investigate effectiveness of NRT for CDTQ.

The main findings were as follows:

- **CO-validated sustained abstinence from smoking:** Sustained abstinence from smoking started early in treatment (6 weeks) was reported in six RCTs comparing NRT with placebo. Meta-analysis indicated that NRT was superior to placebo at many time points during follow-up [ORs at 6 and 12 months were 5.51 (95% CI 2.5 to 11.9) and 4.9 (95% CI 2.0 to 12.1), respectively]. Across all studies, the number of patients sustaining abstinence from early in treatment was very meagre in both arms – at 6 months 24 of 1119 (2.1%) and two of 1114 (0.18%) in the NRT and placebo arms, respectively, and at 12 months 17/1119 (1.5%) and 2/1114 (0.18%), respectively. Meta-analysis employing IPD from five trial reports indicated that NRT was superior to placebo in achieving 6 months of sustained abstinence starting at any time during treatment [RR 2.06 (95% CI 1.34 to 3.15) in favour of NRT] with 6.75% of patients receiving NRT and 3.29% of those receiving placebo achieving sustained abstinence.
- **Point prevalence of abstinence from smoking:** Meta-analyses of point prevalence of abstinence from smoking indicated that NRT was superior to placebo at many time points during follow-up [RR for NRT versus placebo at 6 months was 2.5 (95% CI 1.7 to 3.7) and at 12 months 1.9 (95% CI 1.4 to 2.7)]. A trend was evident toward reduced relative effectiveness at later times during follow-up.
- **CO-validated sustained smoking reduction:** NRT was superior to placebo in sustaining ?:50% reduction in cigarettes smoked per day. In the NRT and placebo arms of the six industry-sponsored trials, 11.5% (n = 129) and 3.3% (n = 37) of patients sustained reduction to

6 months from week six of treatment and 7.7% (n = 86) and 2.0% (n = 22) sustained reduction to 12 months, respectively. Meta-analysis of the results from these trials yielded RRs (NRT versus placebo) of 3.3 (95% CI 2.3 to 4.7) and 3.6 (95% CI 2.3 to 5.8) at 6 and 12 months, respectively.

- **Point prevalence of reduction in smoking:** Meta-analyses indicated that NRT was superior to placebo with regard to the proportions of patients found to have achieved CO-validated ?:50% smoking reduction at various time points during follow-up. At 6 months 265 of 1119 (23.7%) NRT-treated patients and 150 of 1114 (13.5%) placebo-treated patients had reduced smoking by ?:50% and at 12 months the numbers were 246 of 1119 (22.0%) and 171 of 1114 (15.3%), respectively. Meta-analysis of the results from these trials yielded RRs (NRT versus placebo) of 1.7 (95% CI 1.4 to 2.1) and 1.4 (95% CI 1.2 to 1.7) at 6 and 12 months, respectively.
- **QoL:** Data from trials were incomplete. Evidence indicated that compared with participants that failed to sustain smoking reduction those that sustained reduction of ?:50% experienced small increments of improvement in some HRQoL domains measured using the validated SF-36 instrument. Information comparing sustained abstainers with non-abstainers was not available.
- **Adverse events:** No significant treatment-associated serious adverse events were reported in any of the included trials. Minor adverse events previously associated with NRT treatment, including headache, nausea or vomiting and dyspepsia, were commonly observed and occurred at greater frequency for patients receiving NRT than those receiving placebo.

Chapter 4

Economic analysis

Methods

Search strategy

A comprehensive search for literature on the cost-effectiveness of CDTQ with NRT for smoking cessation was conducted. Studies on costs, QoL, cost-effectiveness and modelling were identified from the following sources: bibliographic databases: MEDLINE (Ovid) 1966–July 2006; EMBASE (Ovid) 1980–Week 28 2006; Cochrane Library (Wiley Internet version) [NHS Economic Evaluation Database (EED) and Database of Abstracts and Reviews of Effects (DARE)] 2006 Issue 2; Office of Health Economics Health Economic Evaluation Database (HEED) database, July 2006; Internet sites of national/international economic units. Searches were not limited by language restrictions. Details of searches can be found in Appendix 1.

Two reviewers independently screened all titles and abstracts for relevance. Any discrepancies were resolved by consensus.

Inclusion criteria

Any relevant studies that evaluated cost-effectiveness or cost–utility of CDTQ with NRT were eligible for inclusion, such as RCTs, prospective/retrospective cohort studies and simulation modelling studies.

Data extraction

Data were extracted by one reviewer using a standard data extraction form and independently checked for accuracy by a second reviewer. Disagreements were resolved by discussion and with the involvement of a third reviewer when necessary.

Outcomes

The outcome measures were incremental cost per quitter, or per life-year saved, or ideally, per QALY compared with no or alternative interventions. Studies reporting cost–benefit of CDTQ for smoking cessation were also included.

Quality assessment

Quality assessment for assessments of cost-effectiveness studies was done using standard criteria.[48]

Data analysis and synthesis

Studies were summarised on the basis of key items of information, including form of economic analysis, comparator(s), perspective, time horizon, modelling, effectiveness data, health state valuations, resource use data, unit cost data, price year and discounting.

De novo model of cost-effectiveness of CDTQ using NRT

In order to explore the cost-effectiveness of CDTQ with NRT, a novel decision-analytic model was developed. The choice of model was dependent on both the appropriate structure for the review question and the lack of previously published models.

The cost-effectiveness analysis was expressed in terms of incremental cost per life-year and per QALY. The perspective for the reference case model was NHS/Personal Social Services (PSS). Subject to the availability of suitable data, the costs and benefits of different service strategies and optimum care package (e.g. setting, dosage, supervision, monitoring) were explored in sensitivity analyses.

Results

Existing economic studies

The search for economic studies of CDTQ with NRT yielded, after electronic removal of duplicates, 321 citations. None satisfied the inclusion criteria; the most common reasons for exclusion of studies were that they did not consider CDTQ or did not specify that the population in receipt of the intervention were smokers unwilling or unable to quit in the short term.

Decision analytic model of CDTQ with NRT

Model specification

The model was designed to assess the cost-effectiveness of making NRT available in the context of a CDTQ programme for a suitable population of smokers. The intention behind the policy is that some smokers who would not be willing to attempt to quit abruptly would be

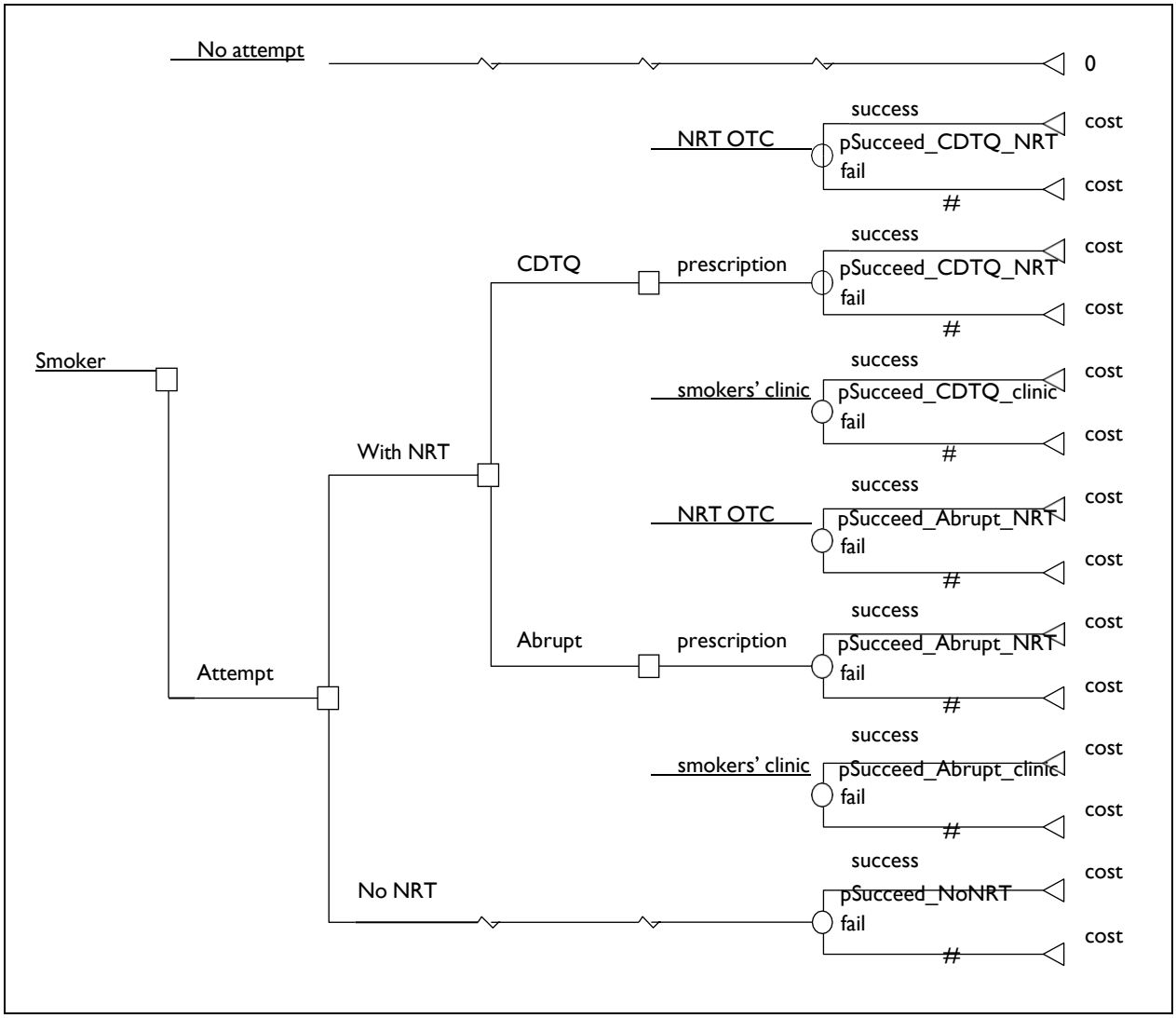

FIGURE 14 *Decision tree for CDTQ at individual smoker level*

willing to attempt CDTQ. However, this must be offset against the possibility that smokers might attempt CDTQ instead of attempting to quit abruptly.

The only therapy modelled was NRT. Possible changes in the habits of smokers using other therapies constitute a separate decision problem, so such smokers were not considered within the current model. The options available to an individual smoker are shown in *Figure 14*.

In the 'full range' option, an individual smoker may or may not attempt to quit smoking. If an attempt is made, this may be with or without NRT. There were no data available on whether attempts without NRT are abrupt or CDTQ, or on any difference in success rate. Since there is no difference in cost, there is no advantage in subdividing this group.

For attempts made with NRT, these may be abrupt or CDTQ, and then, within each of these possibilities, the attempt may be one of:

- OTC NRT
- prescription NRT
- a smokers' clinic (prescription NRT plus behavioural support).

For this model, the outcome measure was expected lifetime QALYs. This was largely determined by whether an individual is or is not a successful long-term quitter. For modelling purposes, this term required a precise definition. In line with previous studies, the definition of successful long-

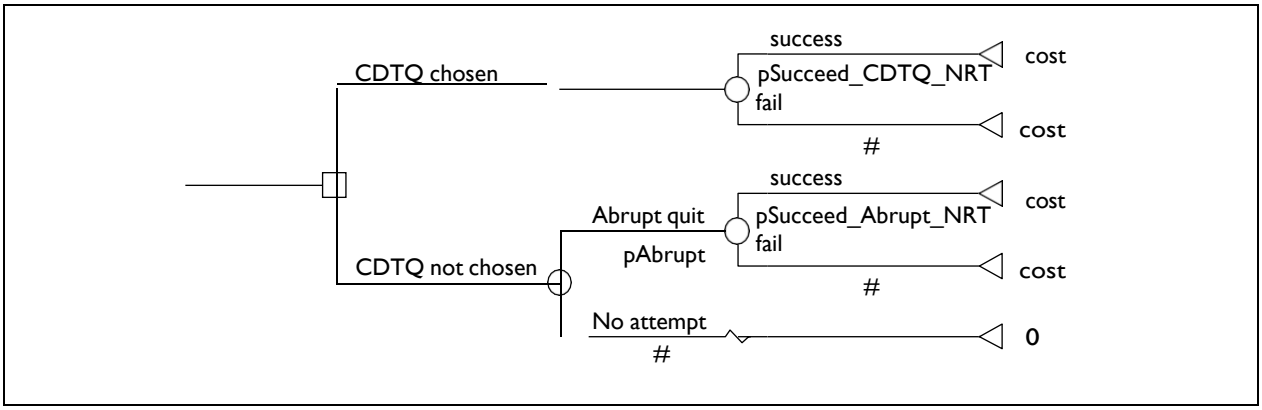

FIGURE 15 *Decision tree for mixed analysis with NRT prescription*

term quitter was taken to be 12 months' sustained abstinence from smoking.

It was acknowledged that successful long-term quitters include some who relapse after a number of years. It was assumed that the risk of relapse was independent of the quit attempt made. Accordingly, a single QALY gain figure was applied to the successful long-term quitters.

There may be a small health gain from short-term quitting. However, this is likely to be negligible compared with the effect of long-term quitting (in terms of both point estimate and the degree of uncertainty surrounding this estimate). Given the considerable difficulties involved in trying to define and measure the short-term gain, it was appropriate to exclude such considerations from the model.

Accordingly, for each possible action by an individual smoker, the possible outcomes were 'successful long-term quitter' and 'fail'.

The model was built using Microsoft Excel and was designed to be analysed at three different levels of complexity. The simplest analysis considers a single smoker considering joining a CTDQ programme. This was compared with any other programme within the model.

The next level was a mixed analysis. This considers smokers who may join a single CDTQ programme. In this case, the comparator consisted of some smokers who attempt to quit using the equivalent abrupt quit programme, and some smokers who make no attempt to quit. Since this version of the model was run at a policy level, the choice of individual smokers in the comparator arm was modelled as a chance node, as shown (for the case of NRT prescription) in *Figure 15*.

In the mixed analysis, the variable pAbrupt shows the smokers who would switch from abrupt quit to CDTQ as a proportion of those trying CDTQ. This proportion was varied across the full range from 0 to 100%: the principal aim of this analysis was to find the threshold (if any) at which the decision to make CDTQ available would change.

The full model compares five policy options, according to which forms of CDTQ are made available. Again, since the model was built from a policy perspective, the choices of individual smokers were modelled as chance outcomes. The difference between the options was in the range of choices available, and hence in the proportions of smokers making each choice (see *Figure 16*).

The various policy options may be defined by the branches omitted from the "full range" option, as shown in *Table 13*.

Data sources

Costs

For each option, the average cost of pursuing that option was estimated. This was based on available data for resource use (therapy and clinicians' time), multiplied by appropriate unit costs (see Appendix 12). For the OTC option, all costs are defrayed by the patient, and in this case the resulting costs to the NHS were therefore zero.

TABLE 13 *Policy options and branches available in the decision tree (*Figure 16*)*

Option	Branches available
CDTQ not available	No CDTQ branches
CDTQ OTC only	After CDTQ, only NRT OTC
CDTQ NRT only	After CDTQ, omit smokers' clinic
CDTQ OTC or clinic	After CDTQ, omit prescription
Full range	All branches available

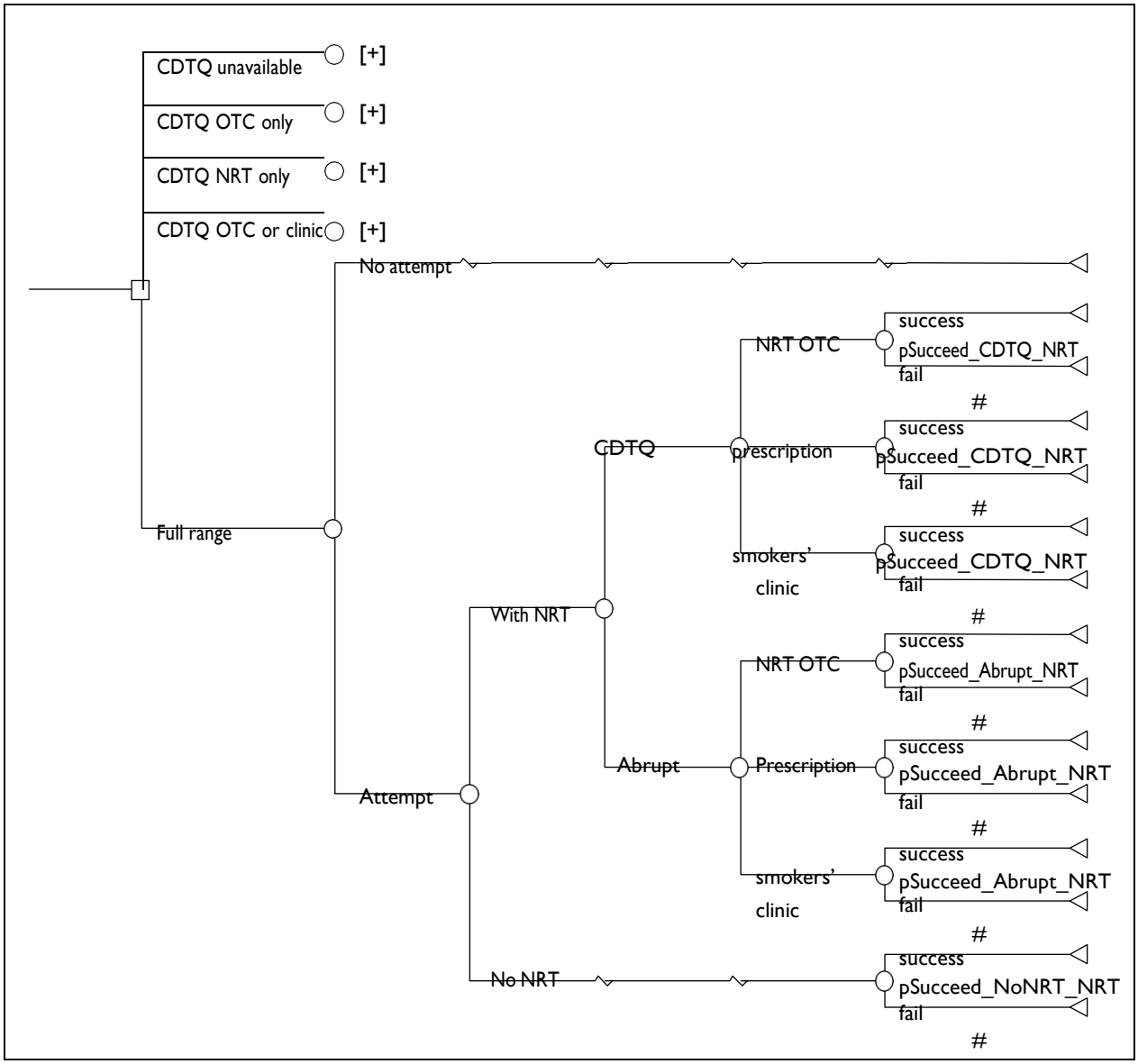

FIGURE 16 *Decision tree for CDTQ.* [+] *indicates that the remainder of this part of the tree is not shown. In each case, the structure is a version of the 'full range' subtree, but with certain branches omitted. See* Table 13 *for details.*

Outcome measures

Ideally, the outcome measure for each branch would be the quality-adjusted life expectancy associated with that outcome. However, for the purpose of incremental analysis, it was sufficient to give an estimate of the QALY gain for a successful quitter compared with one who continues smoking. This was based on data from the 2004 publication of Doll and colleagues[49] (described in Appendix 13). QALY gain by age group, discounted at 3.5%, is summarised in *Table 14*.

TABLE 14 *Undiscounted and discounted QALY gains by smokers who quit at different ages*

	QALY gain	
Age (years)	**Undiscounted**	**Discounted**
<35	8.44	2.22
35–44	7.36	2.58
45–54	4.47	2.14
55–64	1.455	0.99

Success rates for lifetime quitting

Analysis of CDTQ IPD from five studies included for effectiveness (see the section 'Sustained abstinence outcomes based on IPD', p. 18) indicated that 6 months' sustained abstinence was achieved by an average of 6.75% (range 3.2–10.2%) of subjects in receipt of NRT. Using a relapse rate between 6 and 12 months of 21%

TABLE 15 *12 months' sustained abstinence from smoking (abrupt quit)*

Period of sustained abstinence	Intervention arm	No intervention/placebo arm	All
12 months	2266/14181 (15.98%)	1351/13114 (10.30%)	3617/27295 (13.25%)

Data taken from *Table 2* in Woolacott and colleagues.[6]

TABLE 16 *Costs and success rates at 12 months for different choices of individual smokers*

Option	Cost (£)	Success rate (at least 6 months)	Success rate (at least 12 months)	Success rate (lifetime)[h]
No attempt	0	0	0	0
CDTQ with NRT OTC	0	NA	0.0221[a]	0.0155
CDTQ prescription only	104.96	NA	0.0195[b]	0.0137
CDTQ individual counselling	153.79	0.0675	0.0533[c]	0.0373
CDTQ group counselling	128.27	0.0675	0.0533[c]	0.0373
Abrupt with NRT OTC	0	0.0839[d]	0.0663[c]	0.0464
Abrupt prescription only	54.88	0.0741[e]	0.0586[c]	0.0410
Abrupt individual counselling	112.11	NA	0.1598[f]	0.1119
Abrupt group counselling	97.04	NA	0.1598[f]	0.1119
Attempt with no NRT	0	NA	0.0400[g]	0.0280

[a] In the absence of reliable data for this parameter, it was assumed that the success rate would be in the same proportion to the success rates for the corresponding abrupt quit options (0.0221/0.0533 = 0.0663/0.1598).
[b] In the absence of reliable data for this parameter, it was assumed that the success rate would be in the same proportion to the success rates for the corresponding abrupt quit options (0.0195/0.0533 = 0.0586/0.1598).
[c] 21% relapse rate between 6 and 12 months' abstinence was applied. The 21% relapse rate from 6 to 12 months was derived from the meta-analysis of 12 studies conducted by Stapleton and Stapleton.[50]
[d] Estimated using three studies in the meta-analysis reported by Hughes and colleagues[52] [two studies[53,54] reported 6 months' continuous abstinence rate, one study[55] reported 12 months' abstinence rate; for this study the 12-month rate was converted to a 6-month rate by applying a 21% relapse rate].
[e] The RR of abstinence for OTC NRT vs prescription NRT was calculated from the data in the meta-analysis by Hughes and colleagues[52] which meta-analysed three studies;[54–56] RR = 1.168 (in favour of OTC; fixed effects model). This analysis was updated to incorporate a more recent study[57] and obtained RR = 1.132. The abstinence rate for prescription NRT was obtained by applying this RR (RR = 1.132) to the abstinence rate of OTC NRT.
[f] Woolacott and colleagues.[6]
[g] Hughes and colleagues.[58]
[h] The lifetime abstinence rates were obtained by applying a relapse rate of 30% to 1 year abstinence rates.[51]

(from a meta-analysis of 12 studies[50]) yielded a probability of 12 months' sustained abstinence for CDTQ with NRT of $0.79 \times 0.0675 = 0.0533$.

Data from smoking cessation studies reviewed by Woolacott and colleagues[6] indicate that about 16% of smokers who attempt an NRT-abrupt quit sustain abstinence for 12 months (*Table 15*).

A recent meta-analysis[51] estimated a relapse rate of 30% after 12 months of sustained abstinence. Meta-regression showed this was independent of follow-up length ($n = 12$). From this, we estimate the proportion of NRT-treated subjects in a CDTQ NRT programme who achieve lifetime abstinence as $= 0.7 \times 0.0533 = 0.0373$ (and $0.7 \times 0.16 = 0.11$ for abrupt quitters).

Success rates for various interventions at twelve months and lifetime success rates are summarised in *Table 16*.

Estimation of cost-effectiveness

As mentioned above, modelling with differing levels of complexity was undertaken. The results are shown in three parts:

- 'Simple analysis', which considers a single smoker, comparing each CDTQ option with each non-CDTQ option.
- 'Mixed analysis', which compares a single CDTQ option with a mix of 'no attempt' and the corresponding abrupt quit option.
- 'Full analysis', which compares a range of CDTQ options with the full mix of non-CDTQ options.

TABLE 17 *Change to CTDQ with NRT OTC*

From	Difference in cost	Difference in success rate	ICER (£/quit)[a]	ICER (£/QALY) for age group[a]			
				<35 years	35–44 years	45–54 years	55–64 years
Abrupt prescription only	–54.88	–0.0255	*2152*	*969*	*834*	*1006*	*2174*
Abrupt individual counselling	–112.11	–0.0964	*1163*	*524*	*451*	*543*	*1175*
Abrupt group counselling	–97.04	–0.0964	*1007*	*453*	*390*	*470*	*1017*

[a] ICER in italics indicates point in the south-west quadrant of the cost-effectiveness plane. This means reductions in both cost and effectiveness. A low ICER means that the saving in money is not worth making.

TABLE 18 *Change to CTDQ prescription only*

From	Difference in cost	Difference in success rate	ICER (£/quit)[a]	ICER (£/QALY) for age group[a]			
				<35 years	35–44 years	45–54 years	55–64 years
No attempt	104.96	0.0137	7661	3451	2970	3580	7739
Abrupt with NRT OTC	104.96	–0.0327			Abrupt dominates CDTQ		
Abrupt prescription only	50.08	–0.0273			Abrupt dominates CDTQ		
Abrupt individual counselling	–7.15	–0.0982	*73*	*33*	*28*	*34*	*74*
Abrupt group counselling	7.92	–0.0982			Abrupt dominates CDTQ		
Attempt with no NRT	104.96	–0.0143			No NRT dominates CDTQ		

[a] ICER in italics indicates a point in the south-west quadrant of the cost-effectiveness plane. This means reductions in both cost and effectiveness. A low ICER means that the saving in money is not worth making.

In each part, two main cases are considered:

- The base case, which assumes that the lower success rate for CDTQ compared with abrupt quit applies to all CDTQ attempts.
- An alternative case of sensitivity analysis, which assumes that smokers who would have tried abrupt quit in the absence of CDTQ retain the success rate for abrupt quit.

In addition to the sensitivity analysis described above, the calculation of incremental cost-effectiveness ratios (ICERs) in terms of cost per QALY gained for a number of different age ranges provided a further sensitivity analysis for the QALY gain per successful quit attempt.

Simple analysis – base case

In this analysis, the effects of a single smoker changing intended pattern of smoking was considered. The base-case costs and outcomes from the eight possible choices are shown in *Table 16*. The age-related conversions from success rate to QALYs gained are shown in *Table 14*.

Each possible change to a CDTQ option from a non-CDTQ option is considered below.

Change to CDTQ with NRT OTC

This is a change to an option with no NHS costs. A change to this option from 'no attempt' is thus an increased success with no extra costs. This is known as 'borderline dominance': from an NHS perspective, it is clearly preferable if people choose a better option with no extra costs. Changes from 'abrupt with NRT OTC' or 'attempt with no NRT' show borderline dominance in the opposite direction. Finally, changes from abrupt options with NHS costs to CDTQ with NRT OTC involve a reduction in NHS costs with a reduction in effectiveness. The results are shown in *Table 17*. The ICERs are well below standard thresholds. This means that the saving in money is not worth making given the reduction in effectiveness.

Change to CDTQ prescription only

The results for this change are shown in *Table 18*. Changes from no attempt involve an increased cost with a corresponding increase in success and lead to ICERs which suggest that this is a cost-effective change. Changes from abrupt with individual counselling involve a small decrease in costs, but nowhere near enough to compensate for the QALY loss. All other changes are clearly not

TABLE 19 *Change to CTDQ individual counselling*

From	Difference in cost	Difference in success rate	ICER (£/quit)	ICER (£/QALY) for age group			
				<35 years	35–44 years	45–54 years	55–64 years
No attempt	153.79	0.0373	4.123	1,857	1,598	1,927	4,165
Abrupt with NRT OTC	153.79	–0.0091			Abrupt dominates CDTQ		
Abrupt prescription only	98.91	–0.0037			Abrupt dominates CDTQ		
Abrupt individual counselling	41.68	–0.0746			Abrupt dominates CDTQ		
Abrupt group counselling	56.75	–0.0746			Abrupt dominates CDTQ		
Attempt with no NRT	153.79	0.0093	16.537	7,449	6,410	7,727	16,704

TABLE 20 *Change to CTDQ group counselling*

From	Difference in cost	Difference in success rate	ICER (£/quit)	ICER (£/QALY) for age group			
				<35 years	35–44 years	45–54 years	55–64 years
No attempt	128.27	0.0373	3,439	1,549	1,333	1,607	3,474
Abrupt with NRT OTC	128.27	–0.0091			Abrupt dominates CDTQ		
Abrupt prescription only	73.39	–0.0037			Abrupt dominates CDTQ		
Abrupt individual counselling	16.16	–0.0746			Abrupt dominates CDTQ		
Abrupt group counselling	31.23	–0.0746			Abrupt dominates CDTQ		
Attempt with no NRT	128.27	0.0093	13,792	6,213	5,346	6,445	13,932

worthwhile as they involve increased costs with decreased success rates.

Change to CDTQ individual counselling
The results for this change are shown in *Table 19*. Changes from no attempt, or attempt without NRT, give ICERs which suggest that this is a cost-effective change. Changes from abrupt attempts with NRT involve increased cost and reduced effectiveness.

Change to CDTQ group counselling
The results for this change are shown in *Table 20*. Changes from no attempt, or attempt without NRT, give ICERs which suggest that this is a cost-effective change. Changes from abrupt attempts with NRT involve increased cost and reduced effectiveness.

