Varenicline

Single Technology Appraisal Submission

17th January 2007

Pfizer UK Ltd

Summary
Three million deaths a year worldwide can be attributed to smoking (Peto et al 1996). In the United Kingdom, smoking is by far the biggest single cause of preventable chronic illness, disability and premature death, with around 114,000 deaths annually attributable to tobacco use (ASH 2006 http://www.ash.org.uk accessed 10th January 2007). The annual cost to the NHS for treating patients with smoking related diseases is approximately £1.5 billion. With an estimated 12 million smokers, smoking remains the United Kingdom's greatest public health challenge (ibid).

The National Institute for Health and Clinical Excellence (NICE) has recommended that people who smoke should be advised to quit (NICE. 2006), and that pharmacotherapy and/or behavioural support be offered, based on their recognised clinical effectiveness.

Apart from varenicline (Champix®), the pharmacological therapies currently licensed for use in the United Kingdom (UK) are Nicotine Replacement Therapy (NRT) and bupropion. The odds of successfully stopping smoking, as measured by the chemically confirmed abstinence rate at one year, are similar for both therapies; Odds Ratio (OR) 1.78, (95% CI, 1.60–1.99) for NRT , and OR 1.64, (95% CI, 1.16–2.30) for bupropion when each is compared to placebo control (Wu et al. 2006).

In contrast to NRT and bupropion, varenicline has been specifically developed to address many aspects of smoking addiction. It is highly selective for the $\alpha_4\beta_2$ subunit of the nicotinic acetylcholinergic receptor. The agonist properties reduce both the craving for smoking and the withdrawal symptoms associated with stopping. The antagonist properties of the compound may reduce the reward experienced by those smoking, thereby reducing the likelihood of relapse.

Varenicline provides an effective first line treatment option for adult smokers who have expressed a willingness to quit. The odds of successfully stopping smoking using varenicline, as measured by the chemically confirmed abstinence rate at one year, are OR 2.96, (95% CI, 2.12–4.12), compared to placebo control.

In a meta-analysis, varenicline has demonstrated significant clinical superiority over both NRT and bupropion. The odds of successfully stopping smoking using varenicline, measured by the chemically confirmed abstinence rate at one year, are OR 1.66, (95% CI, 1.17-2.36) compared with NRT and OR, of 1.58 (95% CI, 1.22–2.05) compared with bupropion (Wu et al. 2006).

In cost-effectiveness analyses varenicline was both more effective and cost-saving compared with NRT, bupropion and placebo, leading to savings, for treating a 3 million population of smokers willing to quit, of between £328 million and £589 million over their lifetimes.

Those who have successfully stopped smoking after 12 weeks may receive a further 12 weeks of therapy to further improve the odds of successfully quitting. Taking the additional 12 weeks of therapy decreases the relapse rate at one year by a further 6.7%

and is an extremely cost-effective strategy, being more effective and leading to further cost savings.

It is anticipated that the budget impact for England and Wales associated with the introduction of varenicline will be £2 million in 2007 rising to £5 million in 2011.

Pfizer has developed a structured behavioural support programme, called Life Rewards. This provides smokers attempting to quit with varenicline support in dealing with the psychological aspects of addiction and quitting. The programme is also designed to increase compliance. This programme is designed to run alongside existing services and is offered, at no additional cost to patient or the NHS, to all patients prescribed varenicline to assist successful smoking cessation. It can be expected to replace the place that brief counselling had in the clinical trials and thus assist in achieving the trial efficacy values in clinical practice.

Aggressive targets to reduce smoking rates have been set in both England (21% or less by 2010) and Scotland (22% by 2010 from 26.5% in 2004), supported through policies such as smoking bans and smoke free workplaces and areas. Varenicline, with its demonstrated superior clinical efficacy, can play a significant role in achieving this and supporting smokers in their attempts to quit.

Figures

Tables

Abbreviations and Acronyms

ALT (SGPT)	Serum Glutamic-pyruvic transaminase (alanine aminotransferase)
AP	Alkaline Phosphatase
ASH	Action on Smoking and Health
AST (SGOT)	Serum Glutamic-oxaloacetic transaminase (aspartate aminotransferase)
BENESCO	Benefits of Smoking Cessation on Outcomes
BID	Twice a Day
BMC	Bio Med Central
BMI	Body Mass Index
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CE	Cost Effectiveness
CI	Confidence Interval
CK	Creatine Kinase
CO	Carbon Monoxide
CAR	Continuous Abstinence Rate
CHD	Coronary Heart Disease
COPD	Chronic Obstructive Pulmonary Disease
CQR	Continuous Quit Rate
DB	Double Blind
ECG	Electrocardiogram
Ecrf	Electronic Case Report Form
ES	Effect Size
FDA	Food and Drug Administration
GAD	Government Actuary Department
GCP	Good Clinical Practice
GMS	General Medical Services
HECOS	Health and Economic Consequence of Smoking
HTA	Health Technology Assessment
ICER	Incremental Cost Effectiveness Ratio
ITQ	Intention to Quit
ITT	Intention to Treat
LFT	Liver Function Test
LS Mean	Least Squares Mean
LTQR	Long-term Quit Rate
LYG	Life Year Gained
MAO	Monoamine Oxidase
mCEQ	Modified Cigarette Evaluation Questionnaire
MedDRA	Medical Dictionary for Regulatory Activities
Mg	Milligramme
MNWS	Minnesota Nicotine Withdrawal Scale
NDC	New Drugs Committee

NICE	National Institute for Health and Clinical Excellence
NHS	National Health Service
NRT	Nicotine Replacement Therapy
OR	Odds Ratio
OTC	Over the Counter
PPM	Parts Per Million
QSU-Brief	Brief Questionnaire of Smoking Urges
QALY	Quality Adjusted Life Year
RCT	Randomised Controlled Trial
RR	Relative Risk
SAE	Serious Adverse Event
SCQoL	Smoking Cessation Quality of Life Questionnaire
SD	Standard Deviation
SEI	Smoking Effects Inventory
SMC	Scottish Medicines Consortium
SOC	System Organ Class
TQD	Target Quit Date
ULN	Upper Limit of Normal
WHO	World Health Organisation
WSS	World Safety Standards

Section A

1 Description of technology under assessment

1.1 Give the brand name, approved name and, where appropriate, therapeutic class. For devices please provide details of any different versions of the same device.

The brand name in the UK is Champix®.

The approved name is varenicline.

1.2 Does the technology have a UK marketing authorisation/CE marking for the indications detailed in this submission? If so, please give the date on which authorisation was received. If not, please state current UK regulatory status, with relevant dates (for example, date of application and/or expected approval dates).

UK Marketing authorisation for varenicline was received on 27th September 2006.

1.3 What are the (anticipated) indication(s) in the UK? For devices, please provide the (anticipated) CE marking, including the indication for use.

Varenicline is indicated for smoking cessation in adults.

1.4 To what extent is the technology currently being used in the NHS for the proposed indication? Include details of use in ongoing clinical trials. If the technology has not been launched, please supply the anticipated date of availability in the UK.

Varenicline was launched in the United Kingdom on December 4th 2006. Use is at a level expected for a product that has been available for less than two months. As part of the ongoing varenicline phase 3 study programme, an NRT comparator trial has recently completed in the United States and Europe. This trial (A3051044) was an open-label comparison of 12 weeks of varenicline with 10 weeks of NRT transdermal patch, with a follow-up through to week 52. The results of this trial have been provided although they have not been incorporated into any of the base case economic evaluations. They are presented here in the submission as 'Academic in Confidence'.

Other clinical trials

A3051049 CV Patient study
A 12 week, double-blind, placebo-controlled, multi-centre study with a 40 week follow-up evaluating the safety and efficacy of varenicline 1mg BID for smoking cessation in subjects with cardiovascular disease. The study has enrolled around 700 subjects and is due to end in the second half of 2007. The UK has centres that have enrolled patients in this ongoing study.

A3051054 COPD Patient study
A comparison of 12 weeks of treatment with varenicline versus placebo in patients with mild to moderate COPD. Study sites are in the US, Italy, France and Spain.

A3051055 Asian Population study
A prospective, randomised, double-blind, placebo-controlled, multi-centre, multinational study of the efficacy and safety of 12 weeks of varenicline with 12 weeks of follow-up for smoking cessation. The plan is to enrol 330 subjects. Study sites are in China and Singapore.

1.5 Does the technology have regulatory approval outside the UK? If so, please provide details.

Varenicline was approved by the Food and Drug Administration (FDA) for use in the United States in May 2006. Varenicline received Committee for Medicinal Products for Human Use (CHMP) approval for use throughout the European Union in October 2006. Regulatory approval has also been obtained in Mexico, Brazil, Argentina, Uruguay and Pakistan.

1.6 Is the technology subject to any other form of health technology assessment in the UK? If so, what is the timescale for completion?

The Scottish Medicines Consortium has recently completed its appraisal of varenicline. The recommendation is positive and in line with the product label.

Varenicline tablets (Champix®) is accepted for use within NHS Scotland for smoking cessation in adults. It should be used only as a component of a smoking cessation support programme. The benefits of an additional treatment course in those who have stopped smoking after the initial 12 weeks of therapy appear modest.

1.7 For pharmaceuticals, what formulation(s) (for example, ampoule, vial, sustained-release tablet, strength(s) and pack size(s) will be available?

Varenicline is available in 0.5mg and 1.0mg film-coated tablets as follows:

Champix 0.5 mg tablets x 11 and 1 mg tablets x 14; pack size 25 tablets card
Champix 0.5 mg tablets x 11 and 1 mg tablets x 14; pack size 25 tablets carton
Champix 1 mg tablets; pack size 56 tablets bottle
Champix 1 mg tablets; pack size 28 tablets card
Champix 1 mg tablets; pack size 56 tablets card
Champix 1 mg tablets; pack size 28 tablets carton
Champix 1 mg tablets; pack size 56 tablets carton

1.8 What is the proposed course of treatment? For pharmaceuticals, list the dose, dosing frequency, length of course and anticipated frequency of repeat courses of treatment.

Patients should be treated with varenicline for a minimum of 12 weeks. The recommended dose is 1 mg varenicline twice daily, following a 1-week titration as follows:

Days 1 – 3:	0.5 mg once daily
Days 4 – 7:	0.5 mg twice daily
Day 8 – End of treatment	1 mg twice daily

The patient should set a date to stop smoking. Varenicline dosing should start 1-2 weeks before this date. For patients who have successfully stopped smoking at the end of 12 weeks, an additional course of 12 weeks treatment with varenicline 1mg twice daily may be considered. Patients who cannot tolerate adverse effects of varenicline may have the dose lowered temporarily or permanently to 0.5 mg twice daily.

1.9 What is the acquisition cost of the technology (excluding VAT)? For devices, provide the list price and average selling price. If the unit cost of the technology is not yet known, please provide details of the anticipated unit cost, including the range of possible unit costs.

Varenicline costs £1.95 per day per patient.

1.10 What is the setting for the use of the technology?

Varenicline should be used in primary care settings, including with general practitioners, and in smoking cessation clinics in both primary and secondary care.

1.11 For patients being treated with this technology, are there any other aspects that need to be taken into account? For example, are there additional tests or investigations needed for selection, or particular administration requirements, or is there a need for monitoring of patients over and above usual clinical practice for this condition? What other therapies, if any, are likely to be administered at the same time as the intervention as part of a course of treatment?

No additional tests or investigations are needed for selection, and there is no need for monitoring patients taking this medication other than usual clinical practice. No other therapies are required to be administered with varenicline.

Life Rewards

Pfizer has developed a structured behavioural support programme, called Life Rewards, to provide smokers attempting to quit with varenicline support in dealing with the psychological aspects of addiction and quitting; the programme is also designed to increase compliance. This programme will run alongside existing services and is offered, at no additional cost to the patient or the NHS, to all patients prescribed varenicline to assist successful smoking cessation. The provision of this service, alongside available NHS smoking cessation services can be expected to help replicate the efficacy achieved by the presence of opportunities for brief support and counselling in the clinical trials, in day to day use.

2 Statement of the decision problem

In this section the manufacturer or sponsor should specify the decision problem that the submission addresses. The decision problem should be derived from the final scope issued by NICE and should state the key parameters that the information in the Evidence Submission will address.

	Final scope issued by NICE	Decision problem addressed in the submission
Population	Adults who smoke tobacco products	Adults who smoke tobacco products
Intervention	Varenicline	Varenicline
Comparator(s)	Bupropion Nicotine Replacement Therapy Other smoking cessation interventions Placebo	Bupropion Nicotine Replacement Therapy Placebo
Outcomes	Survival Morbidity related to smoking Quit rates at 4 weeks, 6months, 12 months and longer periods Health-related quality of life	Abstinence rate at 12 months (this is the maximum period for which Pfizer has data for varenicline, and data from this time point drives the cost-effectiveness model). The quit rate at three months is also included as the best measure of short term effectiveness. *The 4 week quit rate has been specifically excluded as the duration of pharmacological intervention in the pivotal studies was 12 weeks. The other main comparator used in the clinical and cost-effectiveness analysis is NRT and this has a recommended course length of 10 weeks. Therefore a 4 week time point does not meaningfully measure the efficacy of any of the pharmacological interventions* Health-related quality of life (in relation to quitting). *Survival and smoking related morbidity are related to the giving up (or not) of smoking rather than the method used, and this is consistently recognised in the endpoints selected for clinical trials. The cost-effectiveness modelling will relate the efficacy rates of the interventions to the associated predicted reduction in mortality and morbidity.*
Special considerations and other issues	The intervention will be appraised according to its anticipated marketing authorisation	The submission is in accordance with the marketing authorisation for varenicline

3 Executive summary

Please provide an executive summary that summarises the key sections of the submission. All statements should be directly relevant to the decision problem, be evidence-based and clearly reference the relevant section of the submission. The summary should cover the following items.

- *The UK approved name, brand name, marketing status and principal pharmacological action of the proposed drug.*

The approved name is varenicline.

The brand name in the UK is Champix®

Marketing authorisation for varenicline was received on 27th September 2006. It has been available in the UK since 4th December 2006.

Varenicline (Champix®) has been specifically developed to address many aspects of smoking addiction. It is highly selective for the $\alpha_4\beta_2$ subunit of nicotinic acetylcholinergic receptor. As a partial agonist, varenicline is thought likely to have certain advantages over currently available therapies. The agonist properties of the compound may reduce craving and withdrawal symptoms. The antagonist properties of the compound may reduce the reward experienced by those smoking, thereby reducing the likelihood of relapse.

- *The formulation(s), strength(s), pack size(s), maximum quantity (ies), anticipated frequency of any repeat courses of treatment and acquisition cost (see section 1.9).price.*

Varenicline is available in 0.5mg and 1.0mg film-coated tablets as follows:

Champix 0.5 mg tablets x 11 and 1 mg tablets x 14; pack size 25 tablets card
Champix 0.5 mg tablets x 11 and 1 mg tablets x 14; pack size 25 tablets carton
Champix 1 mg tablets; pack size 56 tablets bottle
Champix 1 mg tablets; pack size 28 tablets card
Champix 1 mg tablets; pack size 56 tablets card
Champix 1 mg tablets; pack size 28 tablets carton
Champix 1 mg tablets; pack size 56 tablets carton

Varenicline costs £1.95 per day per patient.

- *The indication(s) and any restriction(s).*

Indication
Varenicline is indicated for smoking cessation in adults.

Restrictions

- For patients with moderate renal impairment who experience adverse events that are not tolerable, dosing may be reduced to 1 mg once daily.
- For patients with severe renal impairment (estimated creatinine clearance < 30 ml/min), the recommended dose of varenicline is 1 mg once daily. Dosing should begin at 0.5 mg once daily for the first 3 days then increased to 1 mg once daily. Based on insufficient clinical experience with varenicline in patients with end stage renal disease, treatment is not recommended in this patient population.
- No dosage adjustment is necessary for elderly patients. Because elderly patients are more likely to have decreased renal function, prescribers should consider the renal status of an elderly patient.
- Varenicline is not recommended for use in children or adolescents below 18 years of age due to insufficient data on safety and efficacy.
- Varenicline is not recommended for use during pregnancy.
- It is unknown whether varenicline is excreted in human breast milk. A decision on whether to continue/discontinue breast-feeding or to continue/discontinue therapy with varenicline should be made taking into account the benefit of breast-feeding and the benefit of varenicline therapy to the woman.

Contraindications

- Varenicline is only contra-indicated where there is hypersensitivity to the active substance, or to any of the excipients.

Special Warnings and Precautions for Use

- Physiological changes resulting from smoking cessation, with or without treatment with varenicline, may alter the pharmacokinetics or pharmacodynamics of some medicinal products, for which dosage adjustment may be necessary (examples include theophylline, warfarin and insulin). As smoking induces CYP1A2, smoking cessation may result in an increase of plasma levels of CYP1A2 substrates.
- Smoking cessation, with or without pharmacotherapy, has been associated with the exacerbation of underlying psychiatric illness (e.g. depression). Care should be taken with patients with a history of psychiatric illness and patients should be advised accordingly.
- At the end of treatment, discontinuation of varenicline was associated with an increase in irritability, urge to smoke, depression, and/or insomnia in up to 3% of patients. The prescriber should inform the patient accordingly, and discuss, or consider, the need for dose tapering.

• *The recommended course of treatment.*

Patients should be treated with varenicline for a minimum of 12 weeks. The recommended dose is 1 mg varenicline twice daily following a 1-week titration as follows:

Days 1 – 3:	0.5 mg once daily
Days 4 – 7:	0.5 mg twice daily
Day 8 – End of treatment	1 mg twice daily

The patient should set a date to stop smoking. Varenicline dosing should start 1-2 weeks before this date. For patients who have successfully stopped smoking at the end of 12 weeks, an additional course of 12 weeks treatment with varenicline 1mg twice daily may be considered.

Patients who cannot tolerate adverse effects of varenicline may have the dose lowered temporarily or permanently to 0.5 mg twice daily.

- *The main comparator(s).*

The main comparators are NRT, bupropion and placebo.

- *Whether the key clinical evidence in the submission comes from head to head randomised trials (RCTs), from an indirect comparison of two sets of randomised trials involving a common comparator (for example, placebo or other active therapy), or from non-randomised studies.*

The key clinical evidence for the efficacy of varenicline is derived from the results of a programme of three multi-centre double-blind placebo-controlled randomised trials. Two of the trials (A3051028 and A3051036) directly compared varenicline with bupropion and placebo, respectively, to determine smoking cessation efficacy after 12 weeks of treatment. The third trial (A3051035) compared varenicline to placebo for the rate of continuous abstinence from smoking during weeks 13 to 24 in subjects responding to an initial 12-week course of smoking cessation with varenicline 1mg BID.

[redacted]. NICE specifies that in the absence of appropriate head-to-head trial data consideration be given to using the results from an appropriately conducted comparison.

Based on this we have chosen to use the efficacy values for NRT from the results of a published systematic review and meta-analysis of smoking cessation therapies (Wu et al. 2006) for all comparative economic analyses. The comparison within the paper was an adjusted indirect one after the methods of Bucher et al. (1997) and Song et al. (2003). It is notable that these results conform closely to those from the wider evidence base.

For purposes of transparency we also present the results of a pair wise cost-effectiveness analysis of varenicline versus NRT using the results from the open-label study, as a sensitivity analysis.