Simple analysis – alternative case
Making the assumption that smokers who switch to CDTQ from an alternative method retain the success rate of the alternative method, then the change to CDTQ involves only a change in costs with no change in outcome. Any change from an abrupt quit method involving NHS costs to CDTQ OTC is clearly cost-saving for the NHS. A change from 'abrupt individual counselling' to 'CDTQ prescription only' is also cost-saving. All other changes, including those from abrupt with any use of the NHS to the equivalent CDTQ service, involve increased costs for the same outcome.

Mixed analysis – base case
In this analysis, a single form of NRT-assisted CDTQ is considered, and it is assumed that some of the smokers who attempt this form of CDTQ are those who would otherwise make no attempt to quit, while others would now choose CDTQ instead of the equivalent form of abrupt quitting.

CDTQ with NRT OTC
In this case, there are no NHS costs to consider, so only success rates were considered. Changing from no attempt to CDTQ with NRT OTC increased the success rate by 0.0155 whereas changing from abrupt quit with NRT OTC decreased the success rate by 0.0309. The change in success rate can be considered according to the percentage of CDTQ attempts which are changed from abrupt quit. For example, if one smoker changes from abrupt to CDTQ for every three who change from no attempt to CDTQ, that means that 25% of the CDTQ attempts are changed from abrupt quit. The base-case results are shown in *Table 21*. Under the base-case assumptions, if more than 34% of the attempts at CDTQ are made by people who would otherwise have attempted abrupt quit, the net effect of making CDTQ available is to reduce the overall success rate.

TABLE 21 Mixed analysis for CDTQ with NRT OTC

% from abrupt quit	Difference in success rate
0	0.0155
25	0.0039
33	0.0002
34	–0.0003
50	–0.0077
75	–0.0193
100	–0.0309

CDTQ prescription only
In this case, it was assumed that those trying CDTQ prescription only would otherwise have made no quit attempt or would have tried abrupt quit with prescription only. In either case, there is an increase in NHS costs. However, as with NRT OTC, those who changed from abrupt quit to CDTQ have a reduced success rate. The base-case results are shown in *Table 22*. Under base-case assumptions, there is a net gain in success rate only if the proportion changing from abrupt quit is less than 34%. If the proportion is just less than 34%, the change is beneficial in success terms but has a high ICER. The ICER decreases rapidly with small reductions in this proportion.

CDTQ individual counselling
In this case, it was assumed that those trying CDTQ prescription only would otherwise have made no quit attempt or would have tried abrupt quit with individual counselling. The base-case results are given in *Table 23* and show a similar pattern to the results for prescription only above.

CDTQ group counselling
In this case, it was assumed that those trying CDTQ prescription only would otherwise have made no quit attempt or would have tried abrupt quit with group counselling. The base-case results are given in *Table 24* and show a similar pattern to the results for prescription only above.

Mixed analysis – alternative case
In this analysis, it was assumed that people who switch to CDTQ from abrupt quit retain the success rate of abrupt quit. The equivalents of

TABLE 22 Mixed analysis for CDTQ prescription only

% from abrupt quit	Difference in cost	Difference in success rate	ICER (£/quit)	ICER (£/QALY) for age group			
				<35 years	35–44 years	45–54 years	55–64 years
0	104.96	0.0137	7,661	3,451	2,970	3,580	7,739
25	91.24	0.0035	26,446	11,913	10,251	12,358	26,714
30	88.50	0.0014	63,211	28,474	24,501	29,538	63,850
31	87.95	0.0010	88,836	40,016	34,432	41,512	89,733
32	87.40	0.0006	150,687	67,877	58,406	70,414	152,209
33	86.85	0.0002	510,880	230,126	198,016	238,729	516,040
34	86.30	–0.0002		Comparator dominates CDTQ			
50	77.52	–0.0068		Comparator dominates CDTQ			
75	63.80	–0.0171		Comparator dominates CDTQ			
100	50.08	–0.0273		Comparator dominates CDTQ			

TABLE 23 Mixed analysis for CDTQ individual counselling

% from abrupt quit	Difference in cost	Difference in success rate	ICER (£/quit)	ICER (£/QALY) for age group			
				<35 years	35–44 years	45–54 years	55–64 years
0	153.79	0.0373	4,123	1,857	1,598	1,927	4,165
25	125.76	0.0093	13,487	6,075	5,227	6,302	13,623
30	120.16	0.0037	32,214	14,511	12,486	15,053	32,539
31	119.04	0.0026	45,590	20,536	17,671	21,304	46,051
32	117.91	0.0015	79,031	35,600	30,632	36,931	79,830
33	116.79	0.0004	313,120	141,045	121,364	146,318	316,283
34	115.67	–0.0007		Comparator dominates CDTQ			
50	97.74	–0.0187		Comparator dominates CDTQ			
75	69.71	–0.0466		Comparator dominates CDTQ			
100	41.68	–0.0746		Comparator dominates CDTQ			

TABLE 24 *Mixed analysis for CDTQ group counselling*

% from abrupt quit	Difference in cost	Difference in success rate	ICER (£/quit)	ICER (£/QALY) for age group			
				<35 years	35–44 years	45–54 years	55–64 years
0	128.27	0.0373	3,439	1,549	1,333	1,607	3,474
25	104.01	0.0093	11,154	5,024	4,323	5,212	11,267
30	99.16	0.0037	26,584	11,975	10,304	12,422	26,852
31	98.19	0.0026	37,605	16,939	14,576	17,573	37,985
32	97.22	0.0015	65,159	29,351	25,255	30,448	65,817
33	96.25	0.0004	258,034	116,232	100,013	120,577	260,641
34	95.28	–0.0007	Comparator dominates CDTQ				
50	79.75	–0.0187	Comparator dominates CDTQ				
75	55.49	–0.0466	Comparator dominates CDTQ				
100	31.23	–0.0746	Comparator dominates CDTQ				

Tables 21–24 are shown as *Tables 25–28,* respectively. In the OTC case, there is always an increase in success with no change in NHS costs. In all other cases, the ICER remains low until a very high percentage of the CTDQ attempts are made instead of abrupt quitting.

TABLE 25 *Alternative mixed analysis for CDTQ with NRT OTC*

% from abrupt quit	Difference in success rate
0	0.0155
25	0.0116
50	0.0078
75	0.0039
100	0.0000

Full analysis – base case

In this case, the comparator was a mixture of those who would otherwise not attempt to quit with those who would use any of the non-CDTQ attempts to quit. Based on Office for National Statistics (ONS)[1] and IPSOS (UK) Omnibus survey data,[34] 70.7% of quitters do not use NRT. Of those who use NRT, 39% use NRT OTC, 32% use NRT prescription only and 29% use smokers' clinics (see Appendix 14). It was assumed that people would switch to CDTQ in proportion to the different methods of quitting, and separate analyses have been performed with and without the 'no NRT' group. Applying these proportions to the costs and success rates in *Table 16* gives us the values in *Table 29*. The costs for individual and group counselling were applied separately.

TABLE 26 *Alternative mixed analysis for CDTQ prescription only*

% from abrupt quit	Difference in cost	Difference in success rate	ICER (£/quit)	ICER (£/QALY) for age group			
				<35 years	35–44 years	45–54 years	55–64 years
0	104.96	0.0137	7,661	3,451	2,970	3,580	7,739
25	91.24	0.0103	8,880	4,000	3,442	4,149	8,970
50	77.52	0.0069	11,317	5,098	4,386	5,288	11,431
75	63.80	0.0034	18,628	8,391	7,220	8,705	18,816
100	50.08	0.0000	ICER not defined				

TABLE 27 *Alternative mixed analysis for CDTQ individual counselling*

% from abrupt quit	Difference in cost	Difference in success rate	ICER (£/quit)	ICER (£/QALY) for age group			
				<35 years	35–44 years	45–54 years	55–64 years
0	153.79	0.0373	4123	1857	1598	1927	4165
25	125.76	0.0280	4496	2025	1742	2101	4541
50	97.74	0.0187	5240	2361	2031	2449	5293
75	69.71	0.0093	7475	3367	2897	3493	7551

Economic analysis	41.68	0.0000	ICER not defined

TABLE 28 *Alternative mixed analysis for CDTQ group counselling*

% from abrupt quit	Difference in cost	Difference in success rate	ICER (£/quit)	ICER (£/QALY) for age group			
				<35 years	35–44 years	45–54 years	55–64 years
0	128.27	0.0373	3439	1549	1333	1607	3474
25	104.01	0.0280	3718	1675	1441	1737	3756
50	79.75	0.0187	4276	1926	1657	1998	4319
75	55.49	0.0093	5951	2680	2306	2781	6011
100	31.23	0.0000		ICER not defined			

TABLE 29 *Costs and success rates for quitters*

Group	Average cost (£)[a]	Success rate[a]
Any NRT (individual counselling)	50.07	0.0637
Any NRT (group counselling)	45.70	0.0637
Any quit (individual counselling)	14.67	0.0385
Any quit (group counselling)	13.39	0.0385

[a] Weighted averages of costs and success rates in *Table 16*. Weights based on ONS[1] and IPSOS[34] data (see text).

TABLE 30 *CDTQ OTC only versus no quit or any NRT (individual counselling)*

% from abrupt quit	Difference in cost	Difference in success rate	ICER (£/quit)[a]	ICER (£/QALY) for age group[a]			
				<35 years	35–44 years	45–54 years	55–64 years
0	0.00	0.0155		CDTQ dominates comparator			
24	–12.02	0.0002		CDTQ dominates comparator			
25	–12.52	–0.0004	*30,038*	*13,531*	*11,643*	*14,036*	*30,342*
26	–13.02	–0.0011	*12,359*	*5,567*	*4,790*	*5,775*	*12,484*
27	–13.52	–0.0017	*7,999*	*3,603*	*3,101*	*3,738*	*8,080*
28	–14.02	–0.0023	*6,026*	*2,714*	*2,336*	*2,816*	*6,087*
30	–15.02	–0.0036	*4,173*	*1,880*	*1,617*	*1,950*	*4,215*
50	–25.04	–0.0163	*1,533*	*690*	*594*	*716*	*1,548*
75	–37.56	–0.0323	*1,164*	*525*	*451*	*544*	*1,176*
100	–50.07	–0.0482	*1,040*	*468*	*403*	*486*	*1,050*

[a] ICER in italics indicates a point in the south-west quadrant of the cost-effectiveness plane. This means reductions in both cost and effectiveness. A low ICER means that the saving in money is not worth making.

Four options for policy making are presented: CDTQ with NRT available (1) OTC only; (2) OTC + prescription with no consulting; (3) OTC or prescription with consulting; (4) a full range of options.

Option 1 – CDTQ available OTC only

In this case, there is no NHS cost in CDTQ. If only a small proportion of those attempting CDTQ would otherwise have made an abrupt quit attempt, then there is a net reduction in NHS costs for an increase in effectiveness. In this case, CDTQ is said to dominate. If, however, a high proportion of those attempting CDTQ would otherwise have made an abrupt quit attempt, then there is a reduction in effectiveness. *Tables 30* and *31* illustrate the case where the comparator group excludes those who would otherwise quit without NRT. If the percentage from abrupt quit is 25% or more, there is a reduction in effectiveness and also a reduction in NHS cost. As the percentage from abrupt quit increases slightly, the ICER (in the south-west quadrant) decreases rapidly. This means that if the percentage from abrupt quit is only just over 25%, the cost saving is not justified by the reduction in effectiveness.

A similar pattern is shown in *Tables 32* and *33,* where the comparator group includes those who would otherwise attempt to quit without the use of

TABLE 31 *CDTQ OTC only versus no quit or any NRT (group counselling)*

% from abrupt quit	Difference in cost	Difference in success rate	ICER (£/quit)[a]	ICER (£/QALY) for age group[a]			
				<35 years	35–44 years	45–54 years	55–64 years
0	0.00	0.0155		CDTQ dominates comparator			
24	–10.97	0.0002		CDTQ dominates comparator			
25	–11.43	–0.0004	*27,416*	*12,350*	*10,627*	*12,811*	*27693*
26	–11.88	–0.0011	*11,280*	*5,081*	*4,372*	*5,271*	*11,394*
27	–12.34	–0.0017	*7,301*	*3,289*	*2,830*	*3,412*	*7,375*
28	–12.80	–0.0023	*5,500*	*2,477*	*2,132*	*2,570*	*5,555*
30	–13.71	–0.0036	*3,808*	*1,716*	*1,476*	*1,780*	*3,847*
50	–22.85	–0.0163	*1,399*	*630*	*542*	*654*	*1,413*
75	–34.28	–0.0323	*1,063*	*479*	*412*	*497*	*1,074*
100	–45.70	–0.0482	*949*	*427*	*368*	*443*	*958*

[a] ICER in italics indicates a point in the south-west quadrant of the cost-effectiveness plane. This means reductions in both cost and effectiveness. A low ICER means that the saving in money is not worth making.

TABLE 32 *CDTQ OTC only versus no quit or any quit (individual counselling)*

% from abrupt quit	Difference in cost	Difference in success rate	ICER (£/quit)[a]	ICER (£/QALY) for age group[a]			
				<35 years	35–44 years	45–54 years	55–64 years
0	0.00	0.0155		CDTQ dominates comparator			
25	–3.67	0.0059		CDTQ dominates comparator			
40	–5.87	0.0001		CDTQ dominates comparator			
41	–6.02	–0.0003	*22,727*	*10,237*	*8,809*	*10,620*	*22,957*
42	–6.16	–0.0006	*9,492*	*4,276*	*3,679*	*4,436*	*9,588*
43	–6.31	–0.0010	*6,103*	*2,749*	*2,366*	*2,852*	*6,165*
44	–6.46	–0.0014	*4,552*	*2,050*	*1,764*	*2,127*	*4,598*
50	–7.34	–0.0037	*1,969*	*887*	*763*	*920*	*1,989*
75	–11.00	–0.0133	*825*	*372*	*320*	*386*	*833*
100	–14.67	–0.0230	*639*	*288*	*248*	*299*	*646*

[a] ICER in italics indicates a point in the south-west quadrant of the cost-effectiveness plane. This means reductions in both cost and effectiveness. A low ICER means that the saving in money is not worth making.

TABLE 33 *CDTQ OTC only versus no quit or any quit (group counselling)*

% from abrupt quit	Difference in cost	Difference in success rate	ICER (£/quit)[a]	ICER (£/QALY) for age group[a]			
				<35 years	35–44 years	45–54 years	55–64 years
0	0.00	0.0155		CDTQ dominates comparator			
25	–3.35	0.0059		CDTQ dominates comparator			
40	–5.36	0.0001		CDTQ dominates comparator			
41	–5.49	–0.0003	*20,744*	*9,344*	*8,040*	*9,693*	*20,953*
42	–5.62	–0.0006	*8,664*	*3,903*	*3,358*	*4,048*	*8,751*
43	–5.76	–0.0010	*5,571*	*2,509*	*2,159*	*2,603*	*5,627*
44	–5.89	–0.0014	*4,155*	*1,871*	*1,610*	*1,941*	*4,197*
50	–6.70	–0.0037	*1,797*	*810*	*697*	*840*	*1,816*
75	–10.04	–0.0133	*753*	*339*	*292*	*352*	*761*
100	–13.39	–0.0230	*583*	*263*	*226*	*273*	*589*

[a] ICER in italics indicates a point in the south-west quadrant of the cost-effectiveness plane. This means reductions in both cost and effectiveness. A low ICER means that the saving in money is not worth making.

TABLE 34 *CDTQ NRT only versus no quit or NRT (individual counselling)*

% from abrupt quit	Difference in cost	Difference in success rate	ICER (£/quit)[a]	ICER (£/QALY) for age group[a]			
				<35 years	35–44 years	45–54 years	55–64 years
0	41.98	0.0148	2,841	1,280	1,101	1,327	2,869
20	31.97	0.0020	15,621	7,036	6,055	7,299	15,778
21	31.47	0.0014	22,319	10,054	8,651	10,430	22,545
22	30.97	0.0008	40,048	18,040	15,523	18,714	40,453
23	30.47	0.0001	223,055	100,475	86,455	104,231	225,308
24	29.97	–0.0005		Comparator dominates CDTQ			
25	29.47	–0.0011		Comparator dominates CDTQ			
50	16.95	–0.0171		Comparator dominates CDTQ			
75	4.43	–0.0330		Comparator dominates CDTQ			
100	–8.09	–0.0489	*165*	*75*	*64*	*77*	*167*

[a] ICER in italics indicates a point in the south-west quadrant of the cost-effectiveness plane. This means reductions in both cost and effectiveness. A low ICER means that the saving in money is not worth making.

TABLE 35 *CDTQ NRT only versus no quit or NRT (group counselling)*

% from abrupt quit	Difference in cost	Difference in success rate	ICER (£/quit)[a]	ICER (£/QALY) for age group[a]			
				<35 years	35–44 years	45–54 years	55–64 years
0	41.98	0.0148	2,841	1,280	1,101	1,327	2,869
20	32.84	0.0020	16,048	7,229	6,220	7,499	16,210
21	32.39	0.0014	22,970	10,347	8,903	10,734	23,202
22	31.93	0.0008	41,292	18,600	16,005	19,295	41,709
23	31.47	0.0001	230,414	103,790	89,308	107,670	232,742
24	31.02	–0.0005		Comparator dominates CDTQ			
25	30.56	–0.0011		Comparator dominates CDTQ			
50	19.13	–0.0171		Comparator dominates CDTQ			
75	7.71	–0.0330		Comparator dominates CDTQ			
100	–3.72	–0.0489	*76*	*34*	*29*	*36*	*77*

[a] ICER in italics indicates a point in the south-west quadrant of the cost-effectiveness plane. This means reductions in both cost and effectiveness. A low ICER means that the saving in money is not worth making.

NRT. In this case, the effectiveness threshold is at 41% from abrupt quit.

Option 2 – CDTQ available NRT only

In this option, it was assumed that CDTQ is available either OTC or by prescription only, but without counselling. Based on expert opinion, it was assumed that 60% of CDTQ attempts would be OTC and 40% by prescription. The comparator is as for Option 1.

The average cost per CDTQ attempt is generally higher than for the comparator attempt. The effectiveness findings are similar to Option 1. As before, the cost-effectiveness threshold (ICER :s;£30,000) is just below the effectiveness threshold (difference in success in favour of intervention; see *Tables 34–37*). In *Tables 34* and *35,* a different outcome is seen when the percentage from abrupt quit is very high (over 75%). In these cases, where 'no NRT' is excluded from the comparator, CDTQ is actually cost-saving. However, there is also a reduction in effectiveness, and the ICER (in the south-west quadrant) is very low, so that the cost saving would not worth making.

Option 3 – CDTQ available OTC or counselling

In this option, it was assumed that CDTQ was available either OTC or by prescription with counselling. Again, based on expert opinion, it was assumed that 60% of CDTQ attempts would be OTC and 40% by prescription. The comparator is as for Options 1 and 2 above. Results are similar to Option 2, except that the thresholds are somewhat higher (see *Tables 38–41*).

TABLE 36 *CDTQ NRT only versus no quit or any quit (individual counselling)*

% from abrupt quit	Difference in cost	Difference in success rate	ICER (£/quit)	ICER (£/QALY) for age group			
				<35 years	35–44 years	45–54 years	55–64 years
0	41.98	0.0148	2,841	1,280	1,101	1,327	2,869
25	38.32	0.0052	7,415	3,340	2,874	3,465	7,490
35	36.85	0.0013	27,866	12,552	10,801	13,022	28,148
36	36.70	0.0009	39,135	17,628	15,168	18,287	39,530
37	36.56	0.0006	66,063	29,758	25,606	30,871	66,731
38	36.41	0.0002	215,646	97,138	83,584	100,769	217,824
39	36.26	–0.0002		Comparator dominates CDTQ			
50	34.65	–0.0044		Comparator dominates CDTQ			
75	30.98	–0.0141		Comparator dominates CDTQ			
100	27.31	–0.0237		Comparator dominates CDTQ			

TABLE 37 *CDTQ NRT only versus no quit or any quit (group counselling)*

% from abrupt quit	Difference in cost	Difference in success rate	ICER (£/quit)	ICER (£/QALY) for age group			
				<35 years	35–44 years	45–54 years	55–64 years
0	41.98	0.0148	2,841	1,280	1,101	1,327	2,869
25	38.64	0.0052	7,477	3,368	2,898	3,494	7,552
35	37.30	0.0013	28,205	12,705	10,932	13,180	28,490
36	37.16	0.0009	39,626	17,850	15,359	18,517	40,026
37	37.03	0.0006	66,920	30,144	25,938	31,271	67,596
38	36.90	0.0002	218,528	98,436	84,701	102,116	220,735
39	36.76	–0.0002		Comparator dominates CDTQ			
50	35.29	–0.0044		Comparator dominates CDTQ			
75	31.94	–0.0141		Comparator dominates CDTQ			
100	28.59	–0.0237		Comparator dominates CDTQ			

TABLE 38 *CDTQ OTC or counselling versus no quit or any NRT (individual counselling)*

% from abrupt quit	Difference in cost	Difference in success rate	ICER (£/quit)	ICER (£/QALY) for age group			
				<35 years	35–44 years	45–54 years	55–64 years
0	61.52	0.0242	2,540	1,144	984	1,187	2,566
25	49.00	0.0083	5,901	2,658	2,287	2,757	5,961
35	43.99	0.0019	22,716	10,232	8,805	10,615	22,945
36	43.49	0.0013	33,457	15,071	12,968	15,634	33,795
37	42.99	0.0007	64,819	29,198	25,124	30,289	65,474
38	42.49	0.0000	1,600,907	721,129	620,507	748,087	1,617,078
39	41.99	–0.0006		Comparator dominates CDTQ			
50	36.48	–0.0076		Comparator dominates CDTQ			
75	23.96	–0.0235		Comparator dominates CDTQ			
100	11.44	–0.0394		Comparator dominates CDTQ			

Option 4 – CDTQ full range

In this option, it was assumed that the full range of CDTQ choices is available. The assumptions for this option, based on expert opinion, were that 50% of CDTQ attempts would be OTC, 30% prescription only and 20% smokers' clinic. The comparator is as for Options 1, 2 and 3 above. Results follow the same pattern as for Options 2 and 3, with thresholds somewhere in between (see *Tables 42–45*).

Full analysis – alternative case

In the alternative case, it was assumed that those opting for CDTQ who would otherwise have

TABLE 39 *CDTQ OTC or counselling versus no quit or any NRT (group counselling)*

% from abrupt quit	Difference in cost	Difference in success rate	ICER (£/quit)	ICER (£/QALY) for age group			
				<35 years	35–44 years	45–54 years	55–64 years
0	51.31	0.0242	2,118	954	821	990	2,140
25	39.88	0.0083	4,803	2,164	1,862	2,244	4,852
35	35.31	0.0019	18,234	8,214	7,068	8,521	18,419
36	34.85	0.0013	26,814	12,078	10,393	12,530	27,085
37	34.40	0.0007	51,866	23,363	20,103	24,236	52,390
38	33.94	0.0000	1,278,854	576,060	495,680	597,595	1,291,772
39	33.48	–0.0006		Comparator dominates CDTQ			
50	28.46	–0.0076		Comparator dominates CDTQ			
75	17.03	–0.0235		Comparator dominates CDTQ			
100	5.60	–0.0394		Comparator dominates CDTQ			

TABLE 40 *CDTQ OTC or counselling versus no quit or any quit (individual counselling)*

% from abrupt quit	Difference in cost	Difference in success rate	ICER (£/quit)	ICER (£/QALY) for age group			
				<35 years	35–44 years	45–54 years	55–64 years
0	61.52	0.0242	2,540	1,144	984	1,187	2,566
25	57.85	0.0146	3,960	1,784	1,535	1,851	4,000
50	54.18	0.0050	10,847	4,886	4,204	5,069	10,957
58	53.01	0.0019	27,626	12,444	10,708	12,909	27,905
59	52.86	0.0015	34,453	15,519	13,354	16,100	34,801
60	52.71	0.0011	45,848	20,652	17,770	21,424	46,311
61	52.57	0.0008	68,693	30,943	26,625	32,099	69,387
62	52.42	0.0004	137,681	62,018	53,365	64,337	139,072
63	52.27	–0.0000		Comparator dominates CDTQ			
75	50.51	–0.0046		Comparator dominates CDTQ			
100	46.84	–0.0142		Comparator dominates CDTQ			

TABLE 41 *CDTQ OTC or counselling versus no quit or any quit (group counselling)*

% from abrupt quit	Difference in cost	Difference in success rate	ICER (£/quit)	ICER (£/QALY) for age group			
				<35 years	35–44 years	45–54 years	55–64 years
0	51.31	0.0242	2,118	954	821	990	2,140
25	47.96	0.0146	3,283	1,479	1,273	1,534	3,316
50	44.61	0.0050	8,932	4,023	3,462	4,174	9,022
58	43.54	0.0019	22,692	10,222	8,796	10,604	22,922
59	43.41	0.0015	28,292	12,744	10,966	13,221	28,578
60	43.27	0.0011	37,637	16,954	14,588	17,588	38,018
61	43.14	0.0008	56,374	25,394	21,850	26,343	56,943
62	43.01	0.0004	112,955	50,880	43,781	52,783	114,096
63	42.87	0.0000		Comparator dominates CDTQ			
75	41.26	–0.0046		Comparator dominates CDTQ			
100	37.92	–0.0142		Comparator dominates CDTQ			

chosen a different quit attempt method retained the success rate of the alternative method. Again, it follows that CDTQ must, under these assumptions, have a higher success rate than the comparator. Again, the four options for CDTQ were modelled. In Option 1, where there are no NHS costs, CDTQ invariably dominates the comparator. For the other options, the ICERs remain low until the percentage from abrupt quit becomes very high. Full details are given in Appendix 15.

TABLE 42 *CDTQ full range versus no quit or any NRT (individual counselling)*

% from abrupt quit	Difference in cost	Difference in success rate	ICER (£/quit)	ICER (£/QALY) for age group			
				<35 years	35–44 years	45–54 years	55–64 years
0	62.25	0.0193	3,222	1,451	1,249	1,506	3,254
25	49.73	0.0034	14,612	6,582	5,663	6,828	14,759
27	48.73	0.0021	22,877	10,305	8,867	10,690	23,108
28	48.23	0.0015	32,296	14,548	12,518	15,092	32,622
29	47.72	0.0009	55,716	25,097	21,595	26,036	56,279
30	47.22	0.0002	214,752	96,735	83,237	100,351	216,921
31	46.72	–0.0004		Comparator dominates CDTQ			
50	37.21	–0.0125		Comparator dominates CDTQ			
75	24.69	–0.0284		Comparator dominates CDTQ			
100	12.17	–0.0443		Comparator dominates CDTQ			

TABLE 43 *CDTQ full range versus no quit or any NRT (group counselling)*

% from abrupt quit	Difference in cost	Difference in success rate	ICER (£/quit)	ICER (£/QALY) for age group			
				<35 years	35–44 years	45–54 years	55–64 years
0	57.14	0.0193	2,958	1,332	1,146	1,382	2,988
25	45.72	0.0034	13,433	6,051	5,207	6,277	13,569
27	44.80	0.0021	21,035	9,475	8,153	9,829	21,247
28	44.35	0.0015	29,697	13,377	11,511	13,877	29,997
29	43.89	0.0009	51,237	23,080	19,859	23,943	51,755
30	43.43	0.0002	197,504	88,966	76,552	92,291	199,499
31	42.97	–0.0004		Comparator dominates CDTQ			
50	34.29	–0.0125		Comparator dominates CDTQ			
75	22.86	–0.0284		Comparator dominates CDTQ			
100	11.44	–0.0443		Comparator dominates CDTQ			

TABLE 44 *CDTQ full range versus no quit or any quit (individual counselling)*

% from abrupt quit	Difference in cost	Difference in success rate	ICER (£/quit)	ICER (£/QALY) for age group			
				<35 years	35–44 years	45–54 years	55–64 years
0	62.25	0.0193	3,222	1,451	1,249	1,506	3,254
25	58.58	0.0097	6,034	2,718	2,339	2,820	6,095
45	55.64	0.0020	27,583	12,425	10,691	12,889	27,862
46	55.50	0.0016	33,989	15,310	13,174	15,883	34,332
47	55.35	0.0012	44,341	19,973	17,186	20,720	44,789
48	55.20	0.0009	63,908	28,788	24,771	29,864	64,554
49	55.06	0.0005	114,872	51,744	44,524	53,679	116,032
50	54.91	0.0001	579,317	260,953	224,541	270,709	585,168
51	54.76	–0.0003		Comparator dominates CDTQ			
75	51.24	–0.0095		Comparator dominates CDTQ			
100	47.57	–0.0191		Comparator dominates CDTQ			

TABLE 45 *CDTQ full range versus no quit or any quit (group counselling)*

% from abrupt quit	Difference in cost	Difference in success rate	ICER (£/quit)	ICER (£/QALY) for age group			
				<35 years	35–44 years	45–54 years	55–64 years
0	57.14	0.0193	2,958	1,332	1,146	1,382	2,988
25	53.79	0.0097	5,542	2,496	2,148	2,590	5,598
45	51.12	0.0020	25,339	11,414	9,821	11,841	25,595
46	50.98	0.0016	31,224	14,065	12,102	14,591	31,539
47	50.85	0.0012	40,734	18,349	15,788	19,035	41,146
48	50.71	0.0009	58,711	26,446	22,756	27,435	59,304
49	50.58	0.0005	105,532	47,537	40,904	49,314	106,598
50	50.45	0.0001	532,223	239,740	206,288	248,702	537,599
51	50.31	–0.0003	Comparator dominates CDTQ				
75	47.10	–0.0095	Comparator dominates CDTQ				
100	43.75	–0.0191	Comparator dominates CDTQ				

Summary of economic evaluation

The results suggest that compared with no quit attempt, CDTQ delivers ICERs well within margins generally considered cost-effective. Compared with abrupt quitting, CDTQ is less effective and more costly but may address a different population. If CDTQ were to be offered on the NHS as a matter of policy, base-case results suggest that it would only deliver low ICERs if a substantial majority of the people attempting CDTQ were those who would otherwise make no attempt to quit. This result is robust to considerable variations in the forms of CDTQ offered and the assumption about QALYs gained per success.