- *The main clinical results of the randomised trials and any relevant non RCTs.*

Clinical Trials Results Overview
The efficacy of varenicline has been demonstrated in four clinical trials; two identically designed comparative trials, a maintenance trial and one open-label trial including a total of over 3300 chronic smokers.

The Double-Blind Comparative Trials (A3051028, A3051036)
The double-blind comparative trials were 52-week, head-to-head studies, in which 12 weeks of varenicline was compared with sustained-release bupropion and placebo.

The primary outcome measure was the Continuous Abstinence Rate (CAR) for the last 4 weeks of study treatment. The key secondary endpoint was the Continuous Abstinence Rate for Weeks 9 through to 52.

Primary End Point Results
For the Continuous Abstinence Rate Weeks 9 through 12, varenicline demonstrated statistical superiority to both bupropion and placebo.

Continuous Abstinence Rate Weeks 9 through 12 (%)

	Varenicline	**Bupropion**	**Placebo**
A3051028	44.0	29.5	17.7
A3051036	43.9	29.8	17.6

Odds Ratios for Primary Endpoint
Patients have about double the odds of quitting with varenicline than with bupropion

Study A3051028 Odds Ratio=1.93, (95% CI, 1.40-2.68; p<0.001)
Study A3051036 Odds Ratio=1.90, (95% CI, 1.38-2.62; p<0.001)

Patients have about four times greater odds of quitting with varenicline than with placebo

Study A3051028 Odds Ratio=3.85, (95% CI, 2.70-5.50; p<0.001)
Study A3051036 Odds Ratio=3.85, (95% CI, 2.69-5.50; p<0.001)

Secondary endpoint results
For the Continuous Abstinence Rate Weeks 9 through to 52 varenicline demonstrated superiority to bupropion and statistical superiority to placebo.

Continuous Abstinence Rate Weeks 9 through 52 (%)

	Varenicline	**Bupropion**	**Placebo**
A3051028	21.9	16.1	8.4
A3051036	23	14.6	10.3

Odds Ratios for Secondary Endpoint
Patients have about one and a half times greater odds of quitting with varenicline than with bupropion

Study A3051028 Odds Ratio=1.46, (95% CI, 0.99-2.17; p<0.057)
Study A3051036 Odds Ratio=1.77, (95% CI, 1.19-2.63; p=0.004)

Patients have about three times greater odds of quitting with varenicline than with placebo

Study A3051028 Odds Ratio=3.09, (95% CI, 1.95-4.91; p<0.01)
Study A3051036 Odds Ratio=2.66, (95% CI, 1.72-4.11; p<0.01)

The Maintenance of Abstinence Trial (A3051035)
The purpose of this 52 week maintenance trial was to determine whether a further 12 weeks of treatment with varenicline would maintain the rate of abstinence among those successfully treated on one 12-week course of varenicline.

The primary endpoint was the Continuous Abstinence Rate from Week 13 through Week 24. The key secondary endpoint was the Continuous Abstinence Rate from Week 13 through week 52.

Primary Endpoint Results
As measured by the Continuous Abstinence Rate Week 13 through to Week 24, 71% of patients who received an additional 12 weeks of varenicline were still abstinent, compared with 50% of patients who received placebo.

Odds Ratio for Primary Endpoint
At week 24, patients who received varenicline had an Odds Ratio of 2.48, (95% CI, 1.95-3.16 p<0.001) of maintaining abstinence compared to patients who received placebo.

Secondary Endpoint Results
As measured by the Continuous Abstinence Rate, Week 13 through to Week 52, 43.6% of patients who received an additional 12 weeks of varenicline were still abstinent, compared with 36.9% of patients who received placebo.

Odds Ratio for Secondary Endpoint
At week 52, patients who received varenicline had an Odds Ratio of 1.34 (95% CI, 1.06-1.69 p<0.02) of maintaining abstinence compared to patients who received placebo

The Open-Label Varenicline versus NRT transdermal patch trial (A3051044)
The purpose of this 52 week trial was to compare 12 weeks of varenicline therapy to 10 weeks of NRT transdermal patch.

The primary endpoint was the Continuous Abstinence Rate for the last 4 weeks of treatment (Weeks 9 through 12 for varenicline and Weeks 8 through 11 for NRT). The key secondary endpoint was the Continuous Abstinence Rate from the last 4 weeks of treatment through Week 52.

[redacted]

Systematic Review and Meta-Analysis

Existing therapies for smoking cessation include NRT and bupropion. A systematic review and meta-analysis assessed the relative efficacy of varenicline compared to these existing therapies (Wu et al. 2006). This review compared varenicline and NRT after an accepted method for undertaking direct and indirect comparisons (Bucher et al. 1997; Song et al. 2003) that preserves the randomisation of the original trials. A copy of the full systematic review and meta-analysis (Wu et al. 2006) is appended to this submission. A summary of the main findings are presented below.

Overview of the Systematic Review and Meta-Analysis (Wu et. al. 2006)

70 trials of NRT versus control at 1 year were identified, (OR 1.71, 95% CI, 1.55–1.88). This was consistent when examining all placebo-controlled trials (49 RCTs, OR 1.78, 95% CI, 1.60–1.99), NRT gum (OR 1.60, 95% CI, 1.37–1.86) or patch (OR 1.63, 95% CI, 1.41–1.89). NRT also reduced smoking at 3 months (OR 1.98, 95% CI, 1.77–2.21). Bupropion trials were superior to controls at 1 year (12 RCTs, OR1.56, 95% CI, 1.10–2.21) and at 3 months (OR 2.13, 95% CI, 1.72–2.64). Two RCTs evaluated the superiority of bupropion versus NRT at 1 year (OR 1.14, 95% CI, 0.20–6.42).

Varenicline was superior to placebo at 1 year (4 RCTs, OR 2.96, 95% CI, 2.12–4.12) and also at approximately 3 months (OR 3.75, 95% CI, 2.65–5.30). Three RCTs evaluated the effectiveness of varenicline versus bupropion at 1 year (OR 1.58, 95% CI, 1.22–2.05) and at approximately 3 months (OR 1.61, 95% CI, 1.16–2.21).

Using indirect comparisons, varenicline was superior to NRT when compared to placebo controls (OR 1.66, 95% CI, 1.17–2.36) or to all controls at 1 year (OR 1.73, 95% CI, 1.22–2.45). This was also the case for 3-month data. Adverse events were not systematically different across studies.

Interpretation of the findings of the Systematic Review and Meta-Analysis
Varenicline, NRT and bupropion all provide therapeutic effects in assisting with smoking cessation. The current evidence indicates varenicline has a superior therapeutic effect over the other interventions.

- *In relation to the economic evaluation, details of:*
  - *the type of economic evaluation and justification for the approach used*

The Benefit of Smoking Cessation on Outcomes (BENESCO) model, in this submission, follows over time a hypothetical cohort of smokers who make a single attempt to quit smoking at the beginning of the simulation. This cohort is followed from the time the smokers start their attempt to quit smoking until all members of the cohort have either died or reached the maximum age of 100.

In the first year of the simulation, the cohort of patients receiving the intervention attempt to quit according to efficacy values described elsewhere. At the end of each year, the members of the cohort are distributed into various smoking states (i.e. smoker, recent quitter, long term quitter), each of which can be associated with co-morbidities (COPD, lung cancer, CHD, stroke, and asthma exacerbations).

The probability for a subject to transition from one health state to another depends upon the subject's smoking status and health state in the previous year. Each health state is associated with a specific cost and utility value. Patients accumulate costs and outcomes through their transition to the different states, until they die.

The model used was developed, guided by key learnings from the HECOS model (Orme 2001) created for the World Health Organisation, with input from many stakeholders, and widely used to evaluate the cost and life years gained from smoking cessation.

– the pivotal assumptions underlying the model/analysis

Smokers that enter the model may transition to the different smoking states according to the length of time since they quit smoking.

State 1 – Smoker attempting to Quit:

- The patient is attempting to quit and make the transition from smoker to quitter
- This state takes place in the first year and the probability of successfully quitting (moving to the recent quitter state from the smoker state) is dependent upon the smoking cessation method that is used

State 2 – Recent Quitter:

- If abstinent after one year, the subject will be considered a recent quitter. At this time, the health benefits from not smoking will begin, although there is still a risk of relapse
- The rate at which the recent quitters relapse to smoking is independent of the smoking cessation method that was initially used and does not differ between treatment groups
- In the framework of the BENESCO model, this stage lasts up through year 5 providing that there is no relapse to smoking

State 3 – Long-term Quitter:

- If after 5 years from the initial attempt the subject is still abstinent, then the risk of relapsing to smoking is further reduced for the next 5 years (years 6-10 in the model)
- If the subject maintains abstinence through 10 years following their quit attempt, the relapse rate is further reduced again, and the subject remains in this stage until death providing that there is no relapse back to smoking

The BENESCO model health states correspond to those diseases that account for the greatest mortality, morbidity and cost associated with smoking. In this Markov model, all the health states are mutually exclusive (e.g. a patient can not have COPD and CHD in the same cycle). Markov cycle length is of one year.

To avoid the potential of overestimating the effect of the utility in smokers with and without smoking-related morbidity, we have assumed that the baseline utility weight for smokers and long-term quitters is equivalent, and any changes to utility are the result of a smoking related disease. Values have been taken from published data (Fiscella 1996) according to the different age bands. This is a conservative approach for varenicline, as it has been shown that smokers' HrQoL is significantly lower than that of non-smokers (Kind., 1998)

The smoking cessation strategies that have been included as options within the BENESCO model are varenicline, NRT, bupropion and placebo. The efficacy values utilised in the model are listed in the table below. These efficacies represent the quit rates seen at one year following the initiation of a quit attempt.

Varenicline and bupropion efficacy rates have been obtained from direct, head-to-head clinical trial data from the varenicline clinical trial program and comprise the pooled continuous abstinence rates from weeks 9 to 52. The same source was used to provide an estimate of the efficacy of placebo.