The results are sensitive to assumptions about the success rate for the different methods of attempting to quit smoking. If it is assumed that a smoker who might otherwise try abrupt quitting retains the same success rate with CDTQ, then all forms of CDTQ provision appear to deliver ICERs well within the margins generally considered cost-effective.

Chapter 5

Implications for other parties

Indirect benefits to family members of successful quitters, especially children, are widely accepted as probable outcomes of individuals quitting; however, these potential benefits are somewhat difficult to quantify. Similarly, potential benefits for society in general through avoidance of passive smoking and unwelcome exposure to cigarette smoke would also accrue. These benefits to family members and bystanders may be dwarfed by the direct benefits to the quitter.

It is obvious that a lifetime quitter from smoking will save money even if the successful quit was sustained by OTC NRT. Equally obvious is the fact that government revenue from tobacco taxation would fall if large numbers of smokers quit. Consideration of these issues and the degree to which tax revenue losses would be offset by reduced expenditure in the treatment of chronic and acute smoking-related illness is well beyond the scope of this report.

Some may consider that there are ethical issues concerning the manner in which different modes of NRT-supported quitting (CDTQ and abrupt quit) are offered to smokers who seek or are given help and/or advice by the healthcare sector. For example, consider the following two cases:
(1) CDTQ intervention denied some smokers on the grounds that they should make the more cost-effective abrupt quit attempt because they have said they consider themselves able/willing to do so; this would be irrespective of the fact that smokers might prefer the CDTQ mode if given a choice;
(2) CDTQ was directly offered to smokers who stated their inability and unwillingness to attempt the abrupt route; under such a situation, smokers in (1) might be justified in judging the system inequitable.

On the other hand, if recalcitrant smokers, prior to their provision of CDTQ, are first expected to demonstrate their inability and unwillingness for an abrupt quit attempt by actually failing to abstain after an abrupt treatment, then such demonstration could be construed as a waste of resources.

Chapter 6

Factors relevant to NHS

It was assumed the average cost for delivery of CDTQ is £153.79 and there are approximately 10 million smokers in England and Wales. According to surveys, approximately 50% of smokers make at least one quit attempt per year and of these about 30% select some form of NRT support. Assuming these quit attempts with NRT are abrupt attempts, about 1.5 million NRT-supported abrupt quit attempts are made per year. If between 5% and 20% of the five million smokers who do not currently make a quit attempt per year are encouraged to do so because of the availability of CDTQ supported by NRT, then the extra annual cost to the NHS generated by this provision will be between about £38 million and £154 million. These estimates assume no leakage of smokers from those who would attempt an abrupt quit to the alternative CDTQ intervention. If between 10% and 20% of the 1.5 million NRT-supported abrupt quitters (individual counselling) instead transferred to CDTQ (individual counselling), then this would place the extra annual cost to the NHS at somewhere between £45 million and £167 million. If this leakage to CDTQ from abrupt quit was split evenly between abrupt quits delivered by brief advice only with repeat prescription, and those delivered by individual counselling, then these extra cost estimates inflate to between £49 million and £175 million.

These estimates assume that the extra costs are limited to those of drug provision plus those of personnel involved in delivery of the interventions. Thus, any costs that might be incurred due to expansion of smoking cessation services to cope with increased demand are taken to be subsumed within the flexibility of the presently operating framework.

If the lifetime quit success rate generated by CDTQ with NRT is taken as 3.75% and annually 5% of recalcitrant smokers were to be attracted to this new intervention, then about 9000 quitters would be generated annually. If those attracted to the treatment would otherwise not have received any treatment, and were truly incapable of an abrupt quit attempt, then a substantial proportion would represent extra quitters.

Currently, NICE is developing guidelines for smoking-cessation interventions. These will include CDTQ and take into consideration the potential for leakage/diversion of 'abrupt quitters' to a CDTQ route.

Chapter 7

Discussion

Main results

Effectiveness

In studies of NRT-supported smoking reduction, NRT exhibited statistically significant superiority to placebo in achieving sustained smoking abstinence for smokers who declared an inability or unwillingness to attempt an abrupt quit. Meta-analysis employing IPD from five trial reports indicated that NRT was superior to placebo in achieving 6 months of sustained abstinence starting at any time during treatment. The RR in favour of NRT was 2.06 (95% CI 1.34 to 3.15) with approximately 6.7% of patients receiving NRT and 3.3% of those receiving placebo achieving sustained abstinence. This translates to approximately 3.7% lifetime quitters. In this population of recalcitrant smokers, NRT generates abstinence success rates less than half those reported for smokers willing to attempt an abrupt quit with NRT.

The trials included in this report were primarily interested in smoking reduction. In these studies, NRT was superior to placebo at inducing sustained smoking reduction. Approximately 11.5% of NRT-treated smokers sustained a greater than 50% reduction in cigarette consumption for at least 6 months. NRT was not associated with serious treatment-associated adverse events and the frequency and types of minor adverse events tallied with those previously reported for abrupt quit studies with NRT.

Cost-effectiveness

Decision analytic modelling results suggest that compared with no quit attempt, CDTQ delivers low ICERs (range approximately £1500/QALY to approximately £7700/QALY depending on age at quitting and mode of intervention delivery), well within margins generally considered cost-effective. Compared with abrupt quitting, CDTQ is less effective and more expensive but may largely address a different population. The base-case analysis indicated that as a policy option CDTQ with NRT delivers low ICERs within generally accepted margins of cost-effectiveness provided that a substantial majority of those attempting to quit with CDTQ are those who would otherwise not attempt to quit at all. In an alternative analysis, those who would have made an abrupt attempt if CDTQ was unavailable, switch to CDTQ but retain the abstinence success rate of abrupt quitting. In this alternative analysis, all forms of provision of CDTQ delivered low ICER values. The validity of this quit rate assumption for the alternative analysis requires that success rate is more dependent on type of smoker than type of intervention.

Assumptions and limitations

Effectiveness

Cut down to quit (or cut down to stop) is a newly licensed indication for NRT targeted at smokers unwilling or unable to quit in the short term. CDTQ remains to be investigated in RCTs primarily aimed at estimating effectiveness for cessation of smoking rather than reduction in smoking. Good-quality smoking-reduction RCTs have been completed in appropriate populations of recalcitrant smokers, and these allow an estimate of rates of sustained cessation achievable with CDTQ. However, it must be borne in mind that no studies were conducted in the UK. In order to apply findings of the available studies to practice, and practice within the UK in particular, a number of assumptions must be acknowledged. These include: (1) taking the cessation rates estimated in 'reduction' studies as valid measures for 'cessation' (for example, it is possible that if during CDTQ treatment an emphasis is given to smoking cessation relative to reduction some alteration in success rate might be observed); (2) applying RCT evidence about success rates to real-world practice (since CDTQ with NRT is newly licensed in the UK, there is as yet no clue about how success rates will translate in different settings); (3) generalising findings about recalcitrant smokers in other countries to the corresponding UK population of smokers; (4) accepting that smokers 'unable or unwilling' to attempt an abrupt quit represent a stable and detectable subpopulation of smokers that can be recruited for treatment.

Cost-effectiveness

The decision analytic model constructed to estimate the cost-effectiveness of CDTQ with NRT was based on a large number of assumptions.

These included the treatment pathways that smokers might adopt, the success rates of NRT and non-NRT interventions, costs associated with different modes of delivery of the interventions and the QALY gains associated with sustained smoking abstinence. The model attempted to use best-informed estimates in all cases but it is acknowledged that all were associated with unavoidable degrees of uncertainty. The estimation of LYG from cessation was based on the study of British doctors by Doll and colleagues[49] with an adjustment to allow for the socio-economic mismatch between British doctors and the current UK population of smokers (see Appendix 13). This adjustment tends to raise the ICER values obtained. Not making any adjustment would lead to an overestimation of cost-effectiveness. The impact of the adjustment is relatively small and ICER values are generally well below £10,000/QALY.

Further research

No RCT of CDTQ with NRT has been conducted in which sustained cessation from smoking was the primary outcome and the population was smokers unwilling or unable to quit in the short term. Such a trial would require clinic visits that emphasised smoking abstinence rather than reduction and might yield better success rates for sustained abstinence than reduction studies. On the other hand, it is conceivable that emphasis on abstinence could demotivate smokers who initially declare unwillingness or inability to quit. How sustained abstinence should be measured in such populations would involve a departure from methods used for abrupt quit studies in which there is generally a requirement for an early start of abstinence.

Randomised trials in recalcitrant smokers allowing head-to-head comparison of CDTQ delivered with various NRT modalities (e.g. inhalator, nasal spray, lozenge, gum, patch) would be informative. However, it is likely that personal preferences of smokers for particular products could play an important role in determining success rates and this could considerably complicate the design, implementation and interpretation of such trials.

Despite uncertainties relating to CDTQ effectiveness and economic modelling discussed above, in particular with regard to model sensitivity to success rate inputs, there are greater uncertainties about how CDTQ might deliver quitters in the real world should it be adopted. These uncertainties will be associated with how CDTQ is rolled out in practice, by what means and with deployment of what resources recalcitrant smokers would be recruited, and how and by what guidelines it would be implemented. Therefore, further RCTs may be technically desirable, for example to determine if it is justified to generalise to UK smokers the results already obtained elsewhere, and to find out whether smokers who leak from abrupt quitting to CDTQ, because of the latter's availability, retain a higher quit rate than the recalcitrant smoker who will only attempt CDTQ. However, such refinement in precision of findings is unlikely to result in better delivery of smoking cessation interventions in the UK. Research regarding the best ways of implementing a CDTQ strategy and integrating this with abrupt quit options in the context of all UK smoking services therefore can be regarded as being of higher priority. Questions that could usefully be addressed in such research include:

- What should be the relationship between 'abrupt quitting services' and CDTQ services?
- Should the same teams provide both, and what personnel should constitute teams?
- Is counselling an essential feature and, if so, of what should it consist?

Chapter 8

Conclusions

RCT evidence from NRT-supported smoking reduction studies indicates that NRT is an effective intervention relative to placebo in achieving sustained smoking abstinence for smokers who declare unwillingness or inability to attempt an abrupt quit. The success rate in this population was approximately 6.5% for 6 months and approximately 5.3% for 12 months of sustained abstinence in the treatment arm of trials and approximately 3.3% and 2.6% in the placebo arm. These rates are considerably less than those documented for an abrupt quit NRT regime in smokers willing to attempt an abrupt quit with NRT (success approximately 16% for 12 months of sustained abstinence in the NRT arm and 10% in the placebo arm of trials). A 'counselling' mode of delivery would probably be required for an NRT-supported reduction strategy to generate a 6.5% 6 months sustained abstinence success rate amongst recalcitrant smokers in a real-world setting.

Decision analytic modelling based on reasonable assumptions about costs, benefits and success rates suggests that compared with no quit attempt, CDTQ delivers low ICERs within margins generally considered cost-effective. Compared with abrupt quitting, CDTQ is less effective and more expensive but may largely address a different population. Provided that dilution from abrupt quitting forms a small proportion of CDTQ attempts, CDTQ still delivers ICERs within the range of those generally considered cost-effective. In an alternative analysis in which smokers who switch from an abrupt quit to CDTQ retain the success rate of abrupt quitters, then all forms of CDTQ appear cost-effective.

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Contribution of authors

Dechao Wang (Systematic Reviewer) applied the inclusion and exclusion criteria, extracted data, appraised studies, conducted meta-analyses and contributed to writing the background and effectiveness sections. Martin Connock (Systematic Reviewer) applied the inclusion and exclusion criteria, extracted data, appraised studies, conducted meta-analyses and contributed to writing the clinical effectiveness sections. Anne Fry-Smith (Information Specialist) carried out the searches and contributed to the drafting of the report. Pelham Barton (Mathematical Modeller) constructed the decision analytical model and wrote the economics section of the report. Paul Aveyard (NIH Research Career Scientist) provided expert clinical advice and contributed to editing the report. David Moore (Senior Research Analyst) supervised the project and commented on all sections and edited the final report.

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Appendix 1

Literature search strategies

Search strategy – systematic reviews

Cochrane Library

- Cochrane Reviews
- Database of Abstracts of Reviews of Effectiveness (DARE)
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Health Technology Assessment database.

ARIF Database

- An in-house database of reviews compiled by scanning current journals and appropriate Internet sites. Many reviews produced by the organisations listed below are included.

NHSCRD (Internet access)

- DARE
- Health Technology Assessment Database
- Completed and ongoing CRD reviews.

Health Technology Assessments and evidence-based guidelines (Internet access)

- NICE appraisals and work plans for TARs, Interventional Procedures and Guidelines programmes (NCCHTA work pages: www.ncchta.org/nice/)
- Office of Technology Assessment
- NHS Coordinating Centre for Health Technology Assessments
- Canadian Coordinating Office for Health Technology Assessment
- New Zealand Health Technology Assessment
- Wessex STEER Reports
- Agency for Healthcare Research and Quality (AHRQ)
- National Horizon Scanning Centre
- SIGN (Scottish Intercollegiate Guidelines Network).

Clinical Evidence

Bandolier

TRIP Database

Bibliographic databases

- MEDLINE – systematic reviews
- EMBASE – systematic reviews
- Other specialist databases.

Contacts

- Cochrane Collaboration (via Cochrane Library)
- Regional experts, especially Pharmacy Prescribing Unit, Keele University (&MTRAC) and West Midlands Drug Information Service (www.ukmicentral.nhs.uk) for any enquiry involving drug products.

Search strategies – clinical effectiveness

Cochrane Library (Wiley) 2006 Issue 2

#1 (gradual or gradually or reduce or reduction or reduces or reducing or decline or declines), from 1992 to 2006
81377
#2 cut* next down, from 1992 to 2006
54
#3 (quit or quits or quitting or stop or stops or stopping or cease or ceases), from 1992 to 2006
5563
#4 (smoking or smokers or smoker or tobacco or nicotine or cigarette*), from 1992 to 2006
7692
#5 MeSH descriptor Smoking, this term only
3183
#6 MeSH descriptor Nicotine, this term only
891
#7 MeSH descriptor Tobacco, this term only
84
#8 (#4 OR #5 OR #6 OR #7), from 1992 to 2006
7692
#9 MeSH descriptor Smoking Cessation, this term only
1312
#10 MeSH descriptor Tobacco Use Cessation, this term only
21
#11 nrt or nicorette or niquitin or nicotinell, from 1992 to 2006
124
#12 nicotine next replacement, from 1992 to 2006
326
#13 (nicotine next (gum* or inhaled or inhaler or inhalers or inhalator*)), from 1992 to 2006
227

#14 (#1 OR #2 OR #3), from 1992 to 2006
84262
#15 (#9 OR #10), from 1992 to 2006
1308
#16 (#11 OR #12 OR #13), from 1992 to 2006
508
#17 (#14 AND #8 AND #16), from 1992 to 2006
309
#18 (#15 AND #16), from 1992 to 2006
288
#19 (#17 OR #18), from 1992 to 2006
380

Source – Ovid MEDLINE 1966 to July Week 1 2006

1 (gradual or gradually or reduce or reduction or reducing or reduces or decline or declines or cut$ down).mp. (911281)
2 (quit or quits or quitting or stop or stops or stopping or cease or ceases).ti,ab. (41337)
3 (smoking or smokers or smoker or tobacco or nicotine or cigarette$).mp. (158376)
4 (smoking or nicotine or tobacco).sh. (101404)
5 (smoking cessation or "tobacco use cessation").mp. (12326)
6 (nrt or nicotine replacement or nicorette or niquitin or nicotinell).mp. (1194)
7 (nicotine adj1 (gum$ or inhaled or inhaler or inhalers or inhalator$)).mp. (507)
8 1 or 2 (946639)
9 3 or 4 (158376)
10 6 or 7 (1588)
11 8 and 9 and 10 (760)
12 5 and 10 (1015)
13 11 or 12 (1133)
14 limit 13 to (humans and yr="1992 - 2006") (993)

Source – Ovid MEDLINE In-Process, Other Non-Indexed Citations July 12, 2006

1 (gradual or gradually or reduce or reduction or reducing or reduces or decline or declines or cut$ down).mp. (29174)
2 (quit or quits or quitting or stop or stops or stopping or cease or ceases).ti,ab. (1402)
3 (smoking or smokers or smoker or tobacco or nicotine or cigarrette$).mp. (3490)
4 (smoking or nicotine or tobacco).mp. (3261)
5 smoking cessation.mp. (281)
6 (nrt or nicotine replacement or nicorette or niquitin or nicotinell).mp. (53)
7 (nicotine adj1 (gum$ or inhaled or inhaler or inhalers or inhalator$)).mp. (14)
8 or/1-2 (30364)
9 or/3-4 (3490)
10 or/6-7 (63)
11 8 and 9 and 10 (31)
12 5 and 10 (38)
13 11 or 12 (44)

Source – EMBASE (Ovid) 1988 to 2006 Week 27

1 (gradual or gradually or reduce or reduction or reducing or reduces or decline or declines or cut$ down).mp. (672198)
2 (quit or quits or quitting or stop or stops or stopping or cease or ceases).ti,ab. (29006)
3 (smoking or smokers or smoker or tobacco or nicotine or cigarette$).mp. (108591)
4 (smoking or nicotine or tobacco).sh. (55362)
5 (smoking cessation or "tobacco use cessation").mp. (13294)
6 (nrt or nicotine replacement or nicorette or niquitin or nicotinell).mp. (1879)
7 (nicotine adj1 (gum$ or inhaled or inhaler or inhalers or inhalator$)).mp. (1178)
8 1 or 2 (696456)
9 3 or 4 (108591)
10 6 or 7 (2426)
11 8 and 9 and 10 (981)
12 5 and 10 (1704)
13 11 or 12 (1796)
14 limit 13 to (humans and yr="1992 - 2006") (1648)

Source CINAHL – Cumulative Index to Nursing, Allied Health Literature (Ovid) 1982 to July Week 1 2006

1 (gradual or gradually or reduce or reduction or reducing or reduces or decline or declines or cut$ down).mp. (49746)
2 (quit or quits or quitting or stop or stops or stopping or cease or ceases).ti,ab. (5259)
3 (smoking or smokers or smoker or tobacco or nicotine or cigarette$).mp. (17613)
4 (smoking or nicotine or tobacco).sh. (10576)
5 smoking cessation.mp. (4474)
6 (nrt or nicotine replacement or nicorette or niquitin or nicotinell).mp. (575)
7 (nicotine adj1 (gum$ or inhaled or inhaler or inhalers or inhalator$)).mp. (103)
8 nicotine replacement therapy/ (443)
9 or/1-2 (54415)
10 or/3-4 (17613)
11 or/6-8 (608)
12 9 and 10 and 11 (297)
13 5 and 11 (508)
14 12 or 13 (528)
15 limit 14 to yr="1992 - 2006" (526)

Source – PsycINFO (Ovid) 1985 to July Week 1 2006

1 (gradual or gradually or reduce or reduction or reducing or reduces or decline or declines or cut$ down).mp. (78218)

2 (quit or quits or quitting or stop or stops or stopping or cease or ceases).ti,ab. (7703)
3 (smoking or smokers or smoker or tobacco or nicotine or cigarette$).mp. (19438)
4 tobacco smoking/ (9651)
5 nicotine/ (3630)
6 smoking cessation.mp. (4551)
7 (nrt or nicotine replacement or nicorette or niquitin or nicotinell).mp. (472)
8 (nicotine adj1 (gum$ or inhaled or inhaler$ or inhalator$)).mp. (258)
9 or/1-2 (84876)
10 or/3-5 (19438)
11 or/7-8 (677)
12 9 and 10 and 11 (349)
13 6 and 11 (515)
14 12 or 13 (556)
15 limit 14 to (human and yr="1992 - 2006") (474)

Source – Science Citation Index (Web of Science) 1992 to July 2006

#1 TS=((gradual or gradually or reduce or reduction or reducing or reduces or decline or declines or cut* down))
#2 TS=((quit or quits or quitting or stop or stops or stopping or cease or ceases))
#3 TS=((smoking or smokers or smoker or tobacco or nicotine or cigarette*))
#4 TS=((nrt or nicotine replacement or nicorette or niquitin or nicotinell))
#5 TS=((nicotine) SAME (gum* or inhaled or inhaler or inhalers or inhalator*))
#6 #2 OR #1
#7 #5 OR #4
#8 TS=((smoking SAME cessation))
#9 #7 AND #6 AND #3
#10 #8 AND #7
#11 #10 OR #9

Search strategies – economic evaluations

Existing decision analytical models

Source – Ovid MEDLINE 1966 to July Week 2 2006

1 (nrt or nicotine replacement or nicorette or niquitin or nicotinell).mp. (1197)
2 (nicotine adj1 (gum$ or inhaled or inhaler or inhalers or inhalator$)).mp. (507)
3 1 or 2 (1591)
4 decision support techniques/ (5756)
5 markov.mp. (4983)
6 exp models economic/ (4836)
7 decision analysis.mp. (2217)
8 cost benefit analysis/ (38877)
9 economic model$.mp. (667)
10 monte carlo method$.mp. (9184)
11 monte carlo.mp. (11620)
12 exp decision theory/ (6283)
13 (decision$ adj2 (tree$ or analy$ or model$)).mp. (10473)
14 or/4-13 (68756)
15 3 and 14 (42)

Source – EMBASE 1980 to 2006 Week 28

1 (nrt or nicotine replacement or nicorette or niquitin or nicotinell).mp. (1968)
2 (nicotine adj1 (gum$ or inhaled or inhaler or inhalers or inhalator$)).mp. (1286)
3 (nicotine gum or nicotine replacement therapy).sh. (1757)
4 or/1-3 (2569)
5 decision support techniques/ (770)
6 markov.mp. (3187)
7 exp models economic/ (14443)
8 decision analysis.mp. (2026)
9 cost benefit analysis/ (23784)
10 economic model$.mp. (598)
11 monte carlo.mp. (9987)
12 exp decision theory/ (851)
13 (decision$ adj2 (tree$ or analys$ or model$)).mp. (6938)
14 or/5-13 (56659)
15 4 and 14 (38)

Economic evaluation

Source – Ovid MEDLINE 1966 to July Week 2 2006

1 (nrt or nicotine replacement or nicorette or niquitin or nicotinell).mp. (1197)
2 (nicotine adj1 (gum$ or inhaled or inhaler or inhalers or inhalator$)).mp. (507)
3 1 or 2 (1591)
4 economics/ (24316)
5 exp "costs and cost analysis"/ (125207)
6 cost of illness/ (8289)
7 exp health care costs/ (26914)
8 economic value of life/ (4752)
9 exp economics medical/ (9998)
10 exp economics hospital/ (14100)
11 economics pharmaceutical/ (1658)
12 exp "fees and charges"/ (22426)
13 (econom$ or cost or costs or costly or costing or price or pricing or pharmacoeconomic$).tw. (230986)
14 (expenditure$ not energy).tw. (9822)
15 (value adj1 money).tw. (11)
16 budget$.tw. (10089)
17 or/4-16 (339834)
18 3 and 17 (133)

Source – EMBASE 1980 to 2006 Week 28

1 (nrt or nicotine replacement or nicorette or niquitin or nicotinell).mp. (1968)

2 (nicotine adj1 (gum$ or inhaled or inhaler or inhalers or inhalator$)).mp. (1286)
3 (nicotine gum or nicotine replacement therapy).sh. (1757)
4 or/1-3 (2569)
5 cost benefit analysis/ (23784)
6 cost effectiveness analysis/ (44034)
7 cost minimization analysis/ (1000)
8 cost utility analysis/ (1669)
9 economic evaluation/ (3166)
10 (cost or costs or costed or costly or costing).tw. (135178)
11 (economic$ or pharmacoeconomic$ or price$ or pricing).tw. (64706)
12 (technology adj assessment$).tw. (1294)
13 or/5-12 (205698)
14 4 and 13 (228)

Source – HEED July 2006

A series of searches were carried out using the following terms:

- NRT OR nicotine replacement OR nicorette OR niquitin OR nicotinell
- Nicotine AND gum* OR inhaled AND nicotine OR nicotine AND inhaler* OR nicotine AND inhalers OR nicotine AND inhalator*

Source – Cochrane Library (Wiley) (NHS EED and DARE) 2006 Issue 2

#1 nrt or nicorette or niquitin or nicotinell,
#2 nicotine next replacement
#3 (nicotine next (gum* or inhaled or inhaler or inhalers or inhalator*))
#4 #1 OR #2 OR #3

Appendix 2

Results reported in included studies

TABLE 46 *Results presented in published or unpublished reports of studies*[a]

Study	Intervention Treatment duration	Outcome measure	Evaluation time (months)	Unit	Effect size	*p*-Value or 95%CI	Direction of effect	Significant (at $p < 0.05$)
Batra, 2005[43] 980-CHC-1013-028[44]	Nicotine gum (4 mg) 12 months	Sustained reduction (at least 50%) from week 6, self-reported, verified by CO level	10 weeks	%	20.1 vs 11.1 gum vs placebo	$p = 0.021$	Favours gum	Yes
			4	%	15.8 vs 6.7 gum vs placebo	$p = 0.008$	Favours gum	Yes
			13	%	8.2 vs 2.8 gum vs placebo	$p = 0.036$	Favours gum	Yes
		One-day point prevalence abstinence, self-reported, verified by CO level	10 weeks	%	4.9 vs 0.6 gum vs placebo	$p = 0.02$	Favours gum	Yes
			4	%	6.5 vs 2.2	$p = 0.071$	Favours gum	Yes
			13	%	12 vs 4.5 gum vs placebo	$p = 0.012$	Favours gum	Yes
		Seven-day point prevalence abstinence, self-reported, CO level	10 weeks	%	4.4 vs 0.6 gum vs placebo	$p = 0.037$	Favours gum	Yes
			4	%	6.5 vs 1.1	$p = 0.011$	Favours gum	Yes
			13	%	10.9 vs 3.9 gum vs placebo	$p = 0.015$	Favours gum	Yes
Etter, 2004[45]	Nicotine patch (contains 25 mg and delivers 15 mg of nicotine over 16 hours), or gum (contains 4 mg and delivers 2 mg of nicotine), or inhalator (a plug contains 10 mg and delivers 5 mg of nicotine). 6 months, participants who quit smoking continued to receive nicotine or placebo to prevent relapse 6 months	Mean cigarette reduction (ITT)	3	Cigarettes per day (CPD)	9.9 vs 7.5 vs 3.7 patch/gum/inhalator vs placebo vs control	$p < 0.002$ for all pairwise comparisons	Favours Patch/gum/inhalator and placebo	Yes
			6	Cigarettes per day (CPD)	10.9 vs 8.7 vs 4.9 patch/gum/inhalator vs placebo vs control	$p < 0.02$ for all pairwise comparisons	Favours and placebo	Yes
			26	Cigarettes per day (CPD)	9.8 vs 7.7 patch/gum/inhalator vs placebo	$p = 0.03$	Favours patch/gum/inhalator	Yes
			26	Cigarettes per day (CPD)	9.8 vs 7.7 patch/gum/inhalator vs control	$p = 0.02$	Favours patch/gum/inhalator	Yes

continued

TABLE 46 *Results presented in published or unpublished reports of studies[a] (cont'd)*

Study	Intervention Treatment duration	Outcome measure	Evaluation time (months)	Unit	Effect size	*p*-Value or 95%CI	Direction of effect	Significant (at $p < 0.05$)
		Point prevalence reduction (at least 50%)	3	%	30.6 vs 20.4 patch/gum/inhalator vs placebo	$p = 0.007$	Favours patch/gum/inhalator	Yes
			3	%	30.6 vs 8.0 patch/gum/inhalator vs control	$p < 0.001$	Favours patch/gum/inhalator	Yes
			3	%	20.4 vs 8.0 placebo vs control	$p < 0.001$	Favours placebo	Yes
			6	%	35.1 vs 27.9 patch/gum/inhalator vs placebo	$p = 0.073$	Favours patch/gum/inhalator	No
			6	%	35.1 vs 13.6 patch/gum/inhalator vs control	$p < 0.001$	Favours patch/gum/inhalator	Yes
			6	%	27.9 vs 13.6 placebo vs control	$p < 0.001$	Favours placebo	Yes
			26	%	31.3 vs 21.9 patch/gum/inhalator vs placebo	$p = 0.014$	Favours patch/gum/inhalator	Yes
			26	%	31.3 vs 24.0 patch/gum/inhalator vs control	$p < 0.052$	Favours patch/gum/inhalator	No
		Seven-day point prevalence abstinence	3	%	3.4 vs 0.7 patch/gum/inhalator vs placebo	$p = 0.03$	Favours patch/gum/inhalator	Yes
			6	%	5.3 vs 2.2 patch/gum/inhalator vs placebo	$p = 0.063$	Favours patch/gum/inhalator	Yes
			6	%	5.3 vs 4.1 patch/gum/inhalator vs control	$p = 0.48$	Favours patch/gum/inhalator	No
			6	%	2.2 vs 4.1 placebo vs control	$p = 0.19$	Favours control	No

continued

TABLE 46 *Results presented in published or unpublished reports of studies[a] (cont'd)*