The efficacy rate for NRT was derived through adjusted indirect comparison methods (Bucher et al. 1997) from a recently published systematic review and meta-analysis (Wu et al. 2006). As previously noted the methodology used (Bucher et al. 1997, Song et al. 2003) preserves the randomisation of the original trials.

Efficacy rates used in the analysis

Data Item	Data source	Efficacy rate
Varenicline	Pooled varenicline Phase 3 studies A3051028 and A3051036 from the published data	**22.5%**
Bupropion	Pooled varenicline Phase 3 studies A3051028 and A3051036 from the published data	**15.7%**
NRT	Wu et al. Effectiveness of smoking cessation therapies: a systematic review and meta-analysis 2006. *BMC Public Health* 6:300 (11th December 2006)	**14.9%**[a]
placebo	Pooled varenicline Phase 3a studies A3051028 and A3051036 from the published data	**9.4%**

[a]Indirect comparison

– the incremental ratios from the evaluation.

In a cost-effectiveness analysis measuring the effectiveness of varenicline compared with NRT, bupropion and placebo, varenicline was the most effective alternative and was cost-saving compared against all of the comparators, leading to savings of between £328 million and £589 million in the UK.

	Costs (£)	QALYs	Life Years	Incremental results
Varenicline	34,018,920,489	42,135,027	86,711,276	Dominant
Bupropion	34,347,878,880	42,063,665	86,540,790	
NRT	34,514,466,202	42,057,446	86,525,933	
Placebo	34,608,281,768	42,001,477	86,392,224	

Those who have successfully stopped smoking after 12 weeks may receive a further 12 weeks of therapy to further maintain the odds of successfully quitting. Taking the further 12 weeks of therapy decreases the relapse rate at one year by a further 6.7% and is an extremely cost-effective strategy, generating an additional 68,300 QALYs for a further cost-saving of over £44,500,000.

4 Context

In this background section the manufacturer or sponsor should summarise and contextualise the evidence relating to the decision problem. The information provided will not be formally reviewed by the Evidence Review Group.

> *4.1 Please provide a brief overview of the disease/condition for which the technology is being used. Provide details of the treatment pathway and current treatment options at each stage.*

Disease/Condition

Three million deaths a year worldwide can be attributed to smoking (Peto et al 1996), and it is a major aetiological factor for lung cancer, cardiovascular disease and peripheral vascular disease. Smoking also causes respiratory disease, such as chronic obstructive pulmonary disease, including bronchitis and emphysema. Half of all smokers in the UK die prematurely of a smoking-related ailment, with the decrease in life expectancy for regular smokers under the age of 35 years, who do not subsequently quit, estimated to be about 8 years (http://www.nice.org.uk. Accessed on 15.12.06). The annual cost to the NHS of treating patients with smoking related disease is of the order of £1,500m.

The proportion of adults in Great Britain who smoked cigarettes fell substantially during the 1970s and the early 1980s, after which it declined gradually until the early 1990s. Since this time it has levelled out, and in 2003/04 26% of adults aged 16 or over smoked cigarettes, an identical rate to 2002/03. The gap between men and women smokers has narrowed, and in 2003/04, 28% of men and 24% of women were cigarette smokers. In July 2004 the Government set a new target to reduce the overall proportion of cigarette smokers in England to 21% or less by 2010 (http://www.statistics.gov.uk. Accessed on 15.12.06).

Inhaled nicotine is strongly addictive and stopping smoking results in craving and withdrawal symptoms. However smokers who quit before the age of about 35 years have a life expectancy only slightly less than those who have never smoked. Even cessation in middle age improves health and substantially reduces the excess risk of death, and quitting at any age provides both immediate and long-term health benefits. It is estimated that about 4 million smokers a year attempt to quit but that only 3% to 6% of these (1% to 2% of all smokers) succeed (http://www.nice.org.uk. Accessed on 15.12.06).

Smokers have a range of options when the decision has been made to attempt to quit. The most common of which is unaided cessation, so-called ‘cold turkey. Other alternatives

are counseling +/- pharmacotherapy, hypnosis, acupuncture, or use of Over The Counter NRT.

General Practitioners in the UK maintain a record of the smoking habits of all patients and are encouraged to offer advice and support to smokers to help them quit. Smokers can be referred to a local smoking cessation service where counseling will be offered and, if deemed appropriate, pharmacological support prescribed.

4.2 What was the rationale for the development of the new technology?

Varenicline was specifically designed as an aid to smoking cessation and addresses the physical aspects of nicotine addiction. Similarly the behaviour support programme, provided in conjunction with varenicline, provides additional support for smokers dealing with the psychological aspects of addiction and quitting.

4.3 What is the principal mechanism of action of the technology?

Varenicline is a selective nicotinic acetylcholine receptor partial agonist developed specifically for smoking cessation. It is highly selective for the $\alpha_4\beta_2$ subunit of the nicotinic acetylcholinergic receptor. As a partial agonist, varenicline is thought likely to have certain advantages over currently available therapies. The agonist properties of the compound may reduce craving and withdrawal symptoms. The antagonist properties of the compound may reduce the reward experienced by those smoking over the therapy, thereby reducing the likelihood of relapse.

4.4 What is the suggested place for this technology with respect to treatments currently available for managing the disease/condition?

Varenicline is an appropriate therapy to assist any adult patient who has expressed a willingness to quit smoking and is attempting to quit for the first or any other time.

Varenicline provides an effective treatment option for adult smokers who have expressed a willingness to quit. Varenicline has demonstrated significant clinical superiority over NRT and bupropion, the other available pharmacological therapies. The odds of successfully stopping smoking using varenicline, measured by the long term quit rate at one year, are OR 1.66, (95% CI, 1.17-2.36; p=0.004) compared with NRT and OR 1.58, (95% CI, 1.22-2.05; p=0.001) compared with bupropion (Wu et. al. 2006).

4.5 Describe any issues relating to current clinical practice, including any variations or uncertainty about best practice.

A common concern is that the efficacy achieved in clinical trials of smoking cessation therapies is rarely achieved in clinical practice, and it is recognised that the results of clinical trials are often impossible to replicate because of the inability in clinical practice to provide the same level of support to patients that is routinely provided in the trial setting with it being clearly understood that professional support improves long term quit rates.

Pfizer has developed a behaviour support programme for all patients prescribed varenicline to provide the support and counselling that are recognised to improve long term quit rates. This programme will be available at no charge for all patients prescribed varenicline and is designed to run alongside the services currently available in Primary Care and the hospital setting.

4.6 Provide details of any relevant guidelines or protocols.

National initiatives to reduce the numbers of smokers in the UK include the development of an NHS Smoking Cessation Service, the National Service Framework for Coronary Heart Disease (http://www.dh.gov.uk. Accessed on 15.12.06), the new General Medical Services (GMS) contract, and NICE guidance on bupropion and nicotine replacement therapy (NRT) for smoking cessation (http://www.nice.org.uk. Accessed on 15.12.06).

The National Institute for Health and Clinical Excellence (NICE) recommendation is that people who smoke should be advised to quit (NICE. 2006), and that pharmacotherapy and/or behavioural support be offered, based on their recognised clinical effectiveness. This recommendation is also endorsed by NHS Quality Improvement Scotland (2003).

NICE guidance states that, ideally, initial prescriptions of NRT or bupropion should be sufficient to last only until 2 weeks after the target stop date, i.e. after 2 weeks of NRT therapy, and 3-4 weeks for bupropion. Secondly, prescriptions should be given only to people who have demonstrated that their quit attempt is continuing on reassessment. If a smoker's attempt to quit is unsuccessful with treatment using either NRT or bupropion, the NHS should normally fund no further attempts within 6 months. However, if external factors interfere with an individual's initial attempt to stop smoking, it may be reasonable to try again sooner (http://www.nice.org.uk. Accessed on 15.12.05).

NICE guidance for bupropion and NRT was due to be reviewed in March 2005. However, a decision was taken to incorporate this into a Public Health Guidance on the optimal provision of smoking cessation services, including pharmacological treatment (http://www.publichealth.nice.org.uk/page.aspx?o=SmokingCessationPGMain. Accessed on 06.12.05). This guidance is expected in July/August 2007. However, because the scope of the document has already been established, varenicline will not be included.

The Scottish Medicines Consortium has recently completed its appraisal of varenicline. The recommendation is positive and in line with the product label.

Varenicline tablets (Champix®) is accepted for use within NHS Scotland for smoking cessation in adults. It should be used only as a component of a smoking cessation support programme. The benefits of an additional treatment course in those who have stopped smoking after the initial 12 weeks of therapy appear modest.

5 Clinical evidence

Manufacturers and sponsors are required to submit a systematic review of the clinical evidence that relates directly to the decision problem. Systematic and explicit methods should be used to identify, select and critically appraise relevant research, and to collect and analyse data from the studies that are included in the review. Where appropriate, statistical methods (meta-analysis) should be used to analyse and summarise the results of the included studies. The systematic review should be presented in accordance with the QUOROM statement checklist (www.consort-statement.org/QUOROM.pdf).

The systematic review is not required to be exhaustive (that is, it is not necessary to include all evidence relating to the use of the technology), but justification needs to be provided for the exclusion of any evidence. Where manufacturers have identified a study but do not have access to the level of detail required, this should be indicated.

The Institute has a strong preference for evidence from 'head-to-head' randomised controlled trials (RCTs) that directly compare the technology and the appropriate comparator(s). Wherever such evidence is available, and includes relevant outcome evidence, this is preferred over evidence obtained from other study designs. Where no head–to-head RCTs are available, consideration will be given to indirect comparisons, subject to careful and fully described analysis and interpretation.

In the absence of valid RCT evidence, evidence from other study designs will be considered, with reference to the inherent limitation inferred by the study design. The Institute also recognises that RCT data are often limited to selected populations, short time spans and selected comparator treatments. Therefore good-quality observational studies may be submitted to supplement RCT data.