Study	Intervention Treatment duration	Outcome measure	Evaluation time (months)	Unit	Effect size	*p*-Value or 95%CI	Direction of effect	Significant (at $p < 0.05$)
			26	%	12.1 vs10.8 patch/gum/inhalator vs placebo	$p = 0.64$	Favours patch/gum/inhalator	No
			26	%	12.1 vs 11.6 patch/gum/inhalator vs control	$p = 0.84$	Favours patch/gum/inhalator	No
			26	%	10.8 vs 11.6 placebo vs control	$p = 0.75$	Favours control	No
		Four-week point prevalence abstinence	6	%	4.2 vs 1.9 patch/gum/inhalator vs placebo	$p = 0.12$	Favours patch/gum/inhalator	No
			6	%	4.2 vs 3.9 patch/gum/inhalator vs control	$p = 0.85$	Favours patch/gum/inhalator	No
			6	%	1.9 vs 3.9 placebo vs control	$p = 0.14$	Favours control	No
			26	%	11.7 vs 9.3 patch/gum/inhalator vs placebo	$p = 0.37$	Favours patch/gum/inhalator	No
			26	%	11.7 vs 10.0 patch/gum/inhalator vs control	$p = 0.50$	Favours patch/gum/inhalator	No
			26	%	9.3 vs 10.0 placebo vs control	$p = 0.76$	Favours control	No
Wennike, 2003[41] 98-NNCG-014[42]	Nicotine gum (2 or 4 mg), 12 months	Sustained reduction from week 6, self-reported, verified by CO level	4	%	13.7 vs 4.9 gum vs placebo	$p = 0.002$	Favours gum	Yes
			6	%	10.7 vs 3.4 gum vs placebo	$p = 0.004$	Favours gum	Yes
			9	%	10.2 vs 2.9 gum vs placebo	$p = 0.003$	Favours gum	Yes
			12	%	8.8 vs 1.5 gum vs placebo	$p < 0.001$	Favours gum	Yes

continued

TABLE 46 *Results presented in published or unpublished reports of studies[a] (cont'd)*

Study	Intervention Treatment duration	Outcome measure	Evaluation time (months)	Unit	Effect size	*p*-Value or 95%CI	Direction of effect	Significant (at $p < 0.05$)
			24	%	6.3 vs 0.5 gum vs placebo	$p < 0.001$	Favours gum	Yes
		Point prevalence reduction (at least 50%), self-reported, verified by CO level	4	%	24.4 vs10.2 gum vs placebo	$p < 0.001$	Favours gum	Yes
			6	%	20.5 vs 9.2 gum vs placebo	$p = 0.001$	Favours gum	Yes
			9	%	20.5 vs 11.7 gum vs placebo	$p = 0.016$	Favours gum	Yes
			12	%	21.0 vs13.1 gum vs placebo	$p = 0.036$	Favours gum	Yes
			24	%	14.6 vs 9.7 gum vs placebo	$p = 0.134$	Favours gum	No
		Sustained abstinence	4	%	3.9 vs 0.0 gum vs placebo	$p = 0.004$	Favours gum	Yes
			6	%	3.9 vs 0.0 gum vs placebo	$p = 0.004$	Favours gum	Yes
			9	%	2.9 vs 0.0 gum vs placebo	$p = 0.015$	Favours gum	Yes
			12	%	2.9 vs 0.0 gum vs placebo	$p = 0.015$	Favours gum	Yes
			24	%	2.9 vs 0.0 gum vs placebo	$p = 0.015$	Favours gum	Yes
		Point prevalence abstinence	4	%	6.3 vs0.5 gum vs placebo	$p < 0.001$	Favours gum	Yes
			6	%	4.4 vs 1.5 gum vs placebo	$p = 0.087$	Favours gum	No
			9	%	9.3 vs 3.4 gum vs placebo	$p = 0.016$	Favours gum	Yes
			12	%	11.2 vs3.9 gum vs placebo	$p = 0.005$	Favours gum	Yes
			24	%	9.3 vs 3.4 gum vs placebo	$p = 0.015$	Favours gum	Yes

continued

TABLE 46 *Results presented in published or unpublished reports of studies[a] (cont'd)*

Study	Intervention Treatment duration	Outcome measure	Evaluation time (months)	Unit	Effect size	*p*-Value or 95%CI	Direction of effect	Significant (at $p < 0.05$)
Bolliger, 2000[39] 96-NNIN-016[40]	Nicotine inhalator (10 mg nicotine and 1 mg menthol), 18 months	Sustained reduction (at least 50%) from week 6, verified by CO level	4	%	26.0 vs 9.0 inhalator vs placebo	$p < 0.001$	Favours inhalator	Yes
			6	%	20.0 vs 5.0 inhalator vs placebo	$p < 0.001$	Favours inhalator	Yes
			12	%	13.0 vs 4.0 inhalator vs placebo	$p = 0.002$	Favours inhalator	Yes
			18	%	9.5 vs 3.5 inhalator vs placebo	$p = 0.002$	Favours inhalator	Yes
			24	%	9.5 vs 3.0 inhalator vs placebo	$p = 0.024$	Favours inhalator	Yes
		Point prevalence reduction (at least 50%), % from week 6, verified by CO level	4	%	41.5 vs 22.0 inhalator vs placebo	$p < 0.001$	Favours inhalator	Yes
			6	%	31.5 vs 23.0 inhalator vs placebo	$p = 0.072$	Favours inhalator	No
			12	%	29.5 vs 21.5 inhalator vs placebo	$p = 0.085$	Favours inhalator	No
			18	%	24.5 vs 16.0 inhalator vs placebo	$p = 0.046$	Favours inhalators	Yes
			24	%	27.5 vs 23 inhalator vs placebo	$p = 0.357$	Favours inhalator	No
		Sustained abstinence from week 6, verified by CO level	4	%	2.0 vs 0.5 inhalator vs placebo	$p = 0.372$	Favours inhalator	No
			6	%	2.0 vs 0.5 inhalator vs placebo	$p = 0.372$	Favours inhalator	No
			12	%	2.0 vs 0.5 inhalator vs placebo	$p = 0.372$	Favours inhalator	No
			18	%	2.0 vs 0.5 inhalator vs placebo	$p = 0.372$	Favours inhalator	No
			24	%	2.0 vs 0.5 inhalator vs placebo	$p = 0.372$	Favours inhalator	No

continued

TABLE 46 *Results presented in published or unpublished reports of studies[a] (cont'd)*

Study	Intervention Treatment duration	Outcome measure	Evaluation time (months)	Unit	Effect size	*p*-Value or 95%CI	Direction of effect	Significant (at $p < 0.05$)
		Point prevalence abstinence from week 6, verified by CO level	4	%	6.5 vs 2.0 inhalator vs placebo	$p = 0.044$	Favours inhalator	Yes
			6	%	5.5 vs 5.5 inhalator vs placebo	$p = 1.0$		No
			12	%	8.0 vs 6.0 inhalator vs placebo	$p = 0.557$	Favours inhalator	No
			18	%	9.0 vs 6.5 Inhalator vs placebo	$p = 0.455$	Favours inhalator	No
			24	%	10.5 vs 8.5 Inhalator vs placebo	$p = 0.609$	Favours inhalator	No
Rennard, unpublished 98-NNIN-027[36]	Nicotine inhalator (10 mg), 12 months	Sustained reduction	4	%	18.14 vs 8.41 inhalator vs placebo	$p = 0.0041$	Favours inhalator	Yes
			6	%	12.56 vs 3.27 inhalator vs placebo	$p = 0.0005$	Favours inhalator	Yes
			9	%	8.84 vs 1.87 inhalator vs placebo	$p = 0.002$	Favours inhalator	Yes
			12	%	7.91 vs 1.87 inhalator vs placebo	$p = 0.0059$	Favours inhalator	Yes
			15	%	6.98 vs 1.87 inhalator vs placebo	$p = 0.0167$	Favours inhalator	Yes
		Point prevalence reduction	4	%	33.02 vs 21.03 inhalator vs placebo	$p = 0.0065$	Favours inhalator	Yes
			6	%	26.05 vs 14.95 inhalator vs placebo	$p = 0.0058$	Favours inhalator	Yes
			9	%	19.53 vs 9.35 inhalator vs placebo	$p = 0.0037$	Favours inhalator	Yes
			12	%	21.86 vs 11.68 inhalator vs placebo	$p = 0.0064$	Favours inhalator	Yes
			15	%	19.07 vs 13.08 inhalator vs placebo	$p = 0.1144$	Favours inhalator	No

continued

TABLE 46 *Results presented in published or unpublished reports of studies[a] (cont'd)*

Study	Intervention Treatment duration	Outcome measure	Evaluation time (months)	Unit	Effect size	*p*-Value or 95%CI	Direction of effect	Significant (at $p < 0.05$)
		Sustained abstinence, verified by CO level	4	%	1.86 vs 0 inhalator vs placebo	$p = 0.1233$	Favours inhalator	No
			6	%	1.4 vs 0 inhalator vs placebo	$p = 0.2483$	Favours inhalator	No
			9	%	1.4 vs 0 inhalator vs placebo	$p = 0.2483$	Favours inhalator	No
			12	%	0.93 vs .0 inhalator vs placebo	$p = 0.4988$	Favours inhalator	No
			15	%	0.93 vs 0 inhalator vs placebo	$p = 0.4988$	Favours inhalator	No
		Point prevalence abstinence, verified by CO level	4	%	6.05 vs1.87 inhalator vs placebo	$p = 0.0447$	Favours inhalator	Yes
			6	%	7.91 vs 1.87 inhalator vs placebo	$p = 0.0059$	Favours inhalator	Yes
			9	%	7.44 vs1.87 inhalator vs placebo	$p = 0.01$	Favours inhalator	Yes
			12	%	7.91 vs 2.34 inhalator vs placebo	$p = 0.0143$	Favours inhalator	Yes
			15	%	7.91 vs 1.4 inhalator vs placebo	$p = 0.0021$	Favours inhalator	Yes
Wood-Baker, unpublished 98-NNCG-01738	Nicotine gum (2 or 4 mg), 12 months	Sustained reduction (at least 50%) from week 6, verified by CO level	4	%	6.0 vs 6.0 gum vs placebo			
			6	%	4.6 vs 2.8 gum vs placebo	$p = 0.446$	Favours gum	No
			9	%	3.7 vs 2.3 gum vs placebo	$p = 0.575$	Favours gum	No
			12	%	1.4 vs 0.9 gum vs placebo	$p = 1.0$	Favours gum	No
			15	%	1.4 vs 0.9 gum vs placebo	$p = 1.0$	Favours gum	No

continued

TABLE 46 *Results presented in published or unpublished reports of studies[a] (cont'd)*

Study	Intervention Treatment duration	Outcome measure	Evaluation time (months)	Unit	Effect size	*p*-Value or 95%CI	Direction of effect	Significant (at $p < 0.05$)
		Sustained abstinence from week 6, verified by CO level	4	%	0.9 vs 0.5 gum vs placebo	$p = 1.0$	Favours gum	No
			6	%	0.9 vs 0.5 gum vs placebo	$p = 1.0$	Favours gum	No
			9	%	0.9 vs 0.5 gum vs placebo	$p = 1.0$	Favours gum	No
			12	%	0.5 vs 0.5 gum vs placebo			
			15	%	0.5 vs 0.5 gum vs placebo			
		Point prevalence reduction (at least 50%)	4	%	16.1 vs 15.1 gum vs placebo	$p = 0.90$	Favours gum	No
			6	%	15.1 vs 9.2 gum vs placebo	$p = 0.078$	Favours gum	No
			9	%	12.8 vs 12.8 gum vs placebo	$p = 1.0$		No
			12	%	11.0 vs 12.8 gum vs placebo	$p = 0.658$	Favours placebo	No
			15	%	7.8 vs 12.8 gum vs placebo	$p = 0.115$	Favours placebo	No
		Point prevalence abstinence	4	%	3.2 vs 1.4 gum vs placebo	$p = 0.34$	Favours gum	No
			6	%	6.4 vs 2.3 gum vs placebo	$p = 0.058$	Favours gum	No
			9	%	4.1 vs 1.4 gum vs placebo	$p = 0.14$	Favours gum	No
			12	%	4.6 vs 3.2 gum vs placebo	$p = 0.622$	Favours gum	No
			15	%	3.7 vs 4.6 gum vs placebo	$p = 0.811$	Favours placebo	No

continued

TABLE 46 *Results presented in published or unpublished reports of studies[a] (cont'd)*

Study	Intervention Treatment duration	Outcome measure	Evaluation time (months)	Unit	Effect size	*p*-Value or 95%CI	Direction of effect	Significant (at $p < 0.05$)
Haustein, unpublished 980-CHC-9021-0013[37]	Nicotine gum (4 mg), 9 months	Sustained reduction (at least 50%) from week 6, verified by CO level	4	%	10.3 vs 2.1 gum vs placebo	$p = 0.018$	Favours gum	Yes
			6	No. of subjects	7 vs 0	$p = 0.007$	Favours gum	Yes
				No. of subjects	6 vs 0	$p = 0.013$	Favours gum	Yes
			12	No. of subjects	6 vs 0	$p = 0.013$	Favours gum	Yes
		Sustained abstinence from week 2, verified by CO level	4	%	3.1 vs 2.1 gum vs placebo		Favours gum	
		Point prevalence reduction (at least 50%)	4	%	20.6 vs 11.5 gum vs placebo	$p = 0.083$	Favours gum	No
		Point prevalence abstinence	4	No. of subjects	Higher vs lower gum vs placebo		Favours gum	
			12	No. of subjects	Higher vs lower gum vs placebo		Favours gum	

[a] The trial conducted by Rennard and colleagues was published in September 2006 and is not included in this table. Detailed results available in trial sponsor's unpublished reports have been used in this systematic review and are included in subsequent appendices. Data from unpublished study reports where available. Batra = study 980-CHC-1013-028,[44] Bolliger = study 96-NNIN-016,[40] Haustein = study 980-CHC-9021-0013,[37] Rennard = study 98-NNIN-027,[36] Wennike = study 98-NNCG-014,[42] Wood-Baker = study 98-NNCG-017.[38]

Appendix 3

Sustained cessation of smoking

TABLE 47 *Numbers continuing to stop smoking by month of study (from 6 weeks)*

NRT	Study[a]	Active arm		Placebo arm		Month of study
		Stopped	Continued	Stopped	Continued	
Gum	Batra	5	179	0	180	1.5
Gum	Batra	5	179	0	180	4
Gum	Batra	5	179	0	180	6
Gum	Batra	3	181	0	180	10
Gum	Batra	2	182	0	180	12
Gum	Batra	2	182	0	180	13
Inhalator	Bolliger	4	196	1	199	4
Inhalator	Bolliger	4	196	1	199	6
Inhalator	Bolliger	4	196	1	199	12
Inhalator	Bolliger	4	196	1	199	18
Inhalator	Bolliger	4	196	1	199	24
Gum	Haustein	4	93	2	94	2.5
Gum	Haustein	3	94	2	94	4
Gum	Haustein	2	95	0	96	6
Gum	Haustein	2	95	0	96	9
Gum	Haustein	2	95	0	96	12
Inhalator	Rennard	4	211	0	214	4
Inhalator	Rennard	3	212	0	214	6
Inhalator	Rennard	3	212	0	214	9
Inhalator	Rennard	2	213	0	214	12
Inhalator	Rennard	2	213	0	214	15
Gum	Wood-Baker	2	216	1	217	4
Gum	Wood-Baker	2	216	1	217	6
Gum	Wood-Baker	2	216	1	217	9
Gum	Wood-Baker	1	217	1	217	12
Gum	Wood-Baker	1	217	1	217	15
Gum	Wennike	8	197	0	206	4
Gum	Wennike	8	197	0	206	6
Gum	Wennike	6	199	0	206	9
Gum	Wennike	6	199	0	206	12
Gum	Wennike	6	199	0	206	24

[a] Data from unpublished study reports where available. Batra = study 980-CHC-1013-028,[44] Bolliger = study 96-NNIN-016,[40] Haustein = study 980-CHC-9021-0013,[37] Rennard = study 98-NNIN-027,[36] Wennike = study 98-NNCG-014,[42] Wood-Baker = study 98-NNCG-017.[38]

TABLE 48 *Petos odds ratio sustained smoking cessation from week 6*

Study[a]	Month	Peto's OR	LCI	UCI
Batra	1.5	7.39	1.27	43.09
Batra	4	7.39	1.27	43.09
Batra	6	7.39	1.27	43.09
Batra	10	7.31	0.76	70.72
Batra	12	7.27	0.45	116.69
Batra	13	7.27	0.45	116.69
Bolliger	4	3.36	0.58	19.57
Bolliger	6	3.36	0.58	19.57
Bolliger	12	3.36	0.58	19.57
Bolliger	18	3.36	0.58	19.57
Bolliger	24	3.36	0.58	19.57
Haustein	2.5	1.96	0.39	9.93
Haustein	4	1.49	0.25	8.75
Haustein	6	7.39	0.46	119.01
Haustein	9	7.39	0.46	119.01
Haustein	12	7.39	0.46	119.01
Rennard	4	7.46	1.04	53.32
Rennard	6	7.42	0.77	71.75
Rennard	9	7.42	0.77	71.75
Rennard	12	7.39	0.46	118.52
Rennard	15	7.39	0.46	118.52
Wood-Baker	4	1.95	0.20	18.88
Wood-Baker	6	1.95	0.20	18.88
Wood-Baker	9	1.95	0.20	18.88
Wood-Baker	12	1.00	0.06	16.04
Wood-Baker	15	1.00	0.06	16.04
Wennike	4	7.69	1.90	31.11
Wennike	5	7.69	1.90	31.11
Wennike	9	7.61	1.52	38.08
Wennike	12	7.61	1.52	38.08
Wennike	24	7.61	1.52	38.08

[a] Data from unpublished study reports where available. Batra = study 980-CHC-1013-028,[44] Bolliger = study 96-NNIN-016,[40] Haustein = study 980-CHC-9021-0013,[37] Rennard = study 98-NNIN-027,[36] Wennike = study 98-NNCG-014,[42] Wood-Baker = study 98-NNCG-017.[38]

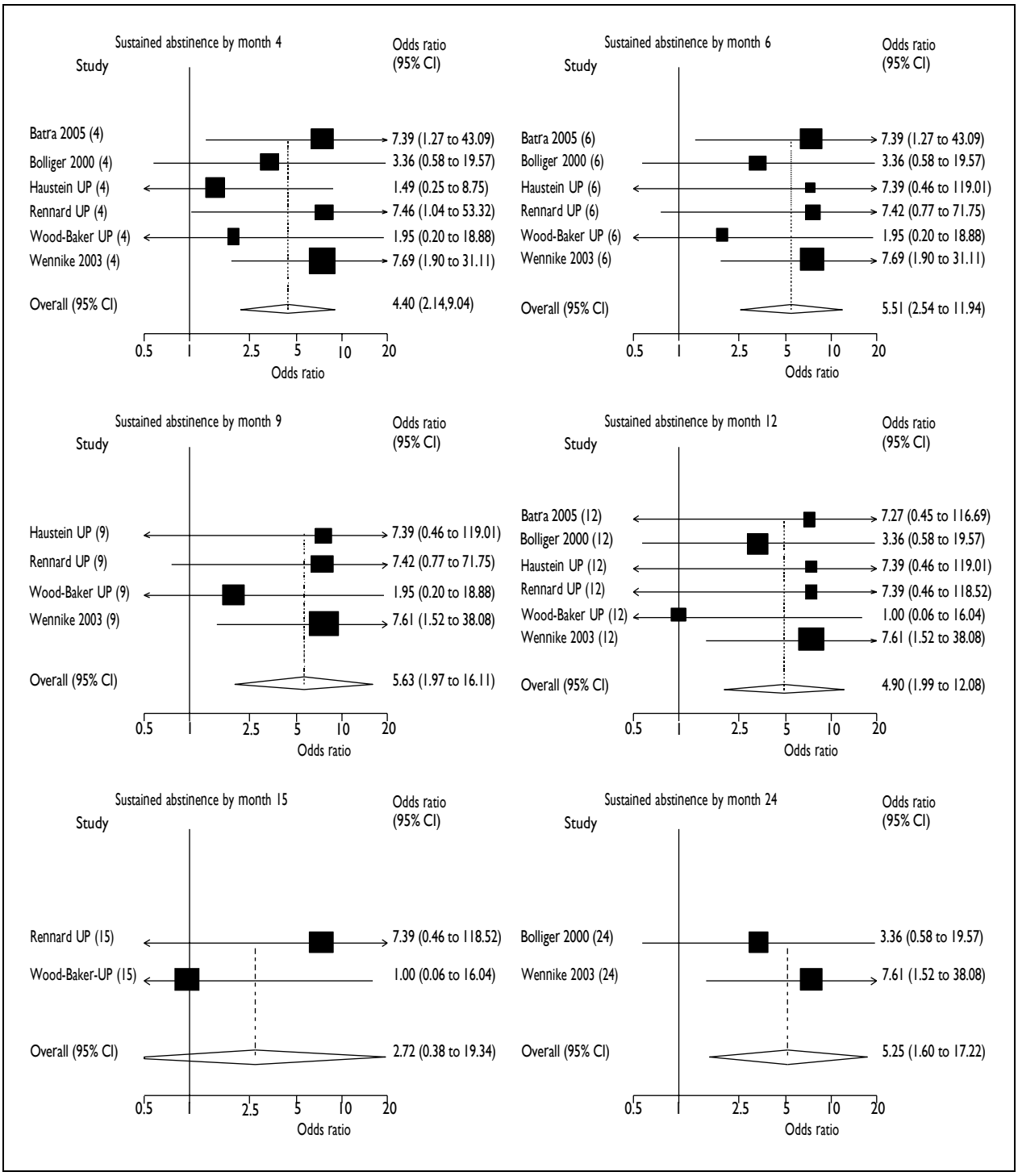

FIGURE 17 *Meta-analysis of odds ratio of sustained abstinence at different time points. Data from unpublished study reports where available. Batra = study 980-CHC-1013-028,[44] Bolliger = study 96-NNIN-016,[40] Haustein = study 980-CHC-9021-0013,[37] Rennard = study 98-NNIN-027,[36] Wennike=study 98-NNCG-014,[42] Wood-Baker = study 98-NNCG-017.[38]*

Appendix 4

Point prevalence abstinence from smoking

TABLE 49 *Number of patients stopped and not stopped smoking by month of study*

		Active arm		Placebo arm		
NRT	**Study[a]**	**Stopped**	**Not stopped**	**Stopped**	**Not stopped**	**Month**
Gum	Batra	7	177	2	178	1.5
Gum	Batra	9	175	1	179	2.5
Gum	Batra	12	172	4	176	4
Gum	Batra	16	168	3	177	6
Gum	Batra	15	169	4	176	9
Gum	Batra	16	168	7	173	12
Gum	Batra	22	162	8	172	13
Inhalator	Bolliger	13	187	4	196	4
Inhalator	Bolliger	11	189	11	189	6
Inhalator	Bolliger	16	184	12	188	12
Inhalator	Bolliger	18	182	13	187	18
Inhalator	Bolliger	21	179	17	183	24
Mixed	Etter	9	256	2	267	3
Mixed	Etter	14	251	6	263	6
Mixed	Etter	32	233	29	240	26
Gum	Haustein	7	90	1	95	2.5
Gum	Haustein	10	87	4	92	4
Gum	Haustein	10	87	3	93	6
Gum	Haustein	13	84	4	92	9
Gum	Haustein	11	86	8	88	12
Inhalator	Rennard	13	202	4	210	4
Inhalator	Rennard	17	198	4	210	6
Inhalator	Rennard	16	199	4	210	9
Inhalator	Rennard	17	198	5	209	12
Inhalator	Rennard	17	198	3	211	15
Gum	Wennike	13	192	1	205	4
Gum	Wennike	9	196	3	203	6
Gum	Wennike	19	186	7	199	9
Gum	Wennike	23	182	8	198	12
Gum	Wennike	19	186	7	199	24
Gum	Wood-Baker	14	204	5	213	6
Gum	Wood-Baker	9	209	3	215	9
Gum	Wood-Baker	10	208	7	211	12
Gum	Wood-Baker	8	210	10	208	15
Gum	Wood-Baker	7	211	3	215	4

[a] Data from unpublished study reports where available. Batra = study 980-CHC-1013-028,[44] Bolliger = study 96-NNIN-016,[40] Haustein = study 980-CHC-9021-0013,[37] Rennard = study 98-NNIN-027,[36] Wennike = study 98-NNCG-014,[42] Wood-Baker = study 98-NNCG-017,[38] and from published study of Etter, 2004.[45]

TABLE 50 *Relative risk of point prevalence of abstinence from smoking*

Study[a]	Month	RR	LCI	UCI
Batra	1.5	3.42	0.72	16.26
Haustein	2.5	6.93	0.87	55.24
Batra	2.5	8.80	1.13	68.79
Etter	3	4.57	1.00	20.94
Batra	4	2.93	0.96	8.93
Bolliger	4	3.25	1.08	9.80
Wennike	4	13.06	1.72	98.94
Wood-Baker	4	2.33	0.61	8.91
Haustein	4	2.47	0.80	7.62
Rennard	4	3.23	1.07	9.76
Wennike	6	3.01	0.83	10.98
Wood-Baker	6	2.80	1.03	7.64
Bolliger	6	1.00	0.44	2.25
Haustein	6	3.30	0.94	11.62
Rennard	6	4.23	1.45	12.37
Batra	6	5.22	1.55	17.60
Etter	6	2.37	0.92	6.07
Batra	9	3.67	1.24	10.84
Wood-Baker	9	3.00	0.82	10.93
Haustein	9	3.22	1.09	9.51
Wennike	9	2.73	1.17	6.35
Rennard	9	3.98	1.35	11.71
Rennard	12	3.38	1.27	9.01
Batra	12	2.24	0.94	5.31
Wood-Baker	12	1.43	0.55	3.68
Wennike	12	2.89	1.32	6.31
Bolliger	12	1.33	0.65	2.75
Haustein	12	1.36	0.57	3.23
Batra	13	2.69	1.23	5.88
Wood-Baker	15	0.80	0.32	1.99
Rennard	15	5.64	1.68	18.97
Bolliger	18	1.38	0.70	2.75
Bolliger	24	1.24	0.67	2.27
Wennike	24	2.73	1.17	6.35
Etter	26	1.12	0.70	1.80

[a] Data from unpublished study reports where available. Batra = study 980-CHC-1013-028,[44] Bolliger = study 96-NNIN-016,[40] Haustein = study 980-CHC-9021-0013,[37] Rennard = study 98-NNIN-027,[36] Wennike = study 98-NNCG-014,[42] Wood-Baker = study 98-NNCG-017,[38] and from published study of Etter, 2004.[45]

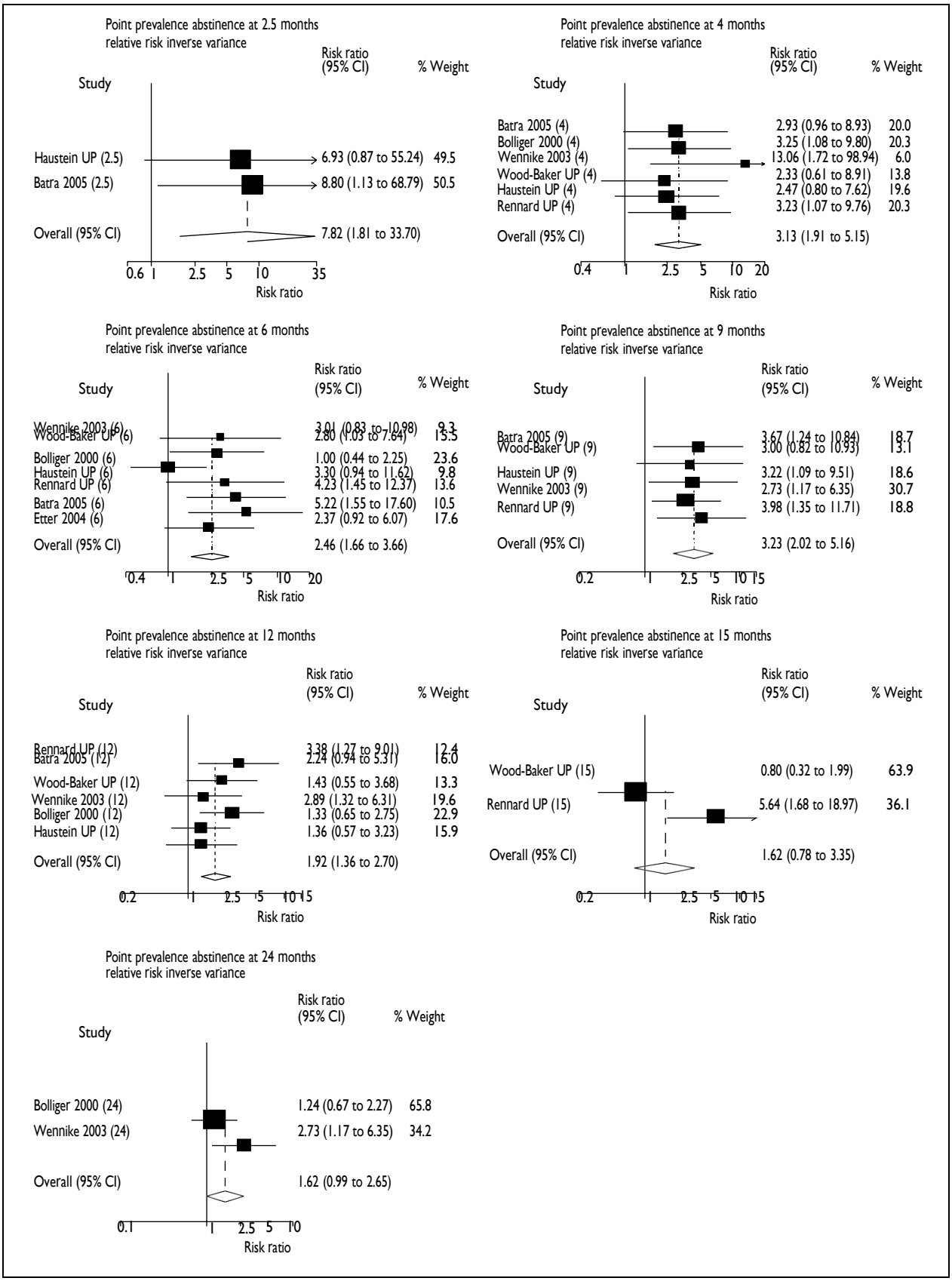

FIGURE 18 *Meta-analysis of relative risk of point prevalence of abstinence at various times of study. Data from unpublished study reports where available. Batra = study 980-CHC-1013-028,[44] Bolliger = study 96-NNIN-016,[40] Haustein = study 980-CHC-9021-0013,[37] Rennard = study 98-NNIN-027,[36] Wennike = study 98-NNCG-014,[42] Wood-Baker = study 98-NNCG-017,[38] and from published study of Etter, 2004.[45]*

Appendix 5

Point prevalence of at least 50% smoking reduction by month

TABLE 51 *Numbers of subjects reduced and not reduced smoking by 50% by month of study*

		Active arm		Placebo arm		
NRT	**Study[a]**	**Stopped**	**Not stopped**	**Stopped**	**Not stopped**	**Month**
Gum	Batra	7	177	2	178	1.5
Gum	Batra	53	131	34	146	1.5
Gum	Batra	49	135	32	148	2.5
Gum	Batra	49	135	32	148	4
Gum	Batra	51	133	20	160	6
Gum	Batra	49	135	26	154	9
Gum	Batra	52	132	34	146	12
Gum	Batra	55	129	33	147	13
Inhalator	Bolliger	83	117	44	156	4
Inhalator	Bolliger	63	137	46	154	6
Inhalator	Bolliger	59	141	43	157	12
Inhalator	Bolliger	49	151	32	168	18
Inhalator	Bolliger	55	145	46	154	24
Gum	Haustein	25	72	12	84	2.5
Gum	Haustein	20	77	11	85	4
Gum	Haustein	20	77	13	83	6
Gum	Haustein	21	76	11	85	9
Gum	Haustein	21	76	14	82	12
Inhalator	Rennard	71	144	45	169	4
Inhalator	Rennard	56	159	32	182	6
Inhalator	Rennard	42	173	20	194	9
Inhalator	Rennard	47	168	25	189	12
Inhalator	Rennard	41	174	28	186	15
Gum	Wennike	50	155	21	185	4
Gum	Wennike	42	163	19	187	6
Gum	Wennike	42	163	24	182	9
Gum	Wennike	43	162	27	179	12
Gum	Wennike	30	175	20	186	24
Gum	Wood-Baker	35	183	33	185	4
Gum	Wood-Baker	33	185	20	198	6
Gum	Wood-Baker	28	190	28	190	9
Gum	Wood-Baker	24	194	28	190	12
Gum	Wood-Baker	17	201	28	190	15

[a] Data from unpublished study reports where available. Batra = study 980-CHC-1013-028,[44] Bolliger = study 96-NNIN-016,[40] Haustein = study 980-CHC-9021-0013,[37] Rennard = study 98-NNIN-027,[36] Wennike = study 98-NNCG-014,[42] Wood-Baker = study 98-NNCG-017,[38] and from published study of Etter, 2004.[45]

TABLE 52 *Relative risk point prevalence of 50% smoking reduction by month of study*

Study[a]	Month	RR	LCI	UCI
Batra	1.5	1.52	1.04	2.23
Batra	2.5	1.50	1.01	2.22
Batra	4	1.50	1.01	2.22
Batra	6	2.49	1.55	4.01
Batra	9	1.84	1.20	2.83
Batra	12	1.50	1.02	2.19
Batra	13	1.63	1.12	2.38
Bolliger	4	1.89	1.39	2.57
Bolliger	6	1.37	0.99	1.90
Bolliger	12	1.37	0.98	1.93
Bolliger	18	1.53	1.03	2.28
Bolliger	24	1.20	0.85	1.68
Haustein	2.5	2.06	1.10	3.86
Haustein	4	1.80	0.91	3.55
Haustein	6	1.52	0.80	2.88
Haustein	9	1.89	0.96	3.70
Haustein	12	1.48	0.80	2.74
Rennard	4	1.57	1.14	2.17
Rennard	6	1.74	1.18	2.58
Rennard	9	2.09	1.27	3.44
Rennard	12	1.87	1.20	2.93
Rennard	15	1.46	0.94	2.27
Wennike	3	2.39	1.49	3.83
Wennike	6	2.22	1.34	3.69
Wennike	9	1.76	1.11	2.79
Wennike	12	1.60	1.03	2.49
Wennike	24	1.51	0.89	2.57
Wood-Baker	4	1.06	0.69	1.64
Wood-Baker	6	1.65	0.98	2.78
Wood-Baker	9	1.00	0.61	1.63
Wood-Baker	12	0.86	0.51	1.43
Wood-Baker	15	0.61	0.34	1.08

[a] Data from unpublished study reports where available. Batra = study 980-CHC-1013-028,[44] Bolliger = study 96-NNIN-016,[40] Haustein = study 980-CHC-9021-0013,[37] Rennard = study 98-NNIN-027,[36] Wennike = study 98-NNCG-014,[42] Wood-Baker = study 98-NNCG-017.[38]

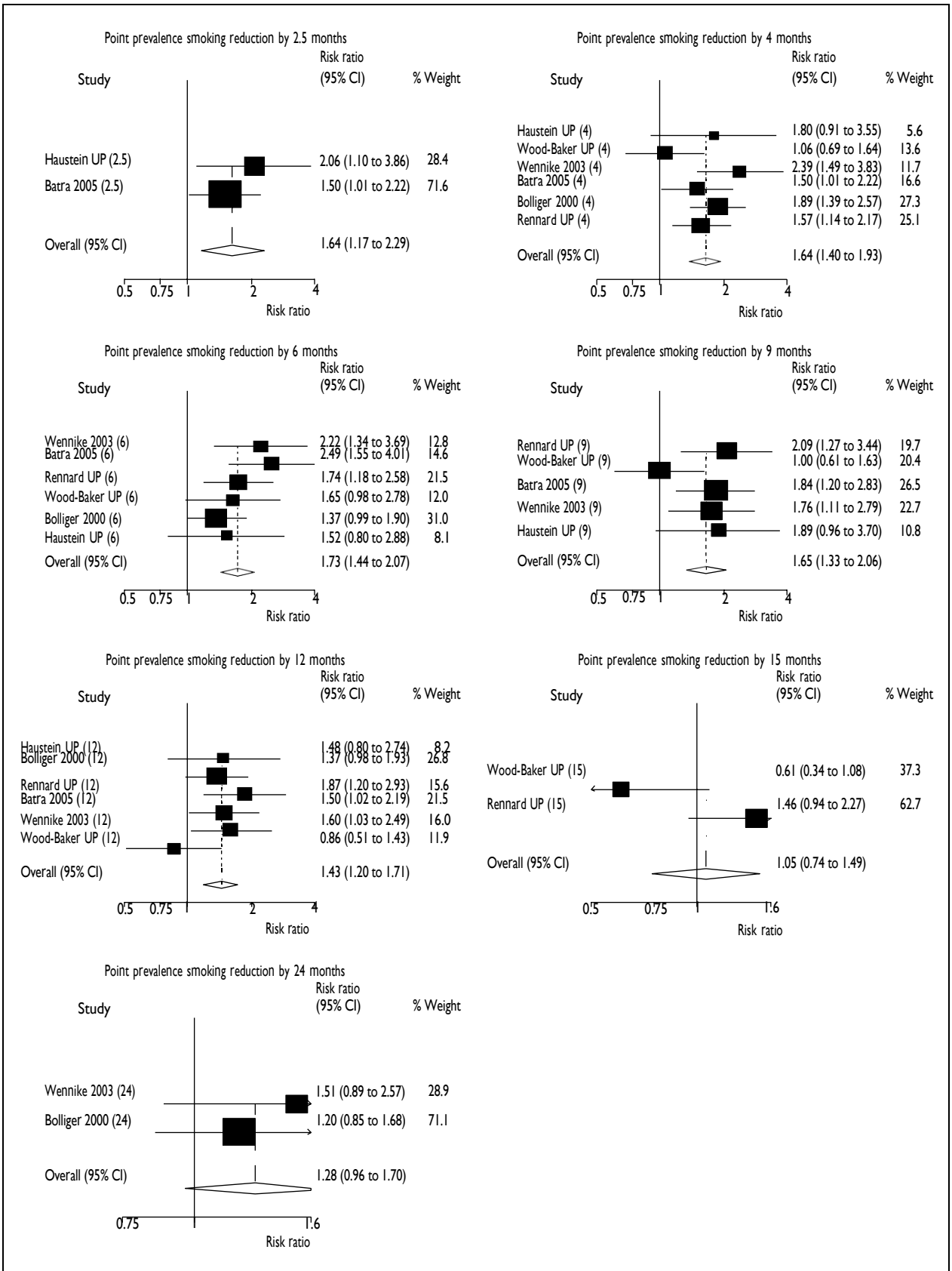

FIGURE 19 *Meta-analysis of point prevalence smoking reduction by 50% at various times during study. Data from unpublished study reports where available. Batra = study 980-CHC-1013-028,[44] Bolliger = study 96-NNIN-016,[40] Haustein = study 980-CHC-9021-0013,[37] Rennard = study 98-NNIN-027,[36] Wennike = study 98-NNCG-014,[42] Wood-Baker = study 98-NNCG-017.[38]*

Appendix 6

Sustained smoking reduction

TABLE 53 *Numbers sustaining reduced smoking by 50% by month of study*

		Active arm		Placebo arm		
NRT	**Study[a]**	**Stopped**	**Not stopped**	**Stopped**	**Not stopped**	**Month**
Gum	Batra	37	147	20	160	2.5
Gum	Batra	29	155	12	168	4
Gum	Batra	23	161	7	173	6
Gum	Batra	17	167	5	175	10
Gum	Batra	16	168	5	175	12
Gum	Batra	15	169	5	175	13
Inhalator	Bolliger	52	148	18	182	4
Inhalator	Bolliger	40	160	10	190	6
Inhalator	Bolliger	26	174	8	192	12
Inhalator	Bolliger	19	181	7	193	18
Inhalator	Bolliger	19	181	6	194	24
Gum	Haustein	16	81	5	91	2.5
Gum	Haustein	10	87	2	94	4
Gum	Haustein	7	90	0	96	6
Gum	Haustein	6	91	0	96	9
Gum	Haustein	6	91	0	96	12
Inhalator	Rennard	39	176	18	196	4
Inhalator	Rennard	27	188	7	207	6
Inhalator	Rennard	19	196	4	210	9
Inhalator	Rennard	17	198	4	210	12
Inhalator	Rennard	15	200	4	210	15
Gum	Wennike	28	177	10	196	4
Gum	Wennike	22	183	7	199	6
Gum	Wennike	21	184	6	200	9
Gum	Wennike	18	187	3	203	12
Gum	Wennike	13	192	1	205	24
Gum	Wood-Baker	13	205	13	205	4
Gum	Wood-Baker	10	208	6	212	6
Gum	Wood-Baker	8	210	5	213	9
Gum	Wood-Baker	3	215	2	216	12
Gum	Wood-Baker	3	215	2	216	15

[a] Data from unpublished study reports where available. Batra = study 980-CHC-1013-028,[44] Bolliger = study 96-NNIN-016,[40] Haustein = study 980-CHC-9021-0013,[37] Rennard = study 98-NNIN-027,[36] Wennike = study 98-NNCG-014,[42] Wood-Baker = study 98-NNCG-017.[38]

TABLE 54 *Relative risk of sustained smoking reduction by 50% by month of study*

Study[a]	Month	RR	LCI	UCI
Batra	2.5	1.81	1.09	2.99
Haustein	2.5	3.17	1.21	8.30
Batra	4	2.36	1.25	4.49
Bolliger	4	2.89	1.75	4.76
Haustein	4	4.95	1.11	21.99
Rennard	4	2.16	1.28	3.65
Wennike	4	2.81	1.40	5.64
Wood-Baker	4	1.00	0.47	2.11
Batra	6	3.21	1.41	7.30
Bolliger	6	4.00	2.06	7.78
Haustein	6	14.85	0.86	256.39
Rennard	6	3.84	1.71	8.63
Wennike	6	3.16	1.38	7.23
Wood-Baker	6	1.67	0.62	4.51
Haustein	9	12.87	0.73	225.29
Rennard	9	4.73	1.64	13.67
Wennike	9	3.52	1.45	8.53
Wood-Baker	9	1.60	0.53	4.81
Batra	10	3.33	1.25	8.82
Batra	12	3.13	1.17	8.37
Bolliger	12	3.25	1.51	7.00
Haustein	12	12.87	0.73	225.29
Rennard	12	4.23	1.45	12.37
Wennike	12	6.03	1.80	20.16
Wood-Baker	12	1.50	0.25	8.89
Batra	13	2.93	1.09	7.91
Rennard	15	3.73	1.26	11.06
Wood-Baker	15	1.50	0.25	8.89
Bolliger	18	2.71	1.17	6.31
Bolliger	24	3.17	1.29	7.76
Wennike	24	13.06	1.72	98.94

[a] Data from unpublished study reports where available. Batra = study 980-CHC-1013-028,[44] Bolliger = study 96-NNIN-016,[40] Haustein = study 980-CHC-9021-0013,[37] Rennard = study 98-NNIN-027,[36] Wennike = study 98-NNCG-014,[42] Wood-Baker = study 98-NNCG-017.[38]

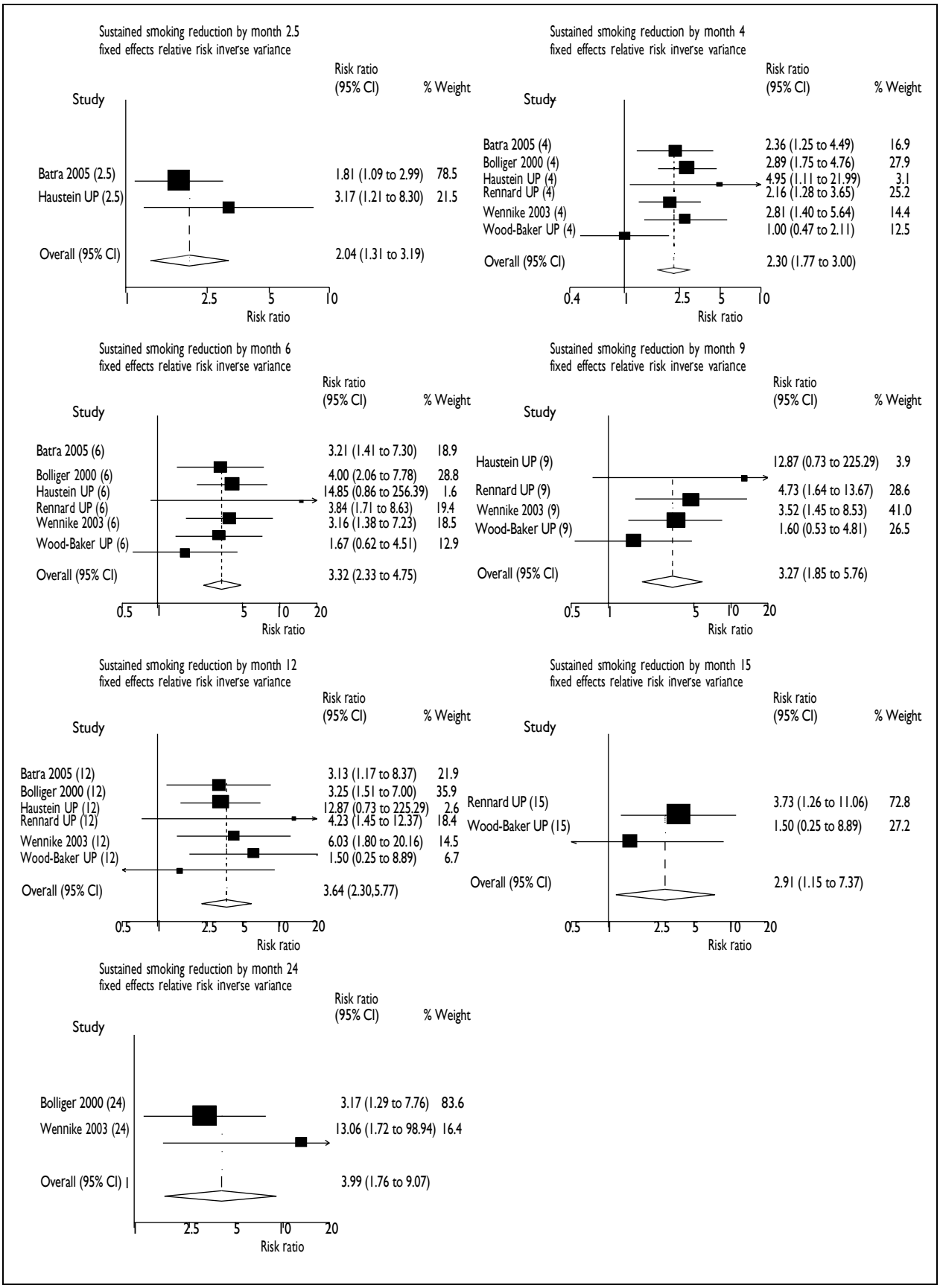

FIGURE 20 *Meta-analysis of sustained smoking reduction for different time points during study. Data from unpublished study reports where available. Batra = study 980-CHC-1013-028,[44] Bolliger = study 96-NNIN-016,[40] Haustein = study 980-CHC-9021-0013,[37] Rennard = study 98-NNIN-027,[36] Wennike = study 98-NNCG-014,[42] Wood-Baker = study 98-NNCG-017.[38]*

Appendix 7

Smoking outcomes considered separately for gum and inhalator NRT

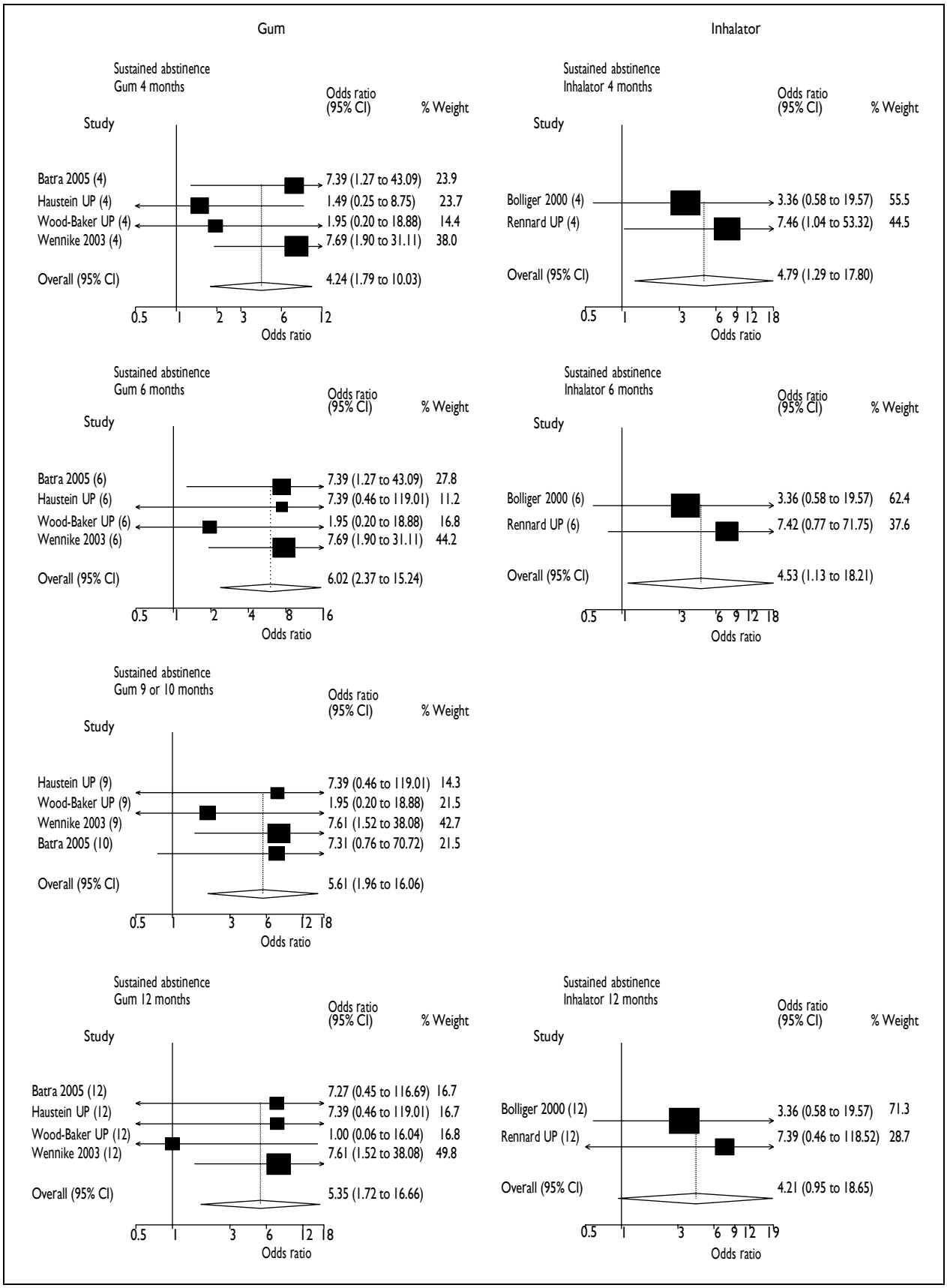

FIGURE 21 *Forest plots of Petos odds ratio NRT versus placebo sustained abstinence. Data from unpublished study reports where available. Batra = study 980-CHC-1013-028,[44] Bolliger = study 96-NNIN-016,[40] Haustein = study 980-CHC-9021-0013,[37] Rennard = study 98-NNIN-027,[36] Wennike = study 98-NNCG-014,[42] Wood-Baker = study 98-NNCG-017.[38]*

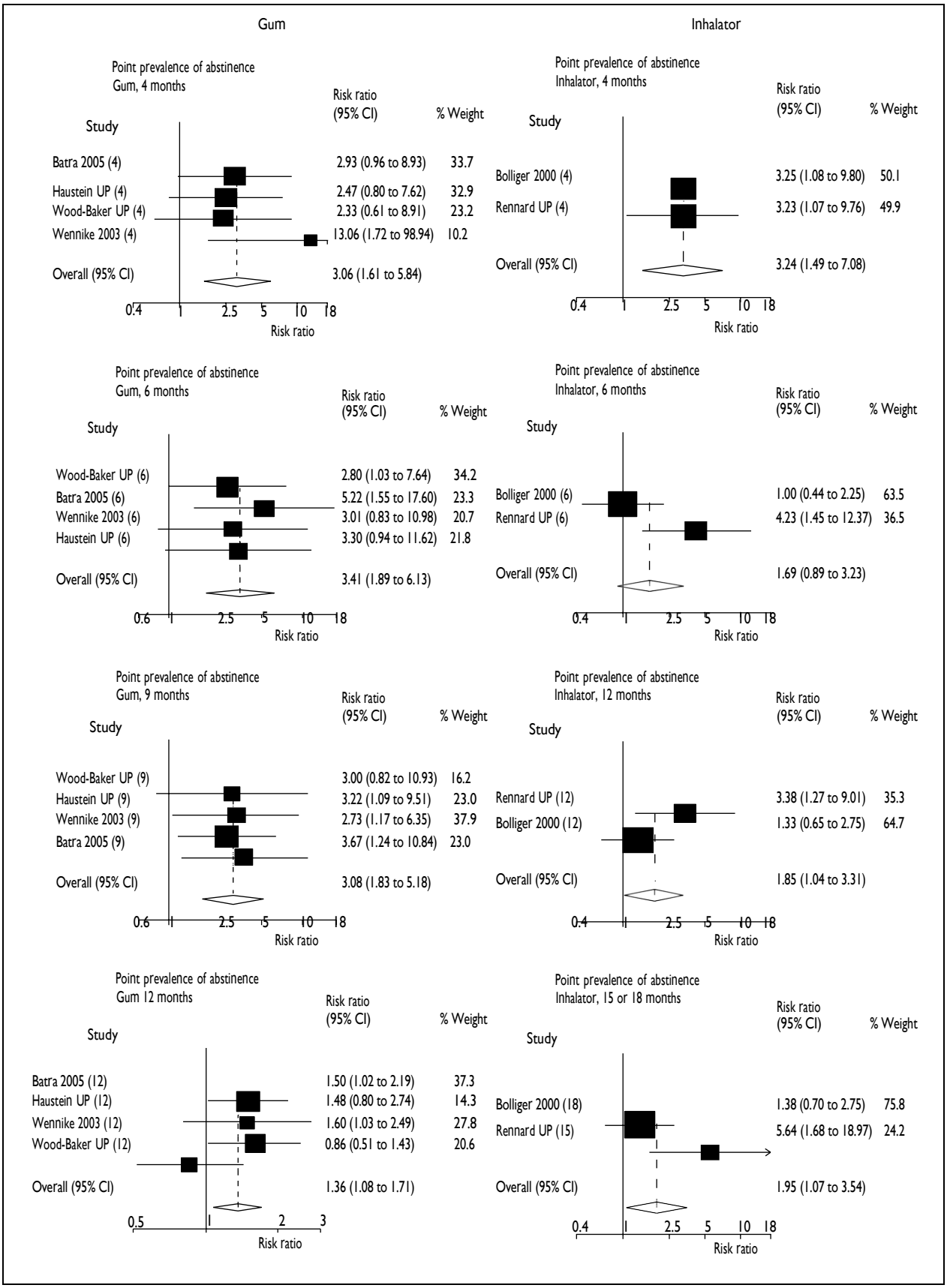

FIGURE 22 *Forest plots for point prevalence of abstinence. Data from unpublished study reports where available. Batra = study 980-CHC-1013-028,[44] Bolliger = study 96-NNIN-016,[40] Haustein = study 980-CHC-9021-0013,[37] Rennard = study 98-NNIN-027,[36] Wennike = study 98-NNCG-014,[42] Wood-Baker = study 98-NNCG-017.[38]*

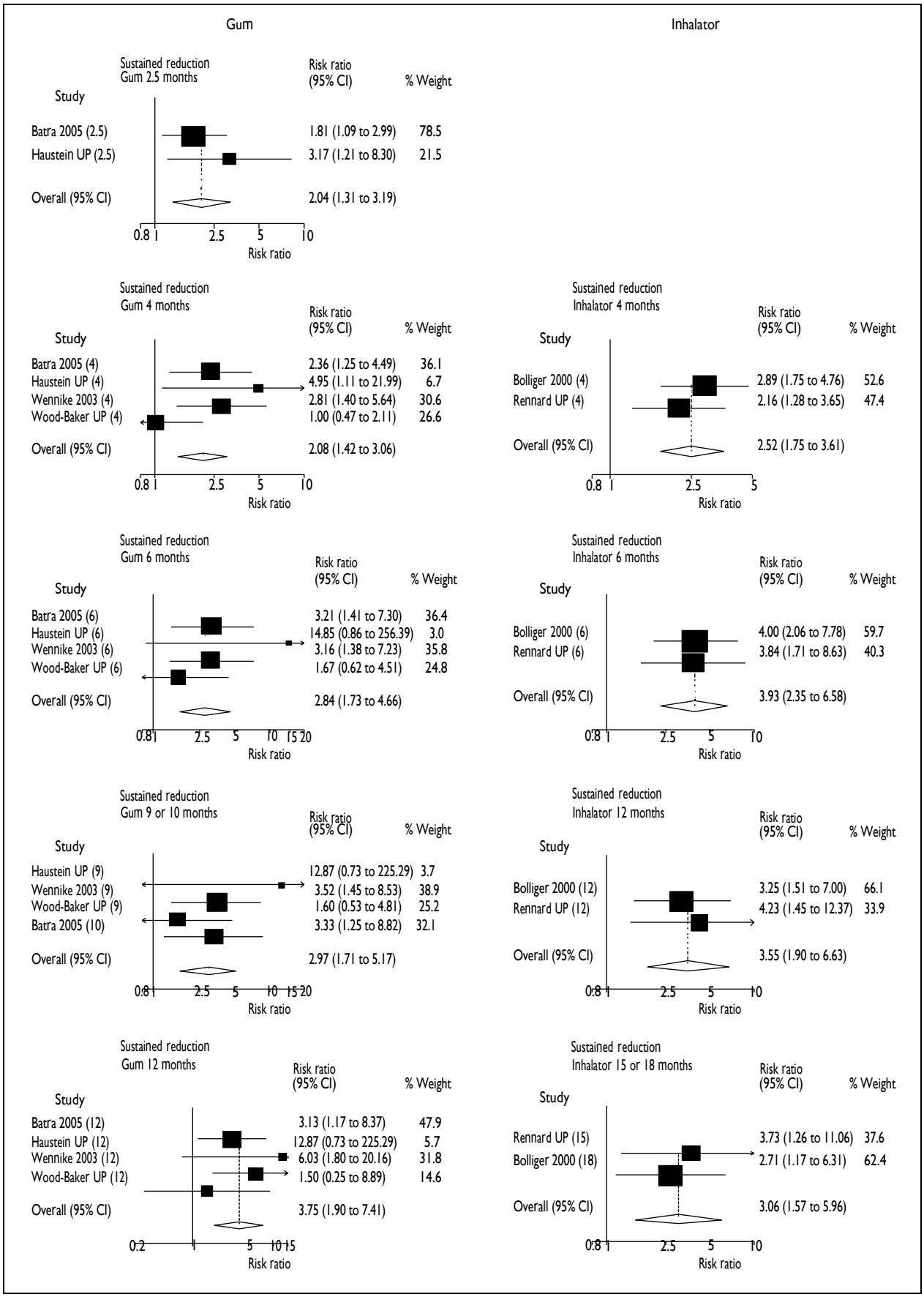

FIGURE 23 *Forest plots for sustained of 50% smoking reduction. Data from unpublished study reports where available. Batra = study 980-CHC-1013-028,[44] Bolliger = study 96-NNIN-016,[40] Haustein = study 980-CHC-9021-0013,[37] Rennard = study 98-NNIN-027,[36] Wennike = study 98-NNCG-014,[42] Wood-Baker = study 98-NNCG-017.[38]*