The response to the following section incorporates a presentation of the results from each of the studies used to support the submission. The results of a recently published systematic review and meta-analysis are also presented to provide supporting data for the efficacy of the main comparators as well as an indirect comparative analysis of varenicline versus NRT required for the economic modelling.

5.1 Identification of studies

Describe the strategies used to retrieve relevant clinical data both from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. Exact details of the search strategy used should be provided in appendix 2, section 9.2.

Search Strategy for Published Literature

In consultation with a medical librarian a search strategy of published literature was established. Searches were conducted independently, in duplicate, using the following ten databases (from inception to December 1, 2006): MEDLINE, EMBASE, Cochrane,

AMED, CINAHL, TOXNET, Development and Reproductive Toxicology, Hazardous Substances Databank, Psych-info and Web of Science. Databases that included the full text of journals (*OVID, ScienceDirect,* and *Ingenta)*, including articles in full text from approximately 1700 journals, since 1993, were searched. In addition, the bibliographies of published systematic reviews (Silagy et al. 2000, 2001, 2002, 2004; Hughes et al 2002, 2004; Lancaster et al 2000; Silagy 2000), and health technology assessments were searched (Nice, 2002). Searches were not limited by language, sex or age.

Search Strategy for Unpublished Manufacturer Data
The Pfizer clinical trials database, Documentum, was searched (7th January 2007). The report on a recently completed open-label study comparing varenicline and NRT was retrieved.

All three phase 3 pivotal clinical trials for varenicline have been published, as well as two of the phase 2 varenicline clinical trials.

5.2 Study selection

5.2.1 Complete list of RCTs

Provide a list of all RCTs that compare the intervention with other therapies (including placebo) in the relevant patient group. The list must be complete and will be validated by independent searches conducted by the assessors.

Where data from a single study have been drawn from more than one source (for example, a poster and a published report) and/or where trials are linked (for example, an open-label extension to an RCT), this should be made clear.

Published studies of trials including varenicline
Phase 3 studies
Gonzales D, Rennard S, Nides M, et. al. Varenicline, an {alpha) 4 beta 2 Nicotinic Acetylcholine Receptor Partial Agonist, vs. Sustained-Release Bupropion and Placebo for Smoking Cessation: A Randomised Controlled Trial. JAMA 2006; 296 47-55.

Jorenby D, Taylor Hays J, Rigotti N, et. al. Efficacy of Varenicline, an {alpha}4 beta2 Nicotinic Acetylcholine Receptor Partial Agonist, vs. Placebo or Sustained-Release Bupropion for Smoking Cessation: A Randomised Controlled Trial. JAMA 2006; 296 56-63.

Tonstad S, Tonnesen P, Hajek P, et. al. Effect of Maintenance Therapy with Varenicline on Smoking Cessation: A Randomised Controlled Trial. JAMA 2006; 296 64-71.

Phase 2 studies
Nides M, Oncken C, Gonzales D, et al. Smoking Cessation with Varenicline, a Selective α4β2 Nicotinic Receptor Partial Agonist. *Arch Int Med* 2006;166:1561-1568.

Oncken C, Gonzales D, Nides M. et al. Efficacy and Safety of the Novel Selective Nicotinic Acetylcholine Receptor Partial Agonist, Varenicline, for Smoking Cessation. *Arch Int Med* 2006; 166:1571-1577.

The complete varenicline phase 2 and phase 3 clinical trials program is listed in Table 1.

Table 1 Summary of Varenicline Clinical Trials Programme

Protocol Type Identifier Country (no. of sites)	**Study start Study end**	**Design**	**Treatment duration Follow-up**
Efficacy: Smoking Cessation - Phase 2 Studies			
Dose-Ranging A3051002 United States (7)	27/12/2004 10/02/2006	Randomised, Parallel Group, Double-blind, Placebo-controlled, Active controlled	Varenicline 6/52 + 1/52 placebo Bupropion 7/52 Placebo 7/52 Optional non-treatment follow-up through Week 52
Dose-Ranging A3051046 Japan	21/02/2000 03/01/2002	Randomised, Parallel Group, Double-blind, Placebo-controlled, Active controlled	Varenicline 6/52 + 1/52 placebo Non-treatment follow-up through Week 52
Titration A3051007 United States (10)	26/09/2001 07/10/2002	Randomised, Parallel Group, Double-blind, Placebo-controlled	Varenicline 12/52 Placebo 12/52 Non-treatment follow-up through Week 52
Titration A3051018 United States (10)	21/12/2001 21/07/2003		
Flexible-dose A3051016 United States (5)	26/12/2001 18/09/2003		
Flexible-dose A3051019	19/03/2002 24/06/2003		
Efficacy: Smoking Cessation - Phase 3 Studies			
Bupropion comparator A3051028 United States (19)	19/06/2003 22/04/2005	Randomised, Parallel Group, Double-blind, Placebo-controlled, Active comparator	Varenicline 12/52 Bupropion 12/52 Placebo 12/52 Non-treatment follow-up through Week 52
Bupropion comparator A3051036 United States (14)	26/06/2003 21/03/2005		
NRT comparator A3051044 United States (6) United Kingdom (4) Netherlands (4) Belgium (4)	17/01/2005 17/11/2006	Randomised, Parallel Group, Open-label, Active comparator	Varenicline 12/52 NRT 10/52 Non-treatment follow-up through Week 52
Efficacy: Maintenance of Abstinence - Phase 3 Study			
Maintenance A3051035 United States (6) Denmark (3) Sweden (3) Norway (3) Czech Republic (100 United Kingdom (3) Canada (6)	13/04/2003 03/03/2005	Open-label, followed by Randomisation to Double-blind varenicline or placebo	Open –label Varenicline 12/52 Double-blind: Varenicline 12/52 Placebo 12/52 Non-treatment follow-up through Week 52
Efficacy: Patients with Cardiovascular disease – Phase 3 Study			
Placebo controlled A3051049 Argentina, Australia, Brazil, Canada, Czech	02/2006 Ongoing	Randomised, Parallel Group, Double-blind, Placebo-controlled	Varenicline 12/52 Placebo 12/52 Non-treatment follow-up through Week 52

Republic, Denmark, France, Germany, Greece, Korea, Mexico, Netherlands, Taiwan, United Kingdom, United States			
Efficacy: Patients with Chronic Obstructive Pulmonary Disease – Phase 3 Study			
Placebo-controlled A3051054 France, Spain, United States	May 2006 Ongoing	Randomised, Parallel Group, Double-blind, Placebo-controlled	Varenicline 12/52 Placebo 12/52 Non-treatment follow-up through Week 52
Efficacy: Asian population – Phase 3 Study			
Placebo-controlled A3051045 Taiwan (5) South Korea (5)	15/022005 29/03/2006	Randomised, Parallel Group, Double-blind, Placebo-controlled	Varenicline 12/52 Placebo 12/52 Non-treatment follow-up through Week 24
Efficacy: Asian population – Phase 3 Study			
Placebo-controlled A3051055 China, Singapore	Oct 2006 Ongoing	Randomised, Parallel Group, Double-blind, Placebo-controlled	Varenicline 12/52 Placebo 12/52 Non-treatment follow-up through Week 24
Safety: Smoking Cessation - Phase 3 Study			
Placebo-controlled A3051037 United States (8) Australia (1)	13/10/2003 02/03/2005	Randomised, Parallel Group, Double-blind, Placebo-controlled	Varenicline 52/52 Placebo 52/52

5.2.2 Inclusion and exclusion criteria

State the inclusion and exclusion criteria that were used to identify the studies detailed in the list of relevant RCTs. If additional inclusion criteria were applied to select studies that have been included in the systematic review, these need to be listed separately.

Inclusion and Exclusion Criteria for Systematic Review

The primary outcome of interest was smoking cessation at one year. The secondary outcomes were short-term smoking cessation defined as three months after initiating treatment, or closest available data to that time point, within one month. Additional secondary outcomes evaluated adverse events. Included were any RCT of NRT of any delivery method, bupropion and varenicline. Included were RCTs of at least one year duration with chemical confirmation of smoking cessation.

Studies had to report smoking cessation as either sustained abstinence at the time periods or point-prevalence of abstinence. When both outcomes were available, sustained abstinence was considered to be a superior clinical marker of abstinence. Dose ranging studies, non-RCTs, post-hoc analyses, maintenance therapy, and studies that reported outcomes as self-report were excluded.

5.2.3 List of relevant RCTs

List all RCTs that compare the technology directly with the appropriate comparator(s) with reference to the specification of the decision problem. If there are none, state this.

Where studies have been excluded from further discussion, a justification should be provided to ensure that the rationale for doing so is transparent. A flow diagram of the numbers of studies included and excluded at each stage should be provided at the end of section 5.2, as per the QUORUM statement flow diagram (www.consort-statement.org/QUOROM.pdf). The total number of studies in the QUORUM statement should equal the total number of studies listed in section 5.2.1.

Where data from a single RCT have been drawn from more than one source (for example, a poster and a published report) and/or where trials are linked (for example, an open-label extension to an RCT), this should be made clear.

There are four , phase 3, randomised controlled trials which compare the technology (varenicline) with the appropriate comparators (Trials A3051028, A3051036, A3051035 and A3051044). See Table 1 and Table 2 for further details.

5.2.4 List of relevant non-randomised controlled trials

Provide details of any non-randomised controlled trials that are considered relevant to the decision problem. Provide justification for their inclusion.

Not applicable to this submission.

5.2.5 Ongoing studies

Provide details of relevant ongoing studies from which additional evidence is likely to be available in the next 12 months.

The following 3 studies are ongoing and it is unclear when the results will be available.

A3051049 CV Patient study
A 12 week, double-blind, placebo-controlled, multi-centre study with a 40 week follow-up evaluating the safety and efficacy of varenicline 1mg BID for smoking cessation in subjects with cardiovascular disease. The study has enrolled around 700 subjects and is due to end in the second half of 2007. The UK has 4 centres that have enrolled patients in this ongoing study.

A3051054 COPD Patient study
A comparison of 12 weeks of treatment with varenicline versus placebo in patients with mild to moderate COPD. Study sites are in the UK, Italy, France and Spain.

A3051055 Asian Population study
A prospective, randomised, double-blind, placebo-controlled, multi-centre, multinational study of the efficacy and safety of 12 weeks of varenicline with 12 weeks of follow-up

for smoking cessation. The study plans to enrol 330 subjects. Study sites are in South Korea and Taiwan.

5.3 Summary of methodology of relevant RCTs

As a minimum, the summary should include information on the following aspects of the RCT, but the list is not exhaustive. Items 2 to 14 of the CONSORT checklist should be provided, as well as a CONSORT flow diagram of patient numbers (http://www.consort-statement.org/). The methodology should not be submitted in confidence without prior agreement with NICE. Where there is more than one RCT, the information should be tabulated.

5.3.1 Methods

Describe the RCT design (for example, duration, degree and method of blinding, and randomisation) and interventions.

Trial Design

Table 2 summarises the 4 varenicline clinical trials of relevance for this submission.

Table 2. Summary of Varenicline trials in Smoking Cessation

Trial Number Date of Completion	Objective(s)	Related Publications	Design, Methods, Assessments	Trial Treatments (number of patients randomised, age range)	Efficacy Outcome Measures (Efficacy, Safety and Tolerability)
A3051028 **Sept 2005**	To evaluate the efficacy and safety of varenicline (1mg twice/day) BID compared to placebo and Bupropion 150mg BID in smoking cessation.	**Manuscripts** Gonzales et al JAMA 2006	RCT, DB, placebo controlled, multi-centre study *Country:* US *Centres:* 19 *Trial duration:* 12 weeks treatment period with 40 weeks non-treatment follow-up phase. *Disease:* Smoking cessation *Jadad score: 5/5*	Placebo (n=344) Bupropion150 mg BID (n=329) Varenicline 1mg BID (n=349) Patients randomised N: 1025 ITT N: 1022 Sex: F/M 469:553 *Age range:* 18-75 years	Primary efficacy measure CO confirmed 4-week continuous quit rate for weeks 9-12 of planned treatment. Secondary efficacy measures Continuous Abstinence Rate from week nine through to week 52 Long term Quit Rate (LTQR) at week 52 Continuous Abstinence Rate from Week 9 through to Week 24 7-day point-prevalence of abstinence at Weeks 12, 24, and 52 4-week point-prevalence abstinence (week 52) Minnesota Nicotine Withdrawal Scale Brief Questionnaire of Smoking Urges Smoking Effects Inventory Change from baseline in body weight Tolerability and safety measures Adverse events including examination by nature, intensity and relationship to treatment. Clinical laboratory determinations, physical examinations, liver function tests, vital sign monitoring, ECGs.
A3051036 **Sept 2005**	To evaluate the efficacy and safety of varenicline (1mg twice/day) BID compared to placebo and Bupropion 150mg BID in smoking cessation.	**Manuscripts** Jorenby et al JAMA 2006	RCT, DB, placebo controlled, multi-centre study *Country:* US *Centres:* 14 *Trial duration:* 12 weeks treatment period including with 40 weeks non-treatment follow-up phase *Disease:* Smoking cessation *Jadad score: 5/5*	Placebo (n=341) Bupropion150 mg BID (n=342) Varenicline 1mg BID (n=344) Patients randomised N: 1027 ITT N: 1023 Sex: F/M 430:593 *Age range:* 18-75 years	Primary efficacy measure CO confirmed 4-week continuous quit rate for weeks 9-12 of planned treatment. Secondary efficacy measures Continuous Abstinence Rate from week nine through to week 52 Long term Quit Rate (LTQR) at week 52 Continuous Abstinence Rate from Week 9 through to Week 24 7-day point-prevalence of abstinence at Weeks 12, 24, and 52 4-week point-prevalence abstinence (week 52) Minnesota Nicotine Withdrawal Scale Brief Questionnaire of Smoking Urges Smoking Effects Inventory Change from baseline in body weight Tolerability and safety measures Adverse events including examination by nature, intensity and

Table 2. Summary of Varenicline trials in Smoking Cessation

Trial Number Date of Completion	Objective(s)	Related Publications	Design, Methods, Assessments	Trial Treatments (number of patients randomised, age range)	Efficacy Outcome Measures (Efficacy, Safety and Tolerability)
					relationship to treatment. Clinical laboratory determinations, physical examinations, liver function tests, vital sign monitoring, ECGs.
A3051035 **Sept 2005**	To evaluate the benefit of an additional 12 week treatment with varenicline (1mg twice/day) BID compared to placebo in subjects responding to an initial 12 weeks of treatment with varenicline 1mg BID therapy for the maintenance of smoking cessation	**Manuscripts** Tonstad et al JAMA 2006	*Country: US, Canada, Norway, Sweden, Denmark, Czech Republic, UK* *Centres:* 24 *Trial duration:* The study had 3 consecutive phases: a 12 week open-label period in which all subjects received 12 weeks of Varenicline 1mg BID; a 12 week double-blind treatment phase with subjects randomised to either placebo or varenicline 1mg BID; and a double-blind non-treatment follow-up phase to week 52 *Disease:* Smoking cessation *Jadad score: 5/5*	Placebo (n=607) Varenicline 1mg BID (n=603) Patients randomised N: 1210 ITT N: 1206 Sex: F/M 611:595 *Age range:* 18-75 years	Primary efficacy measure Continuous abstinence rate from week 13 through to week 24 (double-blind treatment phase) Secondary efficacy measures Continuous Abstinence Rate from week 13 (randomisation) through to week 52 Long Term Quit Rate (LTQR) at week 52 Seven day point prevalence of abstinence Four week point prevalence of abstinence at week 52 Time to first cigarette post-randomisation
A3051044 **Nov 2006**	To evaluate the efficacy and safety of varenicline (1mg twice/day) BID compared to NRT (transdermal patch) in smoking cessation.	**Manuscripts** Nil	Randomised controlled open label multi-centre study. *Country: US, Belgium, France, Netherlands, UK.* *Centres* 24 *Trial duration:* 12 weeks treatment period (varenicline) or 10 weeks treatment period (NRT) with non treatment follow-up to 52 weeks. *Disease:* Smoking cessation *Jadad score: 5/5*	Varenicline 1mg BID (n=377) NRT (n=378) Patients randomised n= 757 ITT n=746 *Sex:* F/M379:367 *Age range:*18-75 years	Primary efficacy measure Continuous quit rate over the last 4 weeks of treatment. Secondary efficacy measures Continuous Abstinence Rate, last 4 weeks of treatment through week 52 Seven day point prevalence of abstinence; End of treatment, week 24 and week 52 4 week point prevalence of abstinence week 52 Long Term Quit Rate (LTQR) at week 52

5.3.2 Participants

Provide details of the inclusion and exclusion criteria, and describe the patient characteristics at baseline. Highlight any differences between study groups.

Trial Population
Inclusion and exclusion criteria for the four trials were similar.

Inclusion Criteria:

- Male or female cigarette smokers between the ages of 18 and 75 years who were motivated to stop smoking
- Females of non-childbearing potential who were not nursing could be included. Females of childbearing potential could be included provided that they were not pregnant, not nursing, and were practicing effective contraception
- Subjects must have smoked an average of at least 10[a] cigarettes per day during the past year and over the month prior to the screening visit, with no period of abstinence greater than three months in the past year
- Subjects who were able to be outpatients and assessed in a clinic setting
- Subjects who had no serious or unstable disease within the past six months and were judged able and willing to complete the study

[a]15 for the open-label varenicline/NRT study

Exclusion Criteria:

Subjects

- who had used bupropion, Zyban, or Wellbutrin* previously **
- for whom treatment with Zyban was not appropriate **
- with diabetes mellitus requiring insulin or oral hypoglycaemics
- with hepatic or renal impairment
- with current or prior diagnosis of anorexia nervosa or bulimia nervosa
- who had taken monoamine oxidase (MAO) inhibitors within the past 14 days
- with clinically significant cardiovascular disease in the past six months
- with uncontrolled hypertension, severe chronic obstructive pulmonary disease, a history of cancer or clinically significant allergic reactions
- with a body mass index (BMI) less than 15 or greater than 38. No subject was enrolled with a weight less than 100 pounds
- currently or within the past 12 months requiring treatment for depression, with current or prior history of panic disorder, psychosis, or bipolar disorder
- with a history of drug (except nicotine) or alcohol abuse or dependence within the past 12 months
- receiving concomitant treatment with another investigational drug within 30 days of the study baseline visit, or with plans to take another investigational drug within 30 days of study completion
- who had been previously randomised in a study that included varenicline
- with a requirement to use other medications during the study that might interfere

with the evaluation of the study drug (e.g. nicotine replacement therapy)
- who had used a nicotine replacement product, clonidine, or nortriptyline within the previous month
- who had used tobacco products other than cigarettes, including pipe tobacco, cigars, snuff, and chew, or marijuana within the past month and did not agree to abstain from use of these products during study participation

*Wellbutrin is the US trade name for bupropion. **Trials A3051028 and A3051036.

Baseline Patient Characteristics

The baseline characteristics of the patients in the four varenicline trials are shown in Tables 3, 4 and 5.