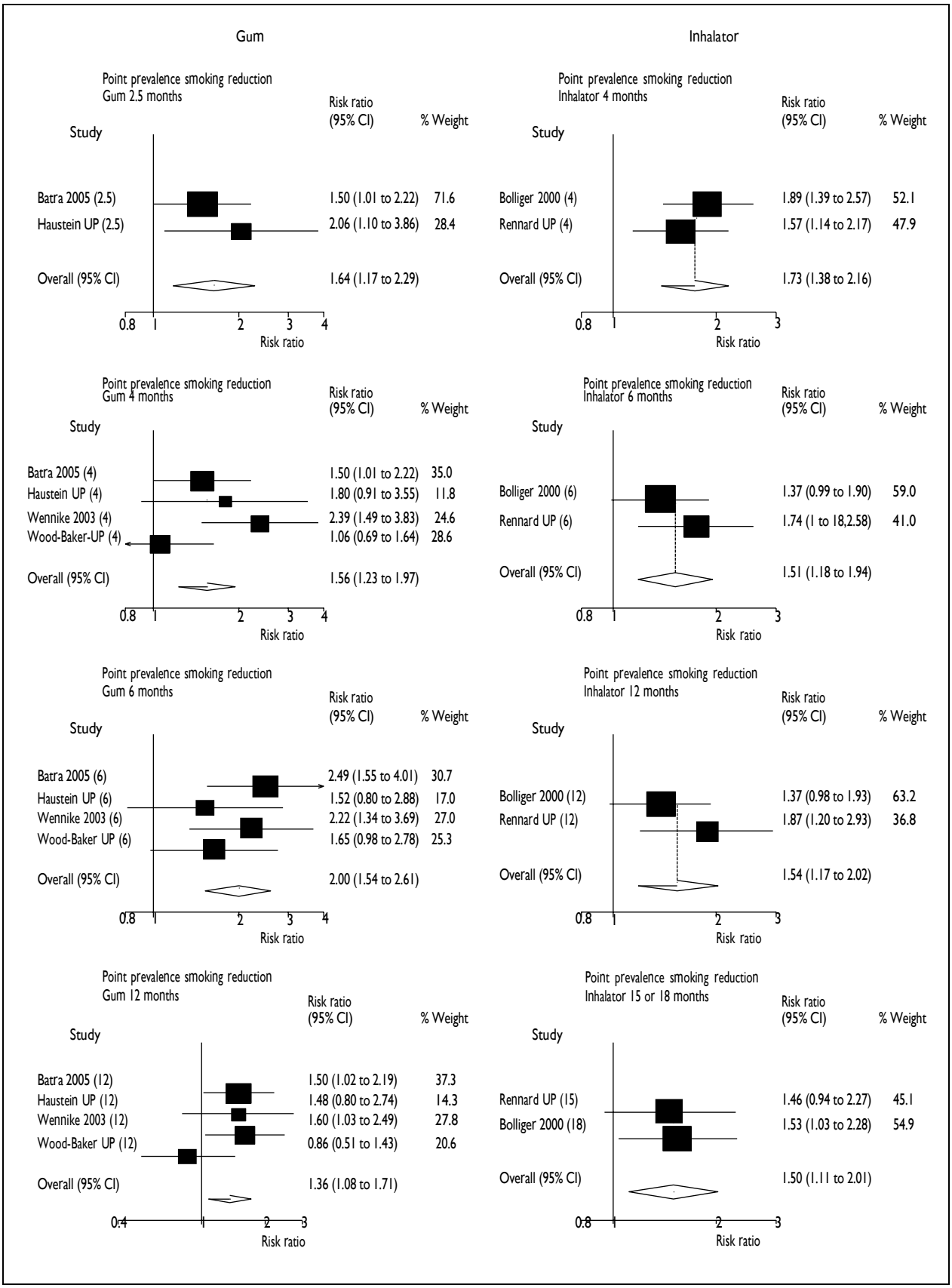

FIGURE 24 *Forest plots for point prevalence of 50% smoking reduction. Data from unpublished study reports where available. Batra = study 980-CHC-1013-028,[44] Bolliger = study 96-NNIN-016,[40] Haustein = study 980-CHC-9021-0013,[37] Rennard = study 98-NNIN-027,[36] Wennike = study 98-NNCG-014,[42] Wood-Baker = study 98-NNCG-017.[38]*

Appendix 8

Adverse events

TABLE 55 *Occurrence of adverse events*

Study Intervention Treatment duration/ evaluation time	Type of event	Unit	Effect size NRT vs placebo	*p*-Value or 95%CI	Direction of effect	Sig ificance (at $p < 0.05$)
Wennike, 2003[41] 98-NNCG-014[42] Nicotine gum (2 or 4 mg), 12 months	Nausea, nausea/vomiting and vomiting	Subjects	6 vs 3		Common in active group	
	Palpitations	Subjects	0 vs 1		Common in placebo group	
	Reported adverse events	No. of adverse events	147 vs 166		Common in placebo group	
	Mild adverse events	%	61 vs 59		Common in active group	
	Moderate adverse events	%	34 vs 36		Common in placebo group	
	Severe adverse events	%	4 vs 5		Common in placebo group	
	Discontinuation due to adverse event	Subjects	2 vs 2		Equal	
	Death	Subjects	1 vs 1		Equal	
	Serious adverse event	Subjects	12 vs 9		Common in active group	
Bolliger, 2000[39] 96-NNIN-016.[40] Nicotine inhalator (10 mg nicotine and 1 mg menthol), 18 months	Nausea, nausea/vomiting and vomiting	Subjects	9 vs 8		Common in active group	
	Palpitations	Subjects	1 vs 2		Common in placebo group	
	Reported adverse events	No. of adverse events	227 vs 193		Common in active group	
	Mild adverse events	%	63 vs 52		Common in active group	
	Moderate adverse events	%	24 vs 34		Common in placebo group	
	Severe adverse events	%	13 vs 14		Common in placebo group	
	Discontinuation due to adverse event	Subjects	2 vs 3		Common in placebo group	
	Throat irritation	OR	3.69	1.13–15.6	Common in active group	Yes
	Coughing	OR	3.4	1.1–10.6	Common in active group	Yes

continued

TABLE 55 *Occurrence of adverse events (cont'd)*

Study Intervention Treatment duration/ evaluation time	Type of event	Unit	Effect size NRT vs placebo	*p*-Value or 95%CI	Direction of effect	Sig ificance (at $p < 0.05$)
	Death	Subjects	1 vs 1		Equal	
	Serious adverse event	Subjects	32 vs 21		Common in active group	
Rennard, unpublished, 98-NNIN-027[36] Nicotine inhalator (10 mg), 12 months	Nausea, nausea/vomiting and vomiting	Subjects	11 vs 5		Common in active group	
	Palpitations	Subjects	1 vs 1		Equal	
	Reported adverse events	No. of adverse events	458 vs 373		Common in active group	
	Mild adverse events	%	58 vs 55		Common in active group	
	Moderate adverse events	%	33 vs 32		Common in active group	
	Severe adverse events	%	9 vs 13		Common in placebo group	
	Dizziness	Subjects	3 vs 10	$p = 0.053$	Common in placebo group	No
	Pharyngitis	Subjects	21 vs 13		Common in active group	No
	Cough	Subjects	12 vs 6		Common in active group	No
	Hypertension	Subjects	8 vs 1	$p = 0.037$	Common in active group	Yes
	Serious adverse event	Subjects	15 vs 13		Common in active group	
Wood-Baker, unpublished 98-NNCG-017.[38] Nicotine gum (2 or 4 mg), 12 months	Nausea, nausea/vomiting and vomiting	Subjects	23 vs 18		Common in active group	
	Palpitations	Subjects	1 vs 1		Equal	
	Reported adverse events	No. of adverse events	466 vs 464		Common in active group	
	Mild adverse events	%	29 vs 27		Common in active group	
	Moderate adverse events	%	38 vs 40		Common in placebo group	
	Severe adverse events	%	33 vs 33		Equal	
	Stomatitis			$p = 0.037$	Common in placebo group	Yes
	Infection			$p = 0.036$	Common in placebo group	Yes

continued

TABLE 55 *Occurrence of adverse events*

Study Intervention Treatment duration/ evaluation time	Type of event	Unit	Effect size NRT vs placebo	*p*-Value or 95%CI	Direction of effect	Sig ificance (at $p < 0.05$)
	Chest infection			$p = 0.036$	Common in active group	Yes
	Death	Subjects	2 vs 0		Common in active group	
	Serious adverse event	Subjects	10 vs 25		Common in placebo group	
	Discontinuation due to adverse event	Subjects	9 vs 4		Common in active group	
Haustein, unpublished, 980-CHC-9021-0013.[37] Nicotine gum (4 mg), 9 months	Nausea/vomiting	Subjects	7 vs 2		Common in active group	
	Vomiting	Subjects	14 vs 1		Common in active group	
	Headache	Subjects	10 vs 9		Common in active group	
	Dizziness	Subjects	4 vs 3		Common in active group	
	Gastrointestinal discomfort	Subjects	37 vs 13		Common in active group	
	Nausea	Subjects	28 vs 14		Common in active group	
	Throat irritation	Subjects	5 vs 2		Common in active group	
	Pharyngitis	Subjects	7 vs 2		Common in active group	
	Erythema	Subjects	0 vs 1		Common in placebo group	
	Hiccups	Subjects	28 vs 1		Common in active group	
	Urticaria	Subjects	2 vs 3		Common in placebo group	
	Reported adverse events	No. of adverse events	399 vs 272		Common in active group	
	Mild adverse events	%	24 vs 22		Common in active group	
	Moderate adverse events	%	45 vs 56		Common in placebo group	
	Severe adverse events	%	32 vs 22		Common in active group	
	Death	Subjects	2 vs 0		Equal	
	Serious adverse event	Subjects	18 vs 7		Common in active group	

continued

TABLE 55 *Occurrence of adverse events*

Study Intervention Treatment duration/ evaluation time	Type of event	Unit	Effect size NRT vs placebo	*p*-Value or 95%CI	Direction of effect	Sig ificance (at $p < 0.05$)
Batra, 2005,[43] 980-CHC-1013-028.[44] Nicotine gum (4 mg), 12 months	Reported adverse events	No. of adverse events	506 vs 370		Common in active group	
	Mild adverse events	%	16 vs 13		Common in active group	
	Moderate adverse events	%	44 vs 46		Common in active group	
	Severe adverse events	%	40 vs 40		Equal	
	Oral discomfort	Times	8 vs 3		Common in active group	
	Throat irritation	Times	10 vs 0		Common in active group	
	Headache	Times	43 vs 52		Common in active group	
	Dyspepsia	Times	12 vs 5		Common in active group	
	Nausea	Occasions	19 vs 11		Common in active group	
	Vomiting	Occasions	1 vs 0		Common in active group	
	Tachycardia	Occasions	3 vs 2		Common in active group	
	Hiccup	Times	28 vs 3		Common in active group	
	Serious adverse event	Subjects	10 vs 6		Common in active group	
Etter, 2004,[45,46] Nicotine patch (contains 25 mg and delivers 15 mg of nicotine over 16 hours), or gum (contains 4 mg and delivers 2 mg of nicotine), or inhalator (a plug contains 10 mg and delivers 5 mg of nicotine). Participants who quit smoking continued to receive nicotine or placebo to prevent relapse. 6 months	Death	Subjects	2 vs 0		Common in active group	
	Serious adverse events		No difference	$p = 0.25$		No

Appendix 9

Studies excluded from the systematic review of effectiveness

TABLE 56 *Excluded studies and reasons for exclusion*

Study	Reason for exclusion
Abdullah AS. How far should we promote smoking reduction in order to promote smoking cessation? *Asian Pac J Cancer Prev* 2005;**6**:231–4.	Review, not systematic
Agusti A, Estopa R, Gonzalez J, Guerra D, Marin D, Roig P, *et al.* Multicenter study of smoking cessation with nicotine chewing gum in health-care professionals. *Med Clin* 1991;**97**:526–30.	Insufficient information on population's willingness/ability to quit
Ahijevych K. Review: all forms of nicotine replacement therapy are effective for smoking cessation. *Evid Based Nurs* 2005;**8**:13.	Commentary piece
Ahluwalia JS, Okuyemi K, Nollen N, Choi WS, Kaur H, Pulvers K, *et al.* The effects of nicotine gum and counseling among African American light smokers: a 2 × 2 factorial design. *Addiction* 2006;**101**:883–91.	Inappropriate population, smokers motivated to quit "*… were interested in quitting smoking in the next two weeks*"
Ahmadi J, Ashkani H, Ahmadi M, Ahmadi N. Twenty-four week maintenance treatment of cigarette smoking with nicotine gum, clonidine and naltrexone. *J Subst Abuse Treat* 2003;**24**:251–5.	Insufficient information on population's willingness/ability to quit
Ali O. Up-coming drugs: cut-down and stop nicotine. *Pract Nurs* 2006;**17**:11.	Commentary piece/recommendation
Anonymous. Using NRT to cut down helps long-term. *Pharma J* 2005;**271**:16	News item
Aparici M, Fernandez Gonzalez AL, Alegria E. Clonidine in the treatment of tobacco withdrawal. Comparison with nicotine chewing gum. *Rev Clin Esp* 6.	Inappropriate population, smokers motivated to quit 1994;**194**:453–
Areechon W, Punnotok J. Smoking cessation through the use of nicotine chewing gum: a double-blind trial in Thailand. *Clin Ther* 1988;**10**:183–6.	Insufficient information on population's willingness/ability to quit
Benowitz NL. Smoking less as a treatment goal for those who cannot stop smoking. *Am J Med* 2004;**116**:203–5.	Commentary piece
Blondal T, Gudmundsson LJ, Tomasson K, Jonsdottir D, Hilmarsdottir H, Kristjansson F, *et al.* The effects of fluoxetine combined with nicotine inhalers in smoking cessation – a randomized trial. *Addiction* 1999;**94**:1007–15.	Inappropriate population, smokers motivated to quit "*… had to be motivated to stop smoking*"
Blondal T. Controlled trial of nicotine polacrilex gum with supportive measures. *Arch Intern Med* 1989;**149**:1818–21.	Inappropriate population, smokers motivated to quit and not randomised
Bohadana A, Nilsson F, Rasmussen T, Martinet Y. Gender differences in quit rates following smoking cessation with combination nicotine therapy: influence of baseline smoking behaviour. *Nicotine Tob Res* 2003;**5**:111–16.	Insufficient information on population's willingness/ability to quit
Bohadana A, Nilsson F, Rasmussen T, Martinet Y. Nicotine inhaler and nicotine patch as a combination therapy for smoking cessation: a randomized, double-blind, placebo-controlled trial. *Arch Intern Med* 2000;**160**:3128–34.	Inappropriate population, smokers motivated to quit "*Motivated to quit …*"
Bohadana,A, Nilsson,F, Martinet,Y. Nicotine inhaler and nicotine patch: a combination therapy for smoking cessation. *Nicotine Tob Res* 1999;**1**:189.	Inappropriate population, smokers motivated to quit "*… motivated …*"
Bolliger CT, Zellweger JP, Danielsson T, van B, X, Robidou A, Westin A, *et al.* Influence of long-term smoking reduction on health risk markers and quality of life. *Nicotine Tob Res* 2002;**4**:433–9.	Quit rates not reported for both arms
Bolliger CT, Zellweger JP, Danielsson T, van Biljon X, Robidou A, Westin A, *et al.* Effectiveness of the nicotine inhaler in smoking reduction. *AmJ Respir Crit Care Med* 1999;**159**:A735.	No quit rates reported

continued

TABLE 56 *Excluded studies and reasons for exclusion (cont'd)*

Study	Reason for exclusion
Bolliger CT. Practical experiences in smoking reduction and cessation. *Addiction* 2000;**95**:S19–24.	Review, not systematic
Bottorff JL. Review: advice from doctors, counselling by nurses, behavioural interventions, nicotine replacement therapy, and several pharmacological treatments increase smoking cessation rates … commentary on Lancaster T, Stead L, Siagy C, *et al. Evid Based Nurs* 2001;**1**:13.	Commentary piece
Bryan J. Breath of fresh air … nicotine replacement therapy. *Health Serv J* 2001;**111**:34–5.	Review, no consideration of cut down to quit
Campbell IA, Lyons E, Prescott RJ. Stopping smoking. Do nicotine chewing-gum and postal encouragement add to doctors' advice? *Practitioner* 1987;**231**:114–17.	Inappropriate population, smokers motivated to quit "… *Agreed to try to quit…* "
Campbell IA, Prescott RJ, Tjeder-Burton SM. Smoking cessation in hospital patients given repeated advice plus nicotine or placebo chewing gum. *Respir Med* 1991;**85**:155–7.	Not randomised
Carpenter MJ, Hughes JR, Solomon LJ, Callas PW. Both smoking reduction with nicotine replacement therapy and motivational advice increase future cessation among smokers unmotivated to quit. *J Consult Clin Psychol* 2004;**72**:371–81.	Both intervention arms received NRT; no-treatment arm lacked adjuvant elements in other arms
Carpenter MJ, Hughes JR, Keely JP. Effect of smoking reduction on later cessation: a pilot experimental study. *Nicotine Tob Res* 2003;**5**:155–62.	Both arms received NRT
Carpenter MJ, Hughes JR, Solomon LJ, Lancaster T. Smoking reduction with nicotine replacement and motivational advice reduced smoking in people unmotivated to quit. *Evid Based Med* 2005;**10**:18.	Commentary piece
Cepeda-Benito A, Reynoso JT, Erath S. Meta-analysis of the efficacy of nicotine replacement therapy for smoking cessation: differences between men and women. *J Consult Clin Psychol* 2004;**72**:712–22.	Review no consideration of cut down to quit
Cinciripini PM, Wetter DW, McClure JB. Scheduled reduced smoking: effects on smoking abstinence and potential mechanisms of action. *Addict Behav* 1997;**22**:759–67.	Overview, not systematic
Clavel F, Benhamou S, Company-Huertas, Flamant R. Helping people to stop smoking: randomised comparison of groups being treated with acupuncture and nicotine gum with control group. *BMJ* 1985;**291**:1538–9.	Insufficient information on population's willingness/ability to quit
Clavel-Chapelon F, Paoletti C, Benhamou S. A randomised 2 × 2 factorial design to evaluate different smoking cessation methods. *Rev Epidemiol Santé Publique* 1992;**40**:187–90.	Insufficient information on population's willingness/ability to quit
Clavel-Chapelon F, Paoletti C, Benhamou S. Smoking cessation rates 4 years after treatment by nicotine gum and acupuncture. *Prev Med* 1997;**26**:25–8.	Insufficient information on population's willingness/ability to quit
Cooper TV, Klesges RC, Debon MW, Zbikowski SM, Johnson KC, Clemens LH, *et al*. A placebo controlled randomized trial of the effects of phenylpropanolamine and nicotine gum on cessation rates and postcessation weight gain in women. *Addict Behav* 2005;**30**:61–75.	Insufficient information on population's willingness/ability to quit
Cooper TV. A placebo-controlled randomized trial of the effects of PPA and nicotine gum on cessation rates and post-cessation weight gain in women. *Diss Abst Int B* 2002;**63** (Issue 5-B).	Inappropriate population, smokers motivated to quit "*Smoking cessation programme*"
Danielsson T, Rossner S, Westin A, Danielsson T, Rossner S, Westin A. Open randomised trial of intermittent very low energy diet together with nicotine gum for stopping smoking in women who gained weight in previous attempts to quit. *BMJ* 2005;**319**:490–3.	Inappropriate population, smokers motivated to quit "… *attempting to stop smoking*"
Dar R, Stronguin F, Etter JF, Dar R, Stronguin F, Etter JF. Assigned versus perceived placebo effects in nicotine replacement therapy for smoking reduction in Swiss smokers. *J Consult Clin Psychol* 2005;**73**:350–3.	No quit rates reported

continued

TABLE 56 *Excluded studies and reasons for exclusion (cont'd)*

Study	Reason for exclusion
Dooley RT. A comparison of relapse prevention with nicotine gum or nicotine fading in modification of smoking. *Aust Psychol* 1992;**27**:191.	Inappropriate population, smokers motivated to quit *"… willingness to attend stop smoking sessions"*
Fagerström KO, Hughes JR, Callas PW. Long-term effects of the Eclipse cigarette substitute and the nicotine inhaler in smokers not interested in quitting. *Nicotine Tob Res* 2002;**4** Suppl 2:S141–5.	Not randomised
Fagerström KO, Hughes JR. Nicotine concentrations with concurrent use of cigarettes and nicotine replacement: a review. *Nicotine Tob Res* 2002; **4** Suppl 2:S73–9.	No quit rates reported
Fagerström KO, Hughes JR, Rasmussen T, Callas PW. Randomised trial investigating effect of a novel nicotine delivery device (Eclipse) and a nicotine oral inhaler on smoking behaviour, nicotine and carbon monoxide exposure, and motivation to quit. *Tob Control* 2000;**9**:327–33.	No quit rates reported
Fagerström KO, Tejding R, Westin A, Lunell E. Aiding reduction of smoking with nicotine replacement medications: hope for the recalcitrant smoker? *Tob Control* 1997;**6**:311–16.	No quit rates reported
Fagerstrom KO. A comparison of psychological and pharmacological treatment in smoking cessation. *J Behav Med* 1982;**5**:343–51.	Inappropriate population, smokers motivated to quit *"… consecutive patients at a smoking withdrawal clinic"*
Fagerström KO. Can reduced smoking be a way for smokers not interested in quitting to actually quit? *Respiration* 2005;**72**:216–20.	Review, not systematic
Fagerström KO. Effects of nicotine chewing gum and follow-up appointments in physician-based smoking cessation. *Prev Med* 1984;**13**:517–27.	Inappropriate population, smokers motivated to quit and not randomised *"… motivated to quit"*
Fortmann SP, Killen JD, Telch MJ, Newman B. Minimal contact for smoking cessation. A placebo controlled trial of nicotine polacrilex and self-directed relapse prevention: initial results of the Stanford Stop Smoking Project. *JAMA* 1988;**260**:1575–80.	Insufficient information on population's willingness/ability to quit
Garvey AJ, Kinnunen T, Nordstrom BL, Utman CH, Doherty K, Rosner B, *et al.* Effects of nicotine gum dose by level of nicotine dependence. *Nicotine Tob Res* 2000;**2**:53–63.	Inappropriate population, smokers motivated to quit "*Subjects chose a date to quit*"
Goldstein MG, Niaura R, Follick MJ, Abrams DB. Effects of behavioral skills training and schedule of nicotine gum administration on smoking cessation. *Am J Psychiatry* 1989;**146**:56–60.	Insufficient information on population's willingness/ability to quit
Gray N. A global approach to tobacco policy. *Lung Cancer* 2003;**39**:113–17.	Review does not consider CDTQ
Gross J, Johnson J, Sigler L, Stitzer ML. Dose effects of nicotine gum. *Addict Behav* 1995;**20**:371–81.	Inappropriate population, smokers motivated to quit "*Volunteers… to participate in a smoking cessation study*"
Hall SM, Munoz RF, Reus VI, Sees KL, Duncan C, Humfleet GL, *et al.* Mood management and nicotine gum in smoking treatment: a therapeutic contact and placebo-controlled study. *J Consult Clinl Psychol* 1996;**64**:1003–9.	Insufficient information on population's willingness/ability to quit
Hall SM, Tunstall C, Rugg D, Jones RT, Benowitz N. Nicotine gum and behavioral treatment in smoking cessation. *J Consult Clinl Psychol* 1985;**53**:256–8.	Inappropriate population, smokers motivated to quit
Hall SM, Tunstall CD, Ginsberg D, Benowitz NL, Jones RT. Nicotine gum and behavioral treatment: a placebo controlled trial. *J Consult Clinl Psychol* 1987;**55**:603–5.	Inappropriate population, smokers motivated to quit
Hatsukami DK, Kotlyar M, Allen S, Jensen J, Li S, Le C, *et al.* Effects of cigarette reduction on cardiovascular risk factors and subjective measures. *Chest* 2005;**128**:2528–37.	Quit rates for both arms not reported

continued

TABLE 56 *Excluded studies and reasons for exclusion (cont'd)*

Study	Reason for exclusion
Hays JT, Ebbert JO. Bupropion for the treatment of tobacco dependence: Guidelines for balancing risks and benefits. *CNS Drugs* 2003;**17**:71–83.	Guidelines/recommendations
Hellwig B. Nicotine replacement therapy and smoking reduction. *Dtsch Apoth Ztg* 1998;**138**:25–8.	Guidelines/recommendations/opinion piece
Herrera N, Franco R, Herrera L, Partidas A, Rolando R, Fagerström KO. Nicotine gum, 2 and 4 mg, for nicotine dependence: a double-blind placebo-controlled trial within a behavior modification support program. *Chest* 1995;**108**:447–51.	"… expressed motivation to stop smoking"
Hjalmarson A, Nilsson F, Sjostrom L, Wiklund O. The nicotine inhaler in smoking cessation. *Arch Intern Med* 1997;**157**:1721–8.	Inappropriate population, smokers motivated to quit. "*willing to follow protocol … at cessation clinic*"
Hjalmarson AI. Effect of nicotine chewing gum in smoking cessation. A randomized, placebo-controlled, double-blind study. *JAMA* 1984;**252**:2835–8.	Inappropriate population, smokers motivated to quit "*… smokers who want to stop"*
Horst WD. Extended use of nicotine replacement therapy to maintain smoking cessation in persons with schizophrenia. *Neuropsychiatr Dis Treat* 2005;**1**:349–55.	Not randomised
Huber D, Gastner J. Smoking cessation: a comparison of behavior therapy, nicotine replacement therapy and their combination. *Verhaltenstherapie und Verhaltensmedizin* 2003;**24**:167–85.	Inappropriate population, smokers motivated to quit "*… strict abstinence was required*"
Huber D. Combined and separate treatment effects of nicotine chewing gum and self-control method. *Pharmacopsychiatry* 1988;**21**:461–2.	Inappropriate population, smokers motivated to quit, an abrupt abstinence study
Hughes J, Lindgren P, Connett J, Nides M, Lung HS. Smoking reduction in the Lung Health Study. *Nicotine Tob Res* 2004;**6**:275–80.	Inappropriate population, smokers motivated to quit "*Willing to participate in a smoking cessation programme*"
Hughes JR, Carpenter MJ. The feasibility of smoking reduction: an update. *Addiction* 2005;**100**:1074–89.	Review, not systematic, quit rates not considered
Hughes JR, Gust SW, Keenan R, Fenwick JW, Skoog K, Higgins ST. Long-term use of nicotine vs placebo gum. *Arch Intern Med* 1991;**151**:1993–8.	Inappropriate population, smokers motivated to quit "*… who wished to stop smoking were recruited*"
Hughes JR, Gust SW, Keenan RM, Fenwick JW, Healey ML. Nicotine vs placebo gum in general medical practice. *JAMA* 1989;**261**:1300–5.	Inappropriate population, smokers motivated to quit "*… desire to stop and willingness to set quit date*"
Hughes JR, Gust SW, Keenan RM, Fenwick JW. Effect of dose on nicotine's reinforcing, withdrawal-suppression and self-reported effects. *J Pharmacol Exp Ther* 1990;**252**:1175–83.	Inappropriate population, smokers motivated to quit "*Wished to stop*"
Jamrozik K, Fowler G, Vessey M, Wald N. Placebo controlled trial of nicotine chewing gum in general practice. *BMJ* 1984;**289**:794–7.	Inappropriate population, smokers motivated to quit "*… trying to give up smoking*"
Jarvik ME, Schneider NG. Degree of addiction and effectiveness of nicotine gum therapy for smoking. *Am J Psychiatry* 1984;**141**:790–1.	Inappropriate population, smokers motivated to quit "*… volunteers who wanted to stop smoking*"
Jarvis MJ, Raw M, Russell MA, Feyerabend C. Randomised controlled trial of nicotine chewing-gum. *BMJ* 1982;**285**:537–40.	"… encouraged to stop on day 1"
Jensen EJ, Schmidt E, Pedersen B, Dahl R. The effect of nicotine, silver acetate, and placebo chewing gum on the cessation of smoking. The influence of smoking type and nicotine dependence. *Int J Addict* 1991;**26**:1223–31.	Wrong intervention
Jimenez-Ruiz C. The safety of nicotine gum in smoking reduction. A double blind, randomised, comparative clinical study. Unpublished trial report.	No quit rates reported

continued

TABLE 56 *Excluded studies and reasons for exclusion (cont'd)*

Study	Reason for exclusion
Jolicoeur DG, Richter KP, Ahluwalia JS, Mosier MC, Resnicow K. Smoking cessation, smoking reduction, and delayed quitting among smokers given nicotine patches and a self-help pamphlet. *Subst Abuse* 2003;**24**:101–6.	Not gum or inhaler
Kanner RE, Connett JE, Williams DE, Buist AS. Effects of randomized assignment to a smoking cessation intervention and changes in smoking habits on respiratory symptoms in smokers with early chronic obstructive pulmonary disease: The Lung Health Study. *Am J Med* 1999;**106**:410–16.	Inappropriate population, smokers motivated to quit "*willingness to be assigned to cessation programme*"
Kornitzer M, Boutsen M, Dramaix M, Thijs J, Gustavsson G. Combined use of nicotine patch and gum in smoking cessation: a placebo-controlled clinical trial. *Prev Med* 1995;**24**:41–7.	Inappropriate population, smokers motivated to quit "*… motivation to stop smoking positively*"
Kornitzer M, Kittel F, Dramaix M, Bourdoux P. A double blind study of 2 mg versus 4 mg nicotine-gum in an industrial setting. *J Psychosom Res* 1987;**31**:171–6.	Inappropriate population, smokers motivated to quit "*If you smoke … and want to stop*"
Lawrie TE, Ries AL. New Treatments for early and late COPD: Part 1, Prevention. *Consultant* 2004; **44**:21–5.	Review no consideration of CDTQ
Le Houezec J, Sawe U. Smoking reduction and temporary abstinence: new approaches for smoking cessation. *J Mal Vasc* 2003;**28**:293–300.	Review, not systematic
Leischow SJ, Ranger-Moore J, Muramoto ML, Matthews E. Effectiveness of the nicotine inhaler for smoking cessation in an OTC setting. *Am J Health Behav* 2004;**28**:291–301.	Inappropriate population, smokers motivated to quit "*… motivated to quit*"
Leischow SJ, Ranger-Moore J, Muramoto ML, Matthews E. The safety and effectiveness of the nicotine inhaler for smoking cessation in an over-the-counter setting. Society for Research on Nicotine and Tobacco 9th Annual Meeting, 2003, p. 100.	Reference not obtainable
Leischow SJ, Muramoto ML, Cook GN, Merikle EP, Castellina SM, Otte P. OTC nicotine patch: effectiveness alone and with brief physician intervention. *Am J Health Behav* 1999;**23**:61–9.	Not gum or inhaler
Leischow SJ, Nilsson F, Franzon M, Hill A, Otte P, Merikle EP. Efficacy of the nicotine inhaler as an adjunct to smoking cessation. *Am J Health Behav* 1996;**20**:364–71.	Inappropriate population, smokers motivated to quit "*… willingness to follow… the quit protocol*"
Luckmann R. Review: advice from doctors and nurses, behavioural interventions, nicotine replacement treatment, and several pharmacological treatments increase smoking cessation rates. *Evid Based Ment Health* 2001;**4**:16.	Commentary piece on a review
Malcolm RE, Sillett RW, Turner JA, Ball KP. The use of nicotine chewing gum as an aid to stopping smoking. *Psychopharmacology* 1980;**70**:295–6.	Inappropriate population, smokers motivated to quit "*… volunteers who wanted to stop smoking*"
Marcos T, Godas T, Corominas J. Nicotine replacement therapy versus gradual smoking withdrawal in smoking cessation. *Med Clin (Barc)* 2004;**123**:127–30.	Not randomised
Marsh HS, Dresler CM, Choi JH, Targett DA, Gamble ML, Strahs KR. Safety profile of a nicotine lozenge compared with that of nicotine gum in adult smokers with underlying medical conditions: a 12-week, randomized, open-label study. *Clin Ther* 2005;**27**:1571–87.	Inappropriate population, smokers motivated to quit "*Considered motivated ready to quit*"
McChargue DE, Gulliver SB, Hitsman B. Applying a stepped-care reduction approach to smokers with schizophrenia. *Psychiatr Times* 2003;**20**:78.	Guideline/recommendation
McGovern PG, Lando HA. An assessment of nicotine gum as an adjunct to freedom from smoking cessation clinics. *Addict Behav* 1992;**17**:137–47.	Inappropriate population, smokers motivated to quit "*… recruited to a smoking cessation clinic*"
McNeill A, Foulds J, Bates C. Regulation of nicotine replacement therapies (NRT): a critique of current practice. *Addiction* 2001;**96**:1757–68.	Opinion piece

continued

TABLE 56 *Excluded studies and reasons for exclusion (cont'd)*

Study	Reason for exclusion
Molyneux A, Lewis S, Leivers U, Anderton A, Antoniak M, Brackenridge A, *et al*. Clinical trial comparing nicotine replacement therapy (NRT) plus brief counselling, brief counselling alone, and minimal intervention on smoking cessation in hospital inpatients. *Thorax* 2003;**58**:484–8.	Inappropriate population, smokers motivated to quit, expected to comply with protocol of cessation study
Moolchan ET, Robinson ML, Ernst M, Cadet JL, Pickworth WB, Heishman SJ, *et al*. Safety and efficacy of the nicotine patch and gum for the treatment of adolescent tobacco addiction. *Pediatrics* 2005;**115**:e407–14.	Inappropriate population, smokers motivated to quit "*… smokers desiring to quit*"
Mori T, Shimao T, Yulchiro G, Namiki M, Hyachi T. A clinical trial of nicotine chewing gum for smoking cessation. 8th World Conference on Tobacco and Health. Abstract.	Not traceable as not full reference
Nakamura M, Saito J, Oshima A, Miyamoto M, Matushita A, Endo S. Effect of nicotine chewing gum in smoking cessation classes. The global war. *Proceedings of the 7th World Conference on Tobacco and Health* 1990;665–7.	Insufficient information on population's willingness/ability to quit
Nebot M, Cabezas C. Does nurse counseling or offer of nicotine gum improve the effectiveness of physician smoking-cessation advice? *Fam Pract Res J* 1992;**12**:263–70.	Inappropriate population, smokers motivated to quit "*… willing to quit*"
New cut-down-then-stop-smoking strategy launched. *Pharm J* 2005;**275**:328.	News piece
New NRT licensing: Changing our advice to patients. *Br J Cardiol* 2005;**12**:434–5.	Discussion paper
Niaura R, Abrams DB, Shadel WG, Rohsenow DJ, Monti PM, Sirota AD, *et al*. Cue exposure treatment for smoking relapse prevention: a controlled clinical trial. *Addiction* 1999;**94**:685–95.	Insufficient information on population's willingness/ability to quit
Niaura R, Goldstein MG, Abrams DB. Matching high- and low-dependence smokers to self-help treatment with or without nicotine replacement. *Prev Med* 1994;**23**:70–7.	Inappropriate population, smokers motivated to quit "*… interested in cessation programme*"
Nicotine replacement therapy is safer. *Prescrire Int* 2001;**10**:163–7.	Review, no consideration of CDTQ
Nides M, Rand C, Dolce J, Murray R, O'Hara P, Voelker H, *et al*. Weight gain as a function of smoking cessation and 2-mg nicotine gum use among middle-aged smokers with mild lung impairment in the first 2 years of the Lung Health Study. *Health Psychol* 1. 1994;**13**:354–61.	Inappropriate population, smokers motivated to quit "*… willingness to participate in a smoking cessation programme*"
Nordstrom BL, Kinnunen T, Utman CH, Garvey AJ. Long-term effects of nicotine gum on weight gain after smoking cessation. *Nicotine Tob Res* 1999;**1**:259–68.	Inappropriate population, smokers motivated to quit, not randomised
Ockene JK, Kristeller J, Goldberg R, Amick TL, Pekow PS, Hosmer D, *et al*. Increasing the efficacy of physician-delivered smoking interventions: a randomized clinical trial. *J Gen Intern Med* 1991;**6**:1–8.	Inappropriate population, smokers motivated to quit "*… those patients interested in using the gum and willing to set a quit date*"
Ockene JK, Kristeller J, Pbert L, Hebert JR, Luippold R, Goldberg RJ, *et al*. The physician-delivered smoking intervention project: can short-term interventions produce long-term effects for a general outpatient population? *Health Psychol* 1994;**13**:278–81.	Same study as Ockene *et al*. (1991).
Page AR, Walters DJ, Schlegel RP, Best JA. Smoking cessation in family practice: the effects of advice and nicotine chewing gum prescription. *Addict Behav* 1986;**11**:443–6.	Insufficient information on population's willingness/ability to quit
Quilez GC, Hernando AL, Rubio DA, Estruch RJ, Fornes Ramis MV. Smoking addiction treatment, with nicotine chewing gum, in primary care. Double-blind study. *Rev Clin Esp* 1993;**192**:157–61.	Inappropriate population, smokers motivated to quit "*people willing to stop*"
Quilez GC, Hernando AL, Rubio DA, Granero FEJ, Vila CMA, Estruch RJ. Double-blind study of the efficacy of nicotine chewing gum for smoking cessation in the primary care setting. *Aten Primaria* 1989;**6**:719–26.	Inappropriate population, smokers motivated to quit

continued

TABLE 56 *Excluded studies and reasons for exclusion (cont'd)*

Study	Reason for exclusion
Reid RD, Pipe A, Dafoe WA. Is telephone counselling a useful addition to physician advice and nicotine replacement therapy in helping patients to stop smoking? A randomized controlled trial. *CMAJ* 1999;**160**:1577–81.	Inappropriate population, smokers motivated to quit "*… interested in quitting within 30 days*"
Riggs RL, Hughes JR, Pillitteri JL. Two behavioral treatments for smoking reduction: a pilot study. *Nicotine Tob Res* 2001;**3**:71–6.	No quit rates reported
Rose JE, Behm FM, Westman EC, Kukovich P. Precessation treatment with nicotine skin patch facilitates smoking cessation. *Nicotine Tob Res* 2006;**8**:89–101.	Not gum or inhalator
Roto P, Ojala A, Sundman K, Jokinen K, Peltomakl R. Nicotine gum and withdrawal from smoking. *Suomen Laararllehtl* 1987;**36**:3445–8.	In Finnish, translation unobtainable
Schneider NG, Olmstead R, Nilsson F, Mody FV, Franzon M, Doan K. Efficacy of a nicotine inhaler in smoking cessation: a double-blind, placebo-controlled trial. *Addiction* 1996;**91**:1293–306.	Insufficient information on population's willingness/ability to quit
Schneider,NG, Jarvik,ME. Nicotine gum vs placebo gum: comparisons of withdrawal symptoms and success rates. *NIDA Res Monogr* 1985;**53**:83–101.	Inappropriate population, smokers motivated to quit
Schneider NG, Olmstead R, Nilsson F, Mody FV, Franzon M, Doan K. Efficacy of nicotine inhaler in smoking cessation: a double blind, placebo-controlled trial. *Addiction* 1997;**92**:630.	Insufficient information on population's willingness/ability to quit
Schuurmans MM, Diacon AH, van Biljon X, Bolliger CT. Effect of pre-treatment with nicotine patch on withdrawal symptoms and abstinence rates in smokers subsequently quitting with the nicotine patch: a randomized controlled trial. *Addiction* 2004;**99**:634.	Not gum or inhalator
Shiffman S, Di Marino ME, Pillitteri JL. The effectiveness of nicotine patch and nicotine lozenge in very heavy smokers. *J Subst Abuse Treat* 2005;**28**:49–55.	Insufficient information on population's willingness/ability to quit
Silagy C, Lancaster T, Stead L, Mant D, Fowler G. Nicotine replacement therapy for smoking cessation. [update of *Cochrane Database Syst Rev* 2002;(4):CD000146; PMID: 12519537].	Systematic review, does not consider CDTQ
Slovinec D'Angelo ME, Reid RD, Hotz S, Irvine J, Segal RJ, Blanchard CM, *et al.* Is stress management training a useful addition to physician advice and nicotine replacement therapy during smoking cessation in women? Results of a randomized trial. *Am J Health Promotion* 2005;**20**:127–34.	Insufficient information on population's willingness/ability to quit
Sutton S, Hallett R. Randomized trial of brief individual treatment for smoking using nicotine chewing gum in a workplace setting. *Am J Public Health* 1987;**77**:1210–11.	Inappropriate population, smokers motivated to quit "*Interested in a stop smoking programme*"
Tonnesen P, Danielsson T. Cutting down smoking then stopping with nicotine replacement therapy: An innovative approach to smoking cessation. *Thorax* 2005;**60**:1136.	Review, not systematic
Tonnesen P, Mikkelsen KL. Smoking cessation with four nicotine replacement regimes in a lung clinic. *Eur Respir J* 2000;**16**:717–22.	Inappropriate population, smokers motivated to quit "*… willing to stop smoking*"
Tonnesen P, Norregaard J, Mikkelsen K, Jorgensen S, Nilsson F. A double-blind trial of a nicotine inhaler for smoking cessation. *JAMA* 1993;**269**:1268–71.	Inappropriate population, smokers motivated to quit "*… motivated to stop completely*"
Tonnesen P. Smoking reduction for smokers not able or motivated to quit? *Respiration* 2002;**69**:475–8.	Review, not systematic
Villa RS, Alvarez ABD, Hermida JRF. Effectiveness of a multicomponent programme to quit smoking with and without nicotine chewing gum. *Psicologia conductual* 1999;**7**:107–11.	Insufficient information on population's willingness/ability to quit

continued

TABLE 56 *Excluded studies and reasons for exclusion (cont'd)*

Study	Reason for exclusion
Wagena EJ, van der Meer RM, Ostelo RJ, Jacobs JE, Van Schayck CP, Wagena EJ, *et al*. The efficacy of smoking cessation strategies in people with chronic obstructive pulmonary disease: results from a systematic review. *Respir Med* 2004;**98**:805–15.	Systematic review, no consideration of CDTQ
West R, Hajek P, Foulds J, Nilsson F, May S, Meadows A, *et al*. A comparison of the abuse liability and dependence potential of nicotine patch, gum, spray and inhaler. *Psychopharmacology* 2000;**149**:198–202.	Inappropriate population, smokers motivated to quit *"… seeking help to stop smoking"*
West R, Shiffman S. Effect of oral nicotine dosing forms on cigarette withdrawal symptoms and craving: a systematic review. *Psychopharmacology* 2001;**155**:115–22.	No quit rates reported
Willemsen MC, Wagena EJ, Van Schayck CP. The efficacy of smoking-cessation methods available in The Netherlands: a systematic review based on Cochrane data. *Ned Tijdschr Geneesk* 2003;**147**:922–7.	Review of reviews does not address CDTQ
Wiseman EJ. Nicotine replacement therapy and smoking reduction as an interim goal. *JAMA* 1998;**279**:194–5.	Opinion piece
Wolfenden L, Wiggers J, Knight J, Campbell E, Rissel C, Kerridge R, *et al*. A programme for reducing smoking in pre-operative surgical patients: randomised controlled trial. *Anaesthesia* 2005;**60**:172–9.	Insufficient information on population's willingness/ability to quit

Appendix 10

Quality of life results reported using the SF-36 instrument

The Wennike study 98-NNCG-014[42] reported study-level SF-36 scores in each domain for successful and unsuccessful smoking reducers and related these to baseline scores. The results are shown in *Tables 57* and *58* below.

TABLE 57 *SF-36 scores reported in study 98-NNCG-014 (successful reducers)*

SF-36 domain		Mean (SD)	SF-36 domain		Mean (SD)
1. Physical functioning	*N*	35	5. Emotional well-being	*N*	38
	Baseline	84.9 (9.8)		Baseline	73.6 (16.5)
	Month 4	92.9 (8.3)		Month 4	74.4 (16.6)
	p	<0.001		*p*	0.041
	N	21		*N*	22
	Baseline	84.8 (8.9)		Baseline	74.5 (15.8)
	Month 12	93.1 (8.3)		Month 12	82.7 (14.3)
	p	0.003		*p*	0.015
	N	15		*N*	15
	Baseline	86.33 (9.15)		Baseline	71.3 (16.55)
	Month 24	90.33 (12.86)		Month 24	77.6 (15.7)
	p	0.213		*p*	0.226
2. Role limitations from physical health	*N*	37	6. Social functioning	*N*	37
	Baseline	74.3 (38.9)		Baseline	77.7 (22.7)
	Month 4	89.9 (27.9)		Month 4	82.8 (22.1)
	p	0.008		*p*	0.09
	N	22		*N*	22
	Baseline	76.1 (37.4)		Baseline	74.3 (24.6)
	Month 12	83 (34.8)		Month 12	83.3 (22.6)
	p	0.56		*p*	0.1
	N	15		*N*	15
	Baseline	80 (38.03)		Baseline	76.8 (21.91)
	Month 24	80 (35.6)		Month 24	83.5 (20.85)
	p	1		*p*	0.375
3. Role limitations from emotional problems	*N*	37	7. Pain	*N*	38
	Baseline	79.3 (32.7)		Baseline	71.8 (27.6)
	Month 4	84.7 (31)		Month 4	77.8 (31.4)
	p	0.054		*p*	0.09
	N	37		*N*	22
	Baseline	75.8 (35.9)		Baseline	74.3 (24.6)
	Month 12	90.9 (25.6)		Month 12	83.3 (22.6)
	p	0.14		*p*	0.10
	N	15		*N*	15
	Baseline	75.6 (34.4)		Baseline	76.83 (21.91)
	Month 24	84.4 (30.5)		Month 24	83.5 (20.85)
	p	0.672		*p*	0.375

continued

TABLE 57 *SF-36 scores reported in study 98-NNCG-014 (successful reducers) (cont'd)*

SF-36 domain		Mean (SD)	SF-36 domain		Mean (SD)
4. Energy/fatigue	*N*	38	8. General health	*N*	38
	Baseline	51.5 (18.2)		Baseline	65 (17)
	Month 4	64.6 (15)		Month 4	78 (16.4)
	p	<0.001		*p*	<0.001
	N	22		*N*	22
	Baseline	52 (18.1)		Baseline	67.3 (17.3)
	Month 12	70 (17.6)		Month 12	78.4 (13.1)
	p	<0.001		*p*	0.011
	N	15		*N*	15
	Baseline	52.7 (18.7)		Baseline	66.67 (19.15)
	Month 24	62.3 (17.9)		Month 24	72.33 (14.38)
	p	0.092		*p*	0.309

TABLE 58 *SF-36 scores reported in study 98-NNCG-014 (unsuccessful reducers)*

SF-36 domain		Mean (SD)	SF-36 domain		Mean (SD)
1. Physical functioning	*N*	169	5. Emotional well-being	*N*	176
	Baseline	84.9 (13.5)		Baseline	77 (15.2)
	Month 4	89.2 (13.8)		Month 4	79.6 (15.6)
	p	<0.001		*p*	0.029
	N	137		*N*	141
	Baseline	85.3 (12)		Baseline	76.7 (15.7)
	Month 12	89.2 (14.1)		Month 12	77.9 (17)
	p	<0.001		*p*	0.11
	N	129		*N*	131
	Baseline	83.6 (16.08)		Baseline	77.01 (15.33)
	Month 24	87.25 (19.67)		Month 24	80.49 (15.45)
	p	<0.001		*p*	0.014
2. Role limitations from physical health	*N*	179	6. Social functioning	*N*	175
	Baseline	83.4 (30.1)		Baseline	83.4 (21.3)
	Month 4	91.2 (23.3)		Month 4	88 (19.6)
	p	0.006		*p*	0.17
	N	142		*N*	140
	Baseline	82.2 (31.9)		Baseline	82.1 (23.1)
	Month 12	89.3 (25.3)		Month 12	86.3 (20.2)
	p	0.012		*p*	0.038
	N	132		*N*	129
	Baseline	79.73 (34.69)		Baseline	82.27 (22.84)
	Month 24	89.02 (27.67)		Month 24	86.92 (20.6)
	p	0.001		*p*	0.023
3. Role limitations from emotional problems	*N*	178	7. Pain	*N*	179
	Baseline	83.5 (29.5)		Baseline	78.1 (21.5)
	Month 4	91 (19.9)		Month 4	82.3 (23.2)
	p	0.037		*p*	0.066
	N	141		*N*	142
	Baseline	81.8 (30.7)		Baseline	78.8 (21.1)
	Month 12	85.8 (29.1)		Month 12	81.5 (24.5)
	p	0.1		*p*	0.095
	N	133		*N*	133
	Baseline	80.2 (32.83)		Baseline	77.93 (21.34)
	Month 24	87.97 (28.23)		Month 24	80.6 (23.55)
	p	0.17		*p*	0.074
4. Energy/fatigue	*N*	180	8. General health	*N*	174
	Baseline	58.2 (18.6)		Baseline	68 (18.7)
	Month 4	64.3 (17.6)		Month 4	74.4 (17.8)
	p	<0.001		*p*	<0.001
	N	141		*N*	138
	Baseline	58.2 (18.3)		Baseline	67.5 (18.5)
	Month 12	63.7 (17.7)		Month 12	67.5 (18.5)
	p	<0.001		*p*	<0.001
	N	131		*N*	128
	Baseline	58.32 (17.97)		Baseline	68.2 (16.95)
	Month 24	63.4 (18.47)		Month 24	73.75 (18)
	p	0.001		*p*	<0.001

The Wood-Baker study 98-NNCG-017[38] reported SF-36 scores for successful and unsuccessful reducers at baseline and after 15 months follow up. The results are shown in *Table 59*.

TABLE 59 *SF-36 scores reported in study 98-NNCG-017*

	Unsuccessful reducers of smoking					
		Baseline		15 months		
SF-36 domain	***N***	**Mean**	**SD**	**Mean**	**SD**	***p*-Value**
Physical functioning	184	72.2	23.5	78.2	22.7	0.001
Role limitations from physical health	183	74.9	34.9	80.3	33.3	0.024
Role limitations from emotional problems	184	72.5	36.1	75.9	37.3	0.417
Energy/fatigue	184	52.8	18.8	57.2	20.3	0.001
Emotional well-being	184	71.4	16.7	73.1	18.1	0.044
Social functioning	184	81.4	22.7	81.3	24.3	0.902
Pain	184	77.1	24.4	76.9	25.2	0.801
General health	183	58.3	20.6	62	20.6	0.011
	Successful reducers of smoking					
		Baseline		**15 months**		
	N	**Mean**	**SD**	**Mean**	**SD**	***p*-Value**
Physical functioning	5	64	25.3	80	10	0.125
Role limitations from physical health	5	80	32.6	90	22.4	0.75
Role limitations from emotional problems	5	80	29.8	86.7	29.8	1
Energy/fatigue	5	57	14.4	65	14.1	0.25
Emotional well-being	5	66.4	20.1	76.8	19.1	0.063
Social functioning	5	80	19	75	17.7	1
Pain	5	61	20.7	78	16.6	0.188
General health	5	55	15.4	70	10	0.063

The Rennard study 98-NNIN-027 SRI[36] reported change in SF-36 scores from baseline to 15 months for successful reducers. The results are shown in *Table 60*.

TABLE 60 *Change from baseline: SF-36 scores for successful reducers reported in study 98-NNIN-027*

		Baseline		Change from baseline at 15 months		
SF-36 domain	***N***	**Mean**	**SD**	**Mean**	**SD**	***p*-Value**
Physical functioning	59	83.3	15.6	–1.1	15.2	0.908
Role limitations from physical health	58	89.2	17.6	–3.9	34	0.427
Role limitations from emotional problems	58	86.8	26.4	2.3	37.4	0.745
Energy/fatigue	58	58.7	18.2	0.6	21.2	0.619
Emotional well-being	59	76.7	19.4	0.9	18.8	0.86
Social functioning	57	91.4	15	–1.1	22.9	0.678
Pain	58	84.2	16.2	–1.5	22.2	0.672
General health	59	69.9	19.1	–0.2	16.9	0.831

The Bolliger study 96-NNIN 016[40] reported SF-36 score changes from baseline for successful reducers. The results are shown in *Table 61*.

TABLE 61 *Change from baseline: SF-36 scores for successful reducers reported in study 96-NNIN 016*

SF-36 domain		Mean (SD)[a]	SF-36 domain		Mean (SD)[a]
1. Physical functioning	*N*	122	5. Emotional well-being	*N*	122
	Baseline	84.7 (13)		Baseline	69.4 (16.7)
	Change by month 4	6.2 (12.7)		Change by month 4	4 (16.1)
	p	<0.001		*p*	0.007
	N	113		*N*	113
	Baseline	85.2 (12.9)		Baseline	69.8 (16.0)
	Change by month 6	1.9 (24.4)		Change by month 6	2.5 (16.9)
	p	<0.001		*p*	0.005
	N	96		*N*	96
	Baseline	85.1 (12.8)		Baseline	69.8 (15.4)
	Change by month 12	6 (12.6)		Change by month 12	4.1 (16.97)
	p	<0.001		*p*	0.003
	N	82			
	Baseline	84.6 (13.1)			
	Change by month 24	7 (13.8)			
	p	<0.001			
2. Role limitations from physical health	*N*	122	6. Social functioning	*N*	122
	Baseline	89.8 (26.7)		Baseline	85.2 (18.8)
	Change by month 4	2.7 (30.3)		Change by month 4	1.9 (23.4)
	p	0.336		*p*	0.281
	N	113		*N*	113
	Baseline	90.5 (267.4)		Baseline	86.5 (17.3)
	Change by month 6	–1.3 (37.5)		Change by month 6	–1.5 (24.5)
	p	0.684		*p*	0.626
	N	96		*N*	96
	Baseline	89.3 (27.6)		Baseline	87.1 (17.2)
	Change by month 12	–3.9 (35.8)		Change by month 12	–6.3 (30.2)
	p	0.3		*p*	0.035
3. Role limitations from emotional problems	*N*	122	7. Pain	*N*	122
	Baseline	81.4 (34.6)		Baseline	85.7 (21.3)
	Change by month 4	7.9 (32.7)		Change by month 4	–0.7 (22.2)
	p	0.007		*p*	0.934
	N	113		*N*	113
	Baseline	82.6 (33.7)		Baseline	86.2 (20.9)
	Change by month 6	1.2 (37.5)		Change by month 6	3.5 (21.2)
	p	0.651		*p*	0.044
	N	96		*N*	96
	Baseline	83.7 (32.8)		Baseline	86 (21.9)
	Change by month 12	1.4 (38.7)		Change by month 12	–6.4 (30.1)
	p	0.805		*p*	0.027
4. Energy/fatigue	*N*	122	8. General health	*N*	122
	Baseline	59.3 (15.8)		Baseline	68.2 (15.3)
	Change by month 4	3.0 (16.3)		Change by month 4	6.3 (15.4)
	p	0.014		*p*	<0.001
	N	113		*N*	113
	Baseline	59.5 (15.3)		Baseline	68.43 (15.13)
	Change by month 6	2.2 (16.4)		Change by month 6	6.9 (16.2)
	p	0.075		*p*	<0.001

continued

TABLE 61 *Change from baseline: SF-36 scores for successful reducers reported in (study 96-NNIN 016) (cont'd)*

SF-36 domain	Mean (SD)[a]	SF-36 domain	Mean (SD)[a]
N	96	*N*	96
Baseline	58.9 (15.3)	Baseline	67.8 (15.3)
Change by month 12	3.7 (19.2)	Change by month 12	6.5 (18)
p	0.034	*p*	<0.001

[a] Except for physical functioning, results at 24 months were unclear with regard to *N* and have not been included.

The Haustein study 980-CHC-9021-0013[37] reported change in SF-36 scores baseline to 12 months for successful reducers. The results are given in *Table 62*.

TABLE 62 *Change from baseline: SF-36 score for successful reducers reported in study 980-CHC-9021-0013*

		Baseline		Change from baseline at 12 months		
SF-36 domain	***N***	**Mean**	**SD**	**Mean**	**SD**	***p*-Value**
Physical functioning	73	84.2	15.3	6.6	12.4	<0.001
Role limitations from physical health	72	78.5	35.7	8.0	40	0.112
Role limitations from emotional problems	73	82.2	30.0	5.5	36	0.276
Energy/fatigue	73	61.2	18.8	8.1	18.2	<0.001
Emotional well-being	73	71.9	18.0	4.0	17.7	0.05
Social functioning	73	85.4	16.8	2.6	19.5	0.243
Pain	73	80.5	23.5	5.6	23.9	0.006
General health	74	64.2	16.5	9.0	16.9	<0.001

Appendix 11

Attendance at scheduled clinic visits

Trials mostly involved baseline, 6-week and 4-, 6-, 9- and 12-month visits to a clinic. However, it is clear from the amount of missing data in trial reports that many patients missed many visits. Attendance information was extracted from six trial reports that provided these data. The results are summarised in *Table 63*.

TABLE 63 *Attendance at scheduled visits detailed in trial reports of RCTs*

Study[a]	*N* (active nicotine)	No. of time points	No. of visits	Possible no. of visits	Probability of visit	LCI	UCI
Wennike	205	8	909	1640	0.55	0.53	0.58
Batra	184	8	945	1472	0.64	0.62	0.67
Haustein	97	7	381	679	0.56	0.52	0.60
Rennard	215	8	1080	1720	0.63	0.60	0.65
Wood-Baker	218	8	824	1744	0.47	0.45	0.50
Bolliger	200	9	1575	1800	0.88	0.86	0.89
Pooled probability of visit	1119	48	5714	9055	0.63	0.45	0.79

[a] Data from unpublished study reports where available. Batra = study 980-CHC-1013-028,[44] Bolliger = study 96-NNIN-016,[40] Haustein = study 980-CHC-9021-0013,[37] Rennard = study 98-NNIN-027,[36] Wennike = study 98-NNCG-014,[42] Wood-Baker = study 98-NNCG-017.[38] The results indicate that on average participants in the NRT arm of the trials attend approximately 63% of scheduled clinic visits.

Appendix 12

Costs associated with different NRT delivery options

The costs associated with CDTQ and abrupt quit options are summarised in the following tables.

CDTQ brief advice plus prescription only (*Table 64*)

Standard package: initial visit (advice) plus 10 monthly prescriptions. Effectiveness was derived from trials with 8–10 additional visits to the clinic after baseline; the package assumes 10 visits since this allows for the motivational influence on effectiveness results derived from repeat clinic visits by participants.