Table 3: Comparative Trials: Baseline Characteristics of Patients and Smoking History at Screening

Patient Characteristic	Varenicline	Bupropion	Placebo
No. Patients			
Trial A3051028			
Total	**349**	**329**	**344**
Male	175 (50.1%)	192 (58.4%)	186 (54.1%)
Female	174 (49.9%)	137 (41.6%)	158 (45.9%)
Trial A3051036			
Total	**343**	**340**	**340**
Male	189 (55.1%)	206 (60.6%)	198 (58.2%)
Female	154 (44.9%)	134 (39.4%)	142 (41.8%)
Age (Years)			
Trial A3051028			
Mean (SD)	42.5 (11.2)	42.0 (11.7)	42.6 (11.8)
Range	18-75	18-75	18-73
Trial A3051036			
Mean (SD)	44.6 (11.5)	43.0 (11.8)	42.3 (11.6)
Range	18-75	18-73	19-75
No. Years Smoked			
Trial A3051028			
Mean	24.3	24.1	24.7
Range	2-56	2-61	1-61
Trial A3051036			
Mean	27.2	25.5	24.3
Range	2-59	2-57	2-60
Cigarettes smoked/day			
Trial A3051028			
Mean	21.0	21.0	21.5
Range	10-70	10-65	10-80
Trial A3051036			
Mean	22.5	21.8	21.5
Range	10-60	10-60	10-60
Lifetime serious quit attempts			
Trial A3051028			
None	54 (15.5%)	47 (14.3%)	58 (16.9%)
1 or more	294 (84.5%)	282 (85.7%)	285 (83.1%)
Trial A3051036			
None	55 (16.0%)	48 (14.1%)	48 (14.1%)
1 or more	288 (84.0%)	292 (85.9%)	292 (85.9%)

Table 4: Maintenance Trial: Baseline Characteristics of Patients and Smoking History at Screening

Patient Characteristic	Open-label Phase	Double-blind Phase	
		Varenicline	Placebo
No. Patients			
Male	941 (48.8%)	303 (50.3%)	292 (48.3%)
Female	986 (51.2%)	299 (49.7%)	312 (51.7%)
Age (Years)			
Mean (SD)	44.2 (10.7)	45.4 (10.4)	45.3 (10.4)
Range	18-75	18-73	20-73
No. Years Smoked			
Mean	27.2	28.2	28.1
Range	2-59	3-58	2-58
No. Cigarettes smoked per day			
Mean	21.6	20.7	20.7
Range	3-99	8-60	10-65
Lifetime Serious Quit attempts			
None	341 (17.7%)	99 (16.4)	103 (17.1)
1 or more	1586 (82.3%)	503 (83.6)	501 (82.9)

Table 5: Open-label Varenicline/NRT Trial: Baseline Characteristics of Patients and Smoking History at Screening

Patient Characteristic	Varenicline	NRT
No. Patients		
Male	182 (48.4%)	185 (50.0%)
Female	194 (51.6%)	185 (50.0%)
Age (Years)		
Mean (SD)	42.9 (10.5)	42.9 (12.0)
Range	19-75	18-73
No. Years Smoked		
Mean	25.9	25.2
Range	2-58	1-68
No. Cigarettes smoked per day		
Mean	25.9	25.2
Range	2-58	1-62
Lifetime Serious Quit attempts		
None	52 (13.9)	38 (10.3)
1 or more	323 (86.1)	332 (89.7)

5.3.3 Patient numbers

Provide details of the numbers of patients who were eligible to enter the RCT, randomised, and allocated to each treatment. Provide details of and the rationale for patients who crossed over treatment groups and/or were lost to follow up/ withdrew from the RCT. This information should be presented as a CONSORT flow chart.

This information is presented as a consort flow chart, with additional detail provided in tabular format, for each of the three randomised controlled trials in varenicline.

First Comparative Trial A3051028

Figure 1: A3051028 Patient flowchart

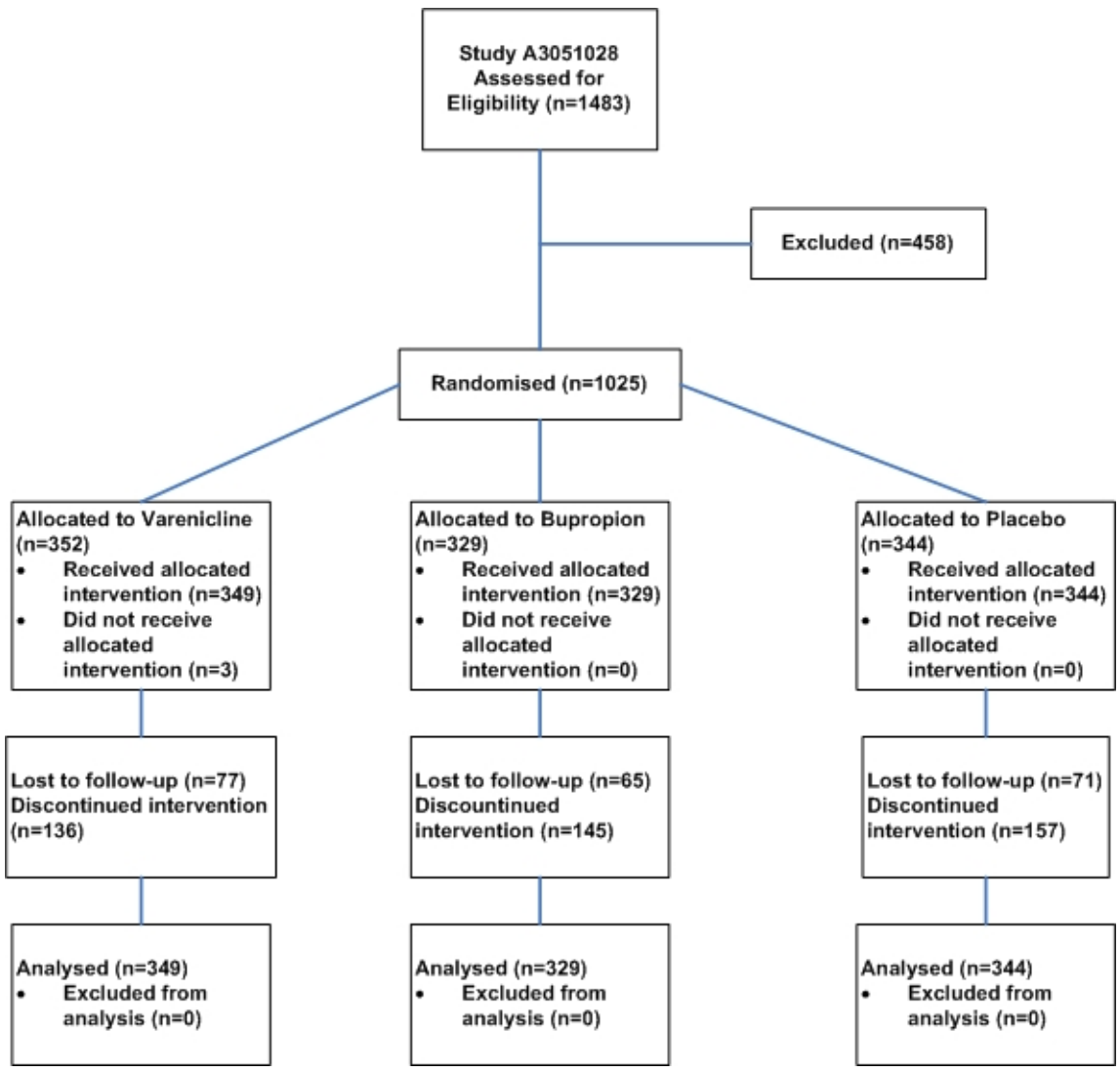


Table 6: Trial A3051028 Subject Disposition (Number (%) of Subjects)

	Varenicline		Zyban		Placebo	
Number screened = 1483						
Assigned to treatment	352		329		344	
Treated[a]	349		329		344	
Completed Study[b]	213	(61.0)	184	(55.9)	187	(54.4)
Discontinued Study	136	(39.0)	145	(44.1)	157	(45.6)
During Treatment Phase	90	(25.8)	104	(31.6)	129	(37.5)
Adverse events	14	(4.0)	34	(10.3)	24	(7.0)
Lack of efficacy	2	(0.6)	1	(0.3)	4	(1.2)
Protocol deviation	4	(1.1)	1	(0.3)	6	(1.7)
Refusal to participate further	23	(6.6)	31	(9.4)	42	(12.2)
Lost to follow-up	43	(12.3)	36	(10.9)	49	(14.2)
Other[c]	4	(1.1)	1	(0.3)	4	(1.2)
During Nontreatment Follow-up Phase	46	(13.2)	41	(12.5)	28	(8.1)
Subject died	0	(0.0)	0	(0.0)	1	(0.3)
Protocol deviation	0	(0.0)	1	(0.3)	0	(0.0)
Refusal to participate further	11	(3.2)	10	(3.0)	5	(1.5)
Lost to follow-up	34	(9.7)	29	(8.8)	22	(6.4)
Other[d]	1	(0.3)	1	(0.3)	0	(0.0)