TABLE 64 *Costs: CDTQ brief advice plus prescription only*

	Number/patient	Unit cost (£)	Answer	Total
GP visits/prescription issues				
Initial visit[a]	1	6.72	6.72	
Ten scheduled scripts[b]	6.3[c]	2.24[d]	14.112	
				20.832
Drug provision				
NRT prescriptions issued[e]				
Initial gum	0.72 × 0.63 = 0.4536	3 × 3.62 = 10.86[f]	4.926	
Initial inhalator	0.28 × 0.63 = 0.1764	24.93[g]	4.397652	
Follow-up gum	0.72 × 9 × 0.63 = 4.0824[h]	2 × 3.62 =7.24[f]	29.556576	
Follow-up inhaler	0.28 × 9 × 0.63= 1.5876[h]	24.93[g]	39.576375	
Pharmacy prescription charge	6.3	0.90[i]	5.67	
				84.1266
				104.9586

[a] Visit lasts 3 minutes for advice; GP cost £2.24/minute.[59]
[b] A total of 10 scheduled scripts for treatment package.
[c] Average uptake of scheduled prescriptions (based on visit attendance reported in six RCTs of 63%): 0.63 X 10 = 6.3.
[d] Each script takes 1 minute of GP time at a cost of £2.24/minute.[59]
[e] Assume average uptake of scheduled prescriptions = 63%. Proportion of prescriptions for gum = 0.72, proportion for inhalator = 0.28 (IPSOS, p. 59[34]).
[f] Average use of gum from trial reports of five RCTs was 2.15 units/day; on average 1 month requires about 65 units with use likely higher early in treatment. We assume 3 packs of 30 units are required at first visit and 2 packs at subsequent attended follow-up visits. BNF 2006 cost of 2- and 4-mg packs of 30 units is £3.25 and £3.99, respectively; assuming 50% use of each, cost of 30 unit pack = £3.62.
[g] Average inhalator use in trials was 2.19 units/day; on average about 60 units are required per month. Inhalator available in packs of 6 (£3.39) and 42 (£11.37), BNF 2006; assume monthly use satisfied by one 42-pack + four 6-pack at cost = £11.37 + £13.56 = £24.93.
[h] 9 remaining visits after initial visit.
[i] Prescribing Pricing Authority (PPA) (http://www.ppa.org.uk/index.htm) link (http://www.ppa.org.uk/edt/October_2006_v3/mindex.htm): Part IIIA – Professional Fees (Pharmacy Contractors).

CDTQ counselling (*Table 65*)

Standard package assumes baseline visit + 10 further visits approximately 1 month apart.

TABLE 65 *Costs: CDTQ counselling*

	Number/patient	Unit cost (£)	Answer	Total	
Initial visit[a]	1	6.72	6.72		
Ten scheduled scripts[b]	6.3[c]	2.24[d]	14.11		
				20.83	
Counselling					
Individual counselling	6.3	6.75[a]	42.53		
Group counselling	0.63[b]	27.00[c]	17.01		
Biochemical validation of smoking status	6.3	1	6.30		
				Individual	69.66
				Group	44.14
Drug provision					
NRT prescriptions issued[d]					
Initial visit gum	$0.72 \times 0.63 = 0.4536$[d]	10.86[e]	4.93		
Initial visit inhalator	$0.28 \times 0.63 = 0.1764$[f]	24.93[g]	4.40		
Follow-up visits gum	$0.72 \times 9 \times 0.63 = 4.0824$[h]	7.24[e]	29.56		
Follow-up visits inhalator	$0.28 \times 9 \times 0.63 = 1.5876$[h]	24.93[g]	39.58		
Pharmacy prescription charge	6.3	0.90[i]	5.67		
				84.1266	
				Individual	153.79
				Group	128.27

[a] Initial GP visit lasts 3 minutes cost £2.24/minute.[59]
[b] Ten patients per session.
[c] Group counselling lasts 1 hour;[6] nurse cost £0.45/minute.[59]
[d] Assume 63% of scheduled scripts are taken up (based on visit attendance reported in six RCTs of 63%).
[e] Average use of gum from trial reports of five RCTs was 2.15 units/day; on average 1 month requires about 65 units with use likely higher early in treatment. We assume 3 packs of 30 units are required at first visit and 2 packs at subsequent attended follow up visits. BNF 2006 cost of 2- and 4-mg packs of 30 units is £3.25 and £3.99, respectively; assuming 50% use of each, cost of 30 unit pack = £3.62.
[f] Average inhalator use in trials was 2.19 units/day; on average about 60 units are required per month.
[g] Inhalator available in packs of 6 (£3.39) and 42 (£11.37), BNF 2006; assume monthly use satisfied by one 42-pack + four 6-pack at cost = £11.37 + £13.56 = £24.93.
[h] 9 remaining visits after initial visit.
[i] Prescribing Pricing Authority (PPA) (http://www.ppa.org.uk/index.htm) link (http://www.ppa.org.uk/edt/October_2006_v3/mindex.htm): Part IIIA – Professional Fees (Pharmacy Contractors).

Abrupt quit; advice plus prescription only (*Table 66*)

Standard package: baseline visit plus six prescriptions spread over approximately 12 weeks. Prescriptions issued every 2 weeks.

TABLE 66 *Costs: abrupt quit; advice plus prescription only*

	Number/patient	Unit cost (£)	Cost (£)
GP advice/prescriptions			
Initial visit (advice)	1	6.72[a]	6.72
6 prescriptions	2.34[b]	2.24[b]	5.24
Drug provision			
NRT prescriptions[c]			
Patch	0.555 × 0.39 × 6 = 1.2987	18.79[d]	24.40
Gum	0.702	13.48[e]	9.46
Inhalator	0.27378	22.74[f]	6.23
Spray	0.06552	10.99[g]	0.72
Pharmacy prescription charge	0.39 × 6 =2.34	0.90[h]	2.11
Total cost			54.88

[a] Initial visit lasts 3 minutes;[60] GP cost £2.24/minute.[59]
[b] Overall uptake of scheduled prescriptions was estimated as 39% (expert opinion); each prescription takes 1 minute of GP time at cost £2.24/minute.[59]
[c] Assume average uptake of scheduled prescriptions across treatment package of six prescriptions is 39%, which was estimated from adherence and concordance of treatment (expert opinion); proportion of prescriptions for patch, gum, inhalator, spray = 0.555, 0.30, 0.117, 0.028, respectively (IPSOS, p. 59,[34] choice of NRT aids). Assume manufacturer's recommended dose.
[d] Assume 7 patches per week; prescription for 14-patch pack at £18.79 (BNF 52, 2006).
[e] Assume equal use of 2- and 4-mg units and 72 units per week; prescription for 2 weeks from one pack of 105 units and one pack of 30 units at £9.86 and £3.62, respectively (BNF 52, 2006).
[f] Assume 42 inhalator units per week; prescription for 2 weeks from two 42-unit inhalator packs at £11.37 (BNF 52, 2006).
[g] Based on 100 sprays per week; prescription for 2 weeks from one 200-spray bottle costing £10.99.
[h] Prescribing Pricing Authority (PPA). (http://www.ppa.org.uk/index.htm) link (http://www.ppa.org.uk/edt/October_2006_v3/mindex.htm): Part IIIA – Professional Fees (Pharmacy Contractors).

Abrupt quit; counselling (*Table 67*)

Packages: initial visit (advice) plus six further visits (advice and prescription) spread over approximately 3 months. Two formats: individual counselling and group counselling.

TABLE 67 *Costs: abrupt quit; counselling*

	Number/patient	Unit cost (£)	Cost (£)
GP initial visit			
Individual counselling	1	6.72[a]	6.72
Group counselling	1	6.72[a]	6.72
GP time + Nurse visits			
GP	0.62 × 6 = 3.72[b]	2.24[b]	8.33
Nurse (individual counselling)	0.62 × 6 = 3.72	6.75[c]	25.11
Nurse (group counselling)	0.062 × 6 = 0.372	27.00[d]	10.04
Biochemical validation of smoking status	0.62 × 6 = 3.72[c]	1.0[e]	3.72
Drug provision			
NRT prescriptions[f]			
Patch	0.555 × 0.62 × 6 = 2.0646	18.79[g]	38.79
Gum	0.30 × 0.62 × 6 = 1.116	13.48[h]	15.04
Inhalator	0.117 × 0.62 × 6 = 0.43524	22.74[i]	9.90
Spray	0.028 × 0.62 × 6 = 0.10416	10.99[j]	1.14
Total cost (individual counselling)			112.11
Total cost (group counselling)			97.04

[a] First visit lasts 3 minutes; GP cost of £2.24/minute.[59]
[b] Assumes uptake of scheduled prescriptions is 62% (see *c*); issue of prescription takes 1 minute of GP time at £2.24/minute.
[c] Individual counselling lasts 15 minutes (expert opinion); nurse cost £0.45/minute;[59] attendance at scheduled visits = 62%, which was estimated from adherence and concordance of treatment (expert opinion).
[d] Scheduled for 10 patients per session; assume 62% attendance. Assume all sessions (6) are run even when attendance is <100%. Group counselling lasts 1 hour (expert opinion); nurse cost £0.45/minute.[59]
[e] Stapleton and colleagues.[60]
[f] Assume average uptake of scheduled prescriptions across treatment package of six prescriptions is 62%; proportion of prescriptions for patch, gum, inhalator, spray = 0.555, 0.30, 0.117, 0.028, respectively (IPSOS, p. 59, choice of NRT aids). Assume manufacturer's recommended dose.
[g] Assume 7 patches per week; prescription for 14-patch pack at £18.79 (BNF 52, 2006).
[h] Assume equal use of 2- and 4-mg units and 72 units per week; prescription for 2 weeks from one pack of 105 units and one pack of 30 units at £9.86 and £3.62, respectively (BNF 52, 2006).
[i] Assume 42 inhaler units per week; prescription for two weeks from two 42-unit inhalator packs at £11.37 (BNF 52, 2006).
[j] Based on 100 sprays per week; prescription for 2 weeks from one 200-spray bottle costing £10.99.

Appendix 13

QALY gained by lifetime quit from smoking

Life-years gained (LYGs) from lifetime quit

To estimate LYGs from quitting, long-term follow-up data are needed of comparable populations that have never smoked, have persistently smoked and have quit smoking at various ages; from these data, life spans can be calculated for each population.

This information is provided in the recent update of the unique study by Doll and colleagues of British male doctors recruited in 1950.[49]

Based on analysis of 50 years of follow-up data, the main conclusions from this study relevant to life gained from quitting smoking were as follows:

1. Previous estimates of life-years lost through 'lifetime smoking' were underestimates.
2. LYGs from a lifetime quit are greater than in previous estimates.
3. Life-years lost by the persistent smoker are approximately equal to them foregoing the improvements in life span that have accrued to lifetime non-smokers through time (i.e. during the 20th century).
4. Quitting allows recovery of a proportion of those life-years foregone due to continued smoking; the absolute LYG and the proportion that is recovered by quitting depend on age at quitting (LYG 10, 9, 6 and 3 years at quit ages <35, 35–45, 45–54, 55–64 years), respectively.

The study was considered the most appropriate data source for this report because: it represents the best and most relevant cohort study available (in terms of follow-up and numbers); all-cause mortality was reported; it was conducted in a UK population; the long follow-up allowed recording of smoking habits over time and this continuum means that past/today/future inferences are more likely to be valid than if cohort data from elsewhere are extrapolated to present and future cohorts in the UK.

The applicability of this study is limited by the following considerations: (1) British doctors represent a different socio-economic group to the generality of present smokers and non-smokers; (2) it is known that socio-economic groupings are linked to life expectancy; (3) cigarettes smoked by earlier generations were probably somewhat more hazardous than those of today (greater tar content, absence of filters); (4) people recruited in 1950 will differ from any cohort recruited now or in the future. However, these are problems that beset any study that attempts an estimate of LYGs from quitting smoking. The alternative approach of modelling based on death rates and life expectancy in different diseases and the probabilities of smokers and non-smokers and quitters getting these diseases, as conducted in some studies, was judged less satisfactory than the empirical data collected over 50 years of follow-up.

Using the estimates from Doll and colleagues[49] for the purposes of economic modelling required the following steps: (1) determining LYG depending on age at quitting; (2) correction of the LYG from quitting at different ages to allow for lack of socio-economic matching between British male doctors and the present population of smokers; (3) conversion of LYG to QALY gained; this was made up from two components: (a) the QALY gain due to the small improvement in utility associated with abstinence during the years of life common to both the abstainer and smoker and (b) the QALY gain from extended life span due to quitting; (4) the QALY gain was then discounted. These steps are described in detail below.

Life-years gained by quitting smoking at different ages

LYGs in terms of extended life expectancy from a lifetime quit from smoking beginning at different ages is shown in *Table 68*.

Effect of socio-economic group on life expectancy

The estimate of LYG from lifetime quitting required adjustment to allow for socio-economic mismatch between medical doctors and the present population of smokers.

TABLE 68 *Life-years gained by lifetime quit from smoking due to extended life span*

Age at quitting (years)	LYG[a]	LYG corrected for socio-economic mismatch[b]	QALY[c]
<35	10	8	6.04
35–45	9	7	5.285
45–54	6	4	3.02
55–64	3	1	0.755

[a] From Doll and colleagues.[49]
[b] 2 years subtracted from preceding column, see section. 'Effect of socio-economic group on life expectancy' (p. 125).
[c] Assumes utility of 0.755.

In this correction, it was assumed that the LYGs would be greater for those socio-economic groups with the greatest life expectancy reported for the UK population.[61] According to the IPSOS survey,[34] smokers can be split by socio-economic class into two groups, here termed Group I and Group II. Group I contributes 42% smokers representing socio-economic classes A, B and C1 and Group II 58% of smokers representing socio-economic classes C2, D and E. National statistics (1997–2001) report average life expectancy for men in classes A, B and C1 to be 79.4, 77.8, and 76.8 years and for women to be 82.2, 81.7 and 81.3 year, respectively.[61] For classes C2, D and E, the corresponding figures for men and women are reported to be 74.6, 73.3 and 71.0 years and 79.3, 78.6 and 77.6 years, respectively. Using the assumption that men and women are equally represented in each social group, the average life expectancy for a population like that of current smokers can be calculated from the data as follows:

Contribution men in Group I: $0.25 \times 0.42 \times [(79.4 + 77.8 + 76.8)/3] = 16.38$ years
Contribution women in Group I: $0.25 \times 0.42 \times [(82.2 + 81.7 + 81.3)/3] = 17.16$ years
Contribution men in Group II: $0.25 \times 0.58 \times [(74.6 + 73.3 + 71.0)/3] = 21.16$ years
Contribution women in Group II: $0.25 \times 0.58 \times [(79.3 + 78.6 + 77.6)/3] = 22.74$ years
Total = **77.47** years

British doctors are assumed to belong to social class A. Assuming equal numbers of men and women, their life expectancy based on National Statistics[61] is 80.8 years.

The difference in life expectancy between British doctors and present-day smokers is then 80.8 – 77.47 = 3.33 years.

If it is assumed that about 40% of this difference is actually due to heavier smoking amongst social classes other than socio-economic class A, then on average 0.6 × 3.33 years = 2 years difference can be attributed to socio-economic class factors independent of smoking. The burden of this adjustment is likely to fall least heavily on good survivors, that is, smokers who quit late in life; however, for simplicity, this average has been applied across all age groups. The data are shown in *Table 68*.

Total QALYs gained by quitting

QALYs gained through extended life expectancy were calculated based on the assumption that the years of life gained occur at the end of life and a population average utility of 0.755 for >65 years of age.[62] The data are shown in *Table 68*.

In addition, QALYs are gained from the slightly improved utility associated with abstinence that accrues during the years of life common to smoker and abstainer (i.e. up to the time extended life expectancy starts for a quitter). This will be greater the earlier quitting takes place. In this report, differences in utility between smokers and abstainers were based on those in Fiscella and Franks[63] taken from the American Cancer Society Cancer Prevention Study II and are shown in *Table 69*. Total QALYs gained were obtained by adding extended life expectancy gain to gain from years that are common to both abstainers and smokers that depend on better utility in abstinence relative to smoking.

Calculating discounted QALY gain

Discounting the total QALY gain is required. If a constant QoL gain Q applies from time U to V years after the discounting point, then the discounted QALY gain is given by

$$\int_u^v Q e^{-\rho t}\, dt \quad \frac{Q}{\rho} \left(e^{-\rho U} - e^{-\rho V}\right)$$

TABLE 69 *Total QALYs gained by lifetime abstinence*

Age at quitting (years)	Decades to age 70	Mean difference in utility (smokers vs non-smokers) by age band	QALYs gained by abstinence to the age 70	QALY from extended life span[a]	Total QALYs gained by abstinence
<35	4	0.0325	2.4[b]	6.04	8.44
35–45	3	0.0625	2.075	5.285	7.36
45–54	2	0.075	1.45	3.02	4.47
55–64	1	0.07	0.7	0.755	1.455

[a] See *Table 68*.
[b] (10 years at 0.0325 utility) + (10 years at 0.0625 utility) + (10 years at 0.075 utility) + (10 years at 0.07 utility) = 2.4 QALYs.

For discounting at 3.5% per year, we take $\rho = \ln(1.035)$. Applying this to the total QALY gain in *Table 69* gives the values shown in *Table 14*.

Although the equation used is only an approximation, the effect of using a variety of age groups is to produce a sensitivity analysis across a wide range of conversion factors from successful quit attempts to QALYs gained.

Appendix 14

Smokers' pathways and proportions of smokers who attempt to quit

There is uncertainty about the pathways that smokers will follow with regard to quitting. Two recent surveys provide relevant information: IPSOS[34] and ONS 2005,[1] an update of ONS 2004. Below, these surveys are used to estimate the likely proportions of smokers who will attempt to quit over 12 months and the quit method used. A time horizon of 12 months is used because this is approximately the duration of a CDTQ attempt and because most survey data refer to this time span.

Proportion of current smokers who will attempt a quit in the next 12 months

Based on survey data of current smokers summarised in *Table 70*, we assume 49% of current smokers will attempt to stop smoking in the next 12 months.

TABLE 70 *Proportions of smokers making quit attempts reported in recent surveys*

Survey	Past year attempted (%)	Next year 'intended' attempt (%)
IPSOS	–	47[a]
ONS 2005	49[b]	53[c]

[a] Page 108 in the survey: intend to change smoking habit.
[b] Table 3.6 in the survey (153/313).
[c] Table 3.10 in the survey.

Proportion who attempt stopping without NRT

The IPSOS survey states that 58% of those intending to reduce or quit in next 12 months will use "willpower only" and 24% some form of NRT; of the rest some don't know and some intend to use some other intervention (p. 148 of the IPSOS report[34]). As no information was available on this latter proportion, it was assumed that 58/(58 + 24) follow a 'non-NRT' route (i.e. 70.7%).

ONS 2005[1] states that 49% of current smokers attempted to stop in last 12 months and that 46% (i.e. 94% of the attempters) "sought help/advice" to do so (see Tables 3.6 and 4.24 in the ONS report[1]). However, the proportion of the 46% who proceeded without NRT is not stated.

Proportions using different modes of NRT support in CDTQ and abrupt quit pathways

The best data are from ONS 2005[1] and are summarised in *Table 71*. It was assumed that these proportions apply irrespective of type of quitting attempt (abrupt quit or CDTQ).

TABLE 71 *Proportion of smokers using different modes of NRT support*

Sources of help/advice (mode of NRT support used)	ONS 2005 data[a] (%)	Proportion
Bought non-prescription NRT (OTC)	11	0.3928
Received prescription NRT	9	0.3214
Referred or self-referred (use smokers clinic[b])	8	0.2857

[a] Location in the ONS report of the information quoted above is Table 4.25, which is an update of Table 4.27 of the 2004 ONS survey.
[b] Assumed NRT was recommended and used.

Appendix 15

Economic analysis results; full analysis (alternative case)

This appendix contains detailed results for the full analysis alternative case (see the section 'Full analysis – alternative case', p. 47).

For Option 1 (CDTQ available OTC only), CDTQ always dominates the alternative. The different cases are shown in *Tables 72–75*.

TABLE 72 *CDTQ OTC only versus no quit or any NRT (individual counselling)*

% from abrupt quit	Difference in cost	Difference in success rate
0	0.00	0.0155
25	–12.52	0.0116
50	–25.04	0.0078
75	–37.56	0.0039
100	–50.07	0.0000

TABLE 73 *CDTQ OTC only versus no quit or any NRT (group counselling)*

% from abrupt quit	Difference in cost	Difference in success rate
0	0.00	0.0155
25	–11.43	0.0116
50	–22.85	0.0078
75	–34.28	0.0039
100	–45.70	0.0000

TABLE 74 *CDTQ OTC only versus no quit or any quit (individual counselling)*

% from abrupt quit	Difference in cost	Difference in success rate
0	0.00	0.0155
25	–3.67	0.0116
50	–7.34	0.0078
75	–11.00	0.0039
100	–14.67	0.0000

TABLE 75 *CDTQ OTC only versus no quit or any quit (group counselling)*

% from abrupt quit	Difference in cost	Difference in success rate
0	0.00	0.0155
25	–3.35	0.0116
50	–6.70	0.0078
75	–10.04	0.0039
100	–13.39	0.0000

For the other three options, there is a low ICER unless the percentage from abrupt quit is very high. Details for Option 2 (CDTQ available OTC or prescription only) are given in *Tables 76–79*, Option 3 (CDTQ available OTC or counselling) in *Tables 80–83* and Option 4 (full range of CDTQ available) in *Tables 84–87*.

TABLE 76 *CDTQ NRT only versus no quit or any NRT (individual counselling)*

% from abrupt quit	Difference in cost	Difference in success rate	ICER (£/quit)	ICER (£/QALY) for age group			
				<35 years	35–44 years	45–54 years	55–64 years
0	41.98	0.0148	2841	1280	1101	1327	2869
25	29.47	0.0111	2658	1197	1030	1242	2685
50	16.95	0.0074	2293	1033	889	1072	2316
75	4.43	0.0037	1199	540	465	560	1211
100	–8.09	0.0000			ICER undefined		

TABLE 77 *CDTQ NRT only versus no quit or any NRT (group counselling)*

% from abrupt quit	Difference in cost	Difference in success rate	ICER (£/quit)	ICER (£/QALY) for age group			
				<35 years	35–44 years	45–54 years	55–64 years
0	41.98	0.0148	2841	1280	1101	1327	2869
25	30.56	0.0111	2757	1242	1068	1288	2785
50	19.13	0.0074	2589	1166	1003	1210	2615
75	7.71	0.0037	2086	939	808	975	2107
100	–3.72	0.0000			ICER undefined		

TABLE 78 *CDTQ NRT only versus no quit or any quit (individual counselling)*

% from abrupt quit	Difference in cost	Difference in success rate	ICER (£/quit)	ICER (£/QALY) for age group			
				<35 years	35–44 years	45–54 years	55–64 years
0	41.98	0.0148	2841	1280	1101	1327	2869
25	38.32	0.0111	3457	1557	1340	1615	3491
50	34.65	0.0074	4689	2112	1817	2191	4736
75	30.98	0.0037	8384	3777	3250	3918	8469
100	27.31	0.0000			ICER undefined		

TABLE 79 *CDTQ NRT only versus no quit or any quit (group counselling)*

% from abrupt quit	Difference in cost	Difference in success rate	ICER (£/quit)	ICER (£/QALY) for age group			
				<35 years	35–44 years	45–54 years	55–64 years
0	41.98	0.0148	2841	1280	1101	1327	2869
25	38.64	0.0111	3485	1570	1351	1629	3521
50	35.29	0.0074	4775	2151	1851	2231	4823
75	31.94	0.0037	8644	3894	3351	4039	8732
100	28.59	0.0000			ICER undefined		

TABLE 80 *CDTQ OTC or counselling versus no quit or any NRT (individual counselling)*

% from abrupt quit	Difference in cost	Difference in success rate	ICER (£/quit)	ICER (£/QALY) for age group			
				<35 years	35–44 years	45–54 years	55–64 years
0	61.52	0.0242	2540	1144	984	1187	2566
25	49.00	0.0182	2697	1215	1045	1260	2725
50	36.48	0.0121	3012	1357	1168	1408	3043
75	23.96	0.0061	3957	1783	1534	1849	3997
100	11.44	0.0000			ICER undefined		

TABLE 81 *CDTQ OTC or counselling versus no quit or any NRT (group counselling)*

% from abrupt quit	Difference in cost	Difference in success rate	ICER (£/quit)	ICER (£/QALY) for age group			
				<35 years	35–44 years	45–54 years	55–64 years
0	51.31	0.0242	2118	954	821	990	2140
25	39.88	0.0182	2196	989	851	1026	2218
50	28.46	0.0121	2350	1058	911	1098	2374
75	17.03	0.0061	2813	1267	1090	1314	2841
100	5.60	0.0000			ICER undefined		

TABLE 82 *CDTQ OTC or counselling versus no quit or any quit (individual counselling)*

% from abrupt quit	Difference in cost	Difference in success rate	ICER (£/quit)	ICER (£/QALY) for age group			
				<35 years	35–44 years	45–54 years	55–64 years
0	61.52	0.0242	2540	1144	984	1187	2566
25	57.85	0.0182	3185	1435	1234	1488	3217
50	54.18	0.0121	4474	2015	1734	2091	4519
75	50.51	0.0061	8342	3758	3233	3898	8427
100	46.84	0.0000			ICER undefined		

TABLE 83 *CDTQ OTC or counselling versus no quit or any quit (group counselling)*

% from abrupt quit	Difference in cost	Difference in success rate	ICER (£/quit)	ICER (£/QALY) for age group			
				<35 years	35–44 years	45–54 years	55–64 years
0	51.31	0.0242	2118	954	821	990	2140
25	47.96	0.0182	2640	1189	1023	1234	2667
50	44.61	0.0121	3684	1659	1428	1721	3721
75	41.26	0.0061	6815	3070	2641	3185	6884
100	37.92	0.0000			ICER undefined		

TABLE 84 *CDTQ full range versus no quit or any NRT (individual counselling)*

% from abrupt quit	Difference in cost	Difference in success rate	ICER (£/quit)	ICER (£/QALY) for age group			
				<35 years	35–44 years	45–54 years	55–64 years
0	62.25	0.0193	3222	1451	1249	1506	3254
25	49.73	0.0145	3432	1546	1330	1604	3467
50	37.21	0.0097	3852	1735	1493	1800	3891
75	24.69	0.0048	5112	2303	1981	2389	5164
100	12.17	0.0000			ICER undefined		

TABLE 85 *CDTQ full range versus no quit or any NRT (group counselling)*

% from abrupt quit	Difference in cost	Difference in success rate	ICER (£/quit)	ICER (£/QALY) for age group			
				<35 years	35–44 years	45–54 years	55–64 years
0	57.14	0.0193	2958	1332	1146	1382	2988
25	45.72	0.0145	3155	1421	1223	1474	3187
50	34.29	0.0097	3550	1599	1376	1659	3586
75	22.86	0.0048	4734	2132	1835	2212	4782
100	11.44	0.0000			ICER undefined		

TABLE 86 *CDTQ full range versus no quit or any quit (individual counselling)*

% from abrupt quit	Difference in cost	Difference in success rate	ICER (£/quit)	ICER (£/QALY) for age group			
				<35 years	35–44 years	45–54 years	55–64 years
0	62.25	0.0193	3,222	1,451	1,249	1,506	3,254
25	58.58	0.0145	4,043	1,821	1,567	1,889	4,083
50	54.91	0.0097	5,684	2,560	2,203	2,656	5,742
75	51.24	0.0048	10,609	4,779	4,112	4,958	10,716
100	47.57	0.0000			ICER undefined		

TABLE 87 *CDTQ full range versus no quit or any quit (group counselling)*

% from abrupt quit	Difference in cost	Difference in success rate	ICER (£/quit)	ICER (£/QALY) for age group			
				<35 years	35–44 years	45–54 years	55–64 years
0	57.14	0.0193	2958	1332	1146	1382	2988
25	53.79	0.0145	3713	1672	1439	1735	3750
50	50.45	0.0097	5222	2352	2024	2440	5275
75	47.10	0.0048	9751	4392	3780	4557	9850
100	43.75	0.0000			ICER undefined		

Appendix 16

Treatment elements beyond NRT reported in included RCTs

Intervention elements, in addition to NRT, described in study reports are listed below (this list excludes necessary contact for outcome measures, such as blood samples, answering questionnaires, having CO measured).

Published descriptions

1. Batra:[43] *"Nine clinic visits"*; few details. Treatment supplied at each visit and between appointments via *"telephone counselling"*.
2. Bolliger:[39] *"Received information about smoking"*.
3. Wennike:[41] No information.
4. Etter:[45,46] *"Received a 20 page booklet, + 2 page information leaflet about NRT products"*.

Unpublished study reports

1. Wood-Baker:[38] *"All intervention groups received moderate behavioural smoking reduction information"*. *"General implications … were discussed. Initial target number* [of cigarettes smoked] *discussed."*
2. Bolliger:[40] Baseline *"investigator or study nurse gave individual counselling"… "the investigator was always available as backup if any questions were raised"*.
3. Rennard:[36] *"Both groups received moderate behavioural smoking reduction information. General implications discussed and a target number* [of cigarettes smoked] *individually discussed."*
4. Wennike:[42] *"General implications of smoking and its effects were discussed. All groups received moderate behavioural smoking reduction information."*
5. Batra:[44] Essentially no information.
6. Haustein:[37] *"A structured programme of advice/instructions provided."*

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Feedback

The HTA Programme and the authors would like to know your views about this report.

The Correspondence Page on the HTA website (http://www.hta.ac.uk) is a convenient way to publish your comments. If you prefer, you can send your comments to the address below, telling us whether you would like us to transfer them to the website.

We look forward to hearing from you.

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