Second Comparative Trial A3051036

Figure 2: A3051036 Patient flowchart

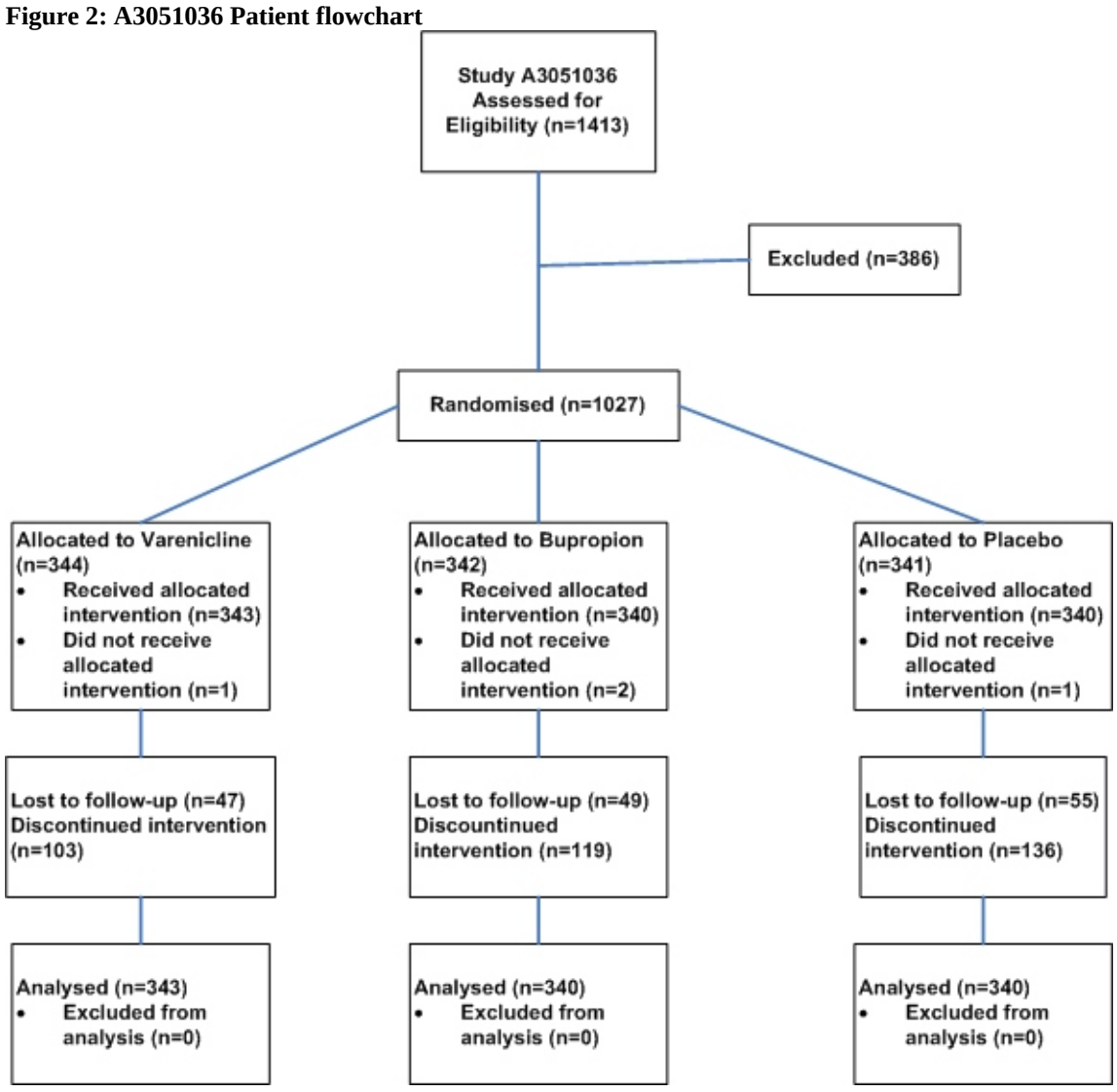


Table 7: Trial A3051036 Subject Disposition (Number (%) of Subjects)

	Varenicline		Zyban		Placebo	
Number screened = 1413						
Assigned to treatment	344		342		341	
Treated[a]	343		340		340	
Completed Study[b]	240	(70.0)	221	(65.0)	204	(60.0)
Discontinued Study	103	(30.0)	119	(35.0)	136	(40.0)
During Treatment Phase	83	(24.2)	100	(29.4)	118	(34.7)
Adverse events	14	(4.1)	16	(4.7)	13	(3.8)
Lack of efficacy	1	(0.3)	0		3	(0.9)
Protocol deviations	2	(0.6)	9	(2.6)	4	(1.2)
Pregnancy	1	(0.3)	1	(0.3)	0	0
Refusal to participate further	28	(8.2)	31	(9.1)	51	(15.0)
Lost to follow-up	33	(9.6)	39	(11.5)	43	(12.6)
Other[c]	4	(1.2)	4	(1.2)	4	(1.2)
During Nontreatment Follow-up Phase	20	(5.8)	19	(5.6)	18	(5.3)
Subject died	0	0	1	(0.3)	0	0
Protocol deviations	0	0	2	(0.6)	1	(0.3)
Refusal to participate further	3	(0.9)	6	(1.8)	4	(1.2)
Lost to follow-up	14	(4.1)	10	(2.9)	12	(3.5)
Other[d]	3	(0.9)	0	0	1	(0.3)

Maintenance Trial A3051035

Figure 3: A3051035 Patient Flowchart

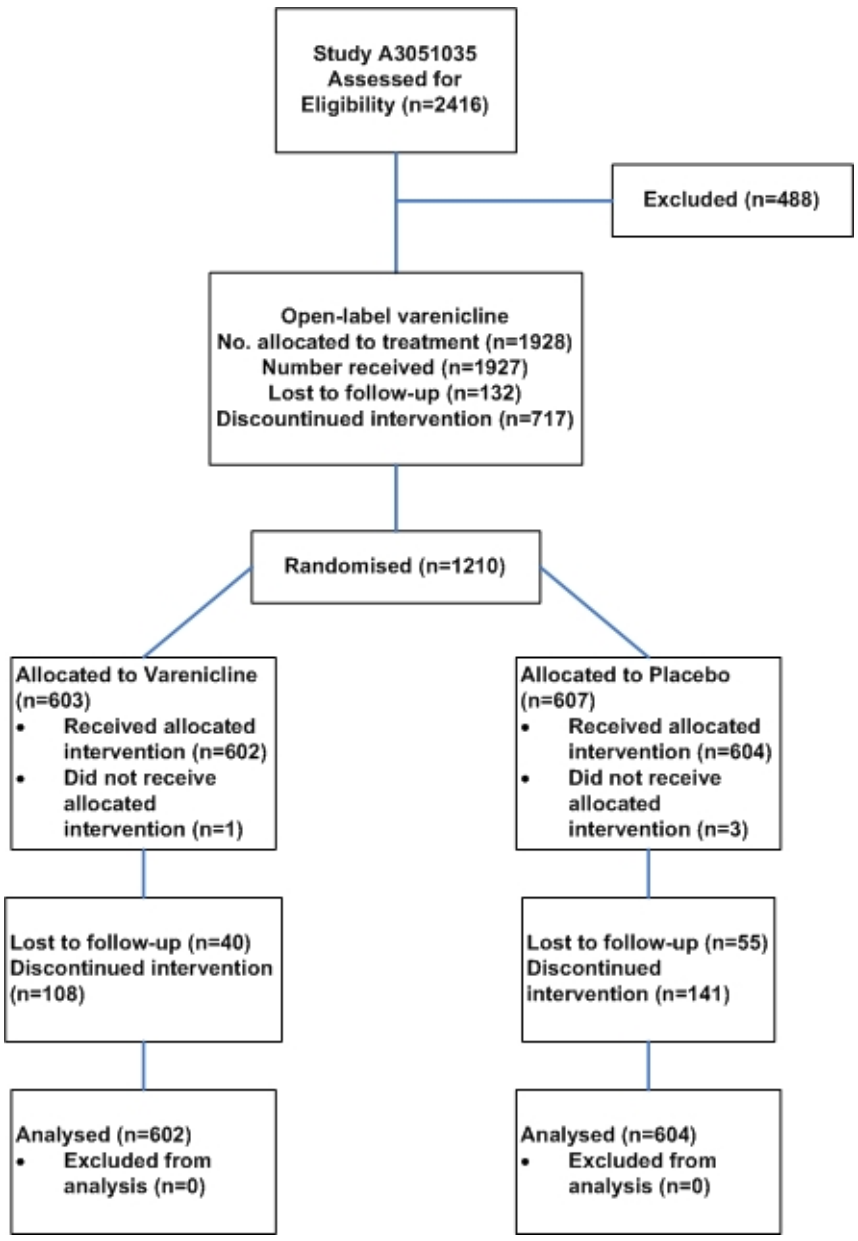


Table 8: Trial A3051035 Subject Disposition (No. (%) of Subjects) Open-Label Treatment Phase

	Varenicline	
Number screened = 2416		
Assigned to treatment	1928	
Treated[a]	1927	
Completed open-label phase	1210	(62.8)
Discontinued from study	717	(37.2)
Discontinuations by reason:		
Adverse events	200	(10.4)
Lack of efficacy	29	(1.5)
Protocol deviation	71	(3.7)
Pregnancy	1	(0.1)
Refusal to participate further	150	(7.8)
Lost to follow-up	132	(6.9)
Other[b]	134	(7.0)

Table 9: Trial A3051035 Subject Disposition (No. (%) of Subjects) Double-Blind Treatment Phase

	Double-blind Varenicline		Double-blind Placebo	
Randomized	603		607	
Treated[a]	602		604	
Completed study	494	(82.1)	463	(76.7)
Discontinued from study	108	(17.9)	141	(23.3)
Treatment Phase (Weeks 13-24)	47	(7.8)	94	(15.6)
Discontinuations by reason:				
Adverse events	8	(1.3)	8	(1.3)
Lack of efficacy	4	(0.7)	5	(0.8)
Protocol deviation	3	(0.5)	2	(0.3)
Refusal to participate further	19	(3.2)	44	(7.3)
Lost to follow up	12	(2.0)	31	(5.1)
Other[b]	1	(0.2)	4	(0.7)
Nontreatment Follow-up Phase	61	(10.1)	47	(7.8)
Discontinuations by reason:				
Death	2	(0.3)	0	(0.0)
Adverse Events	2	(0.4)	1	(0.2)
Lack of efficacy	0	(0.0)	2	(0.3)
Refusal to participate further	27	(4.5)	19	(3.1)
Lost to follow up	28	(4.7)	24	(4.0)
Other[c]	2	(0.3)	1	(0.2)

Figure 4: A3051044 Study Flow Chart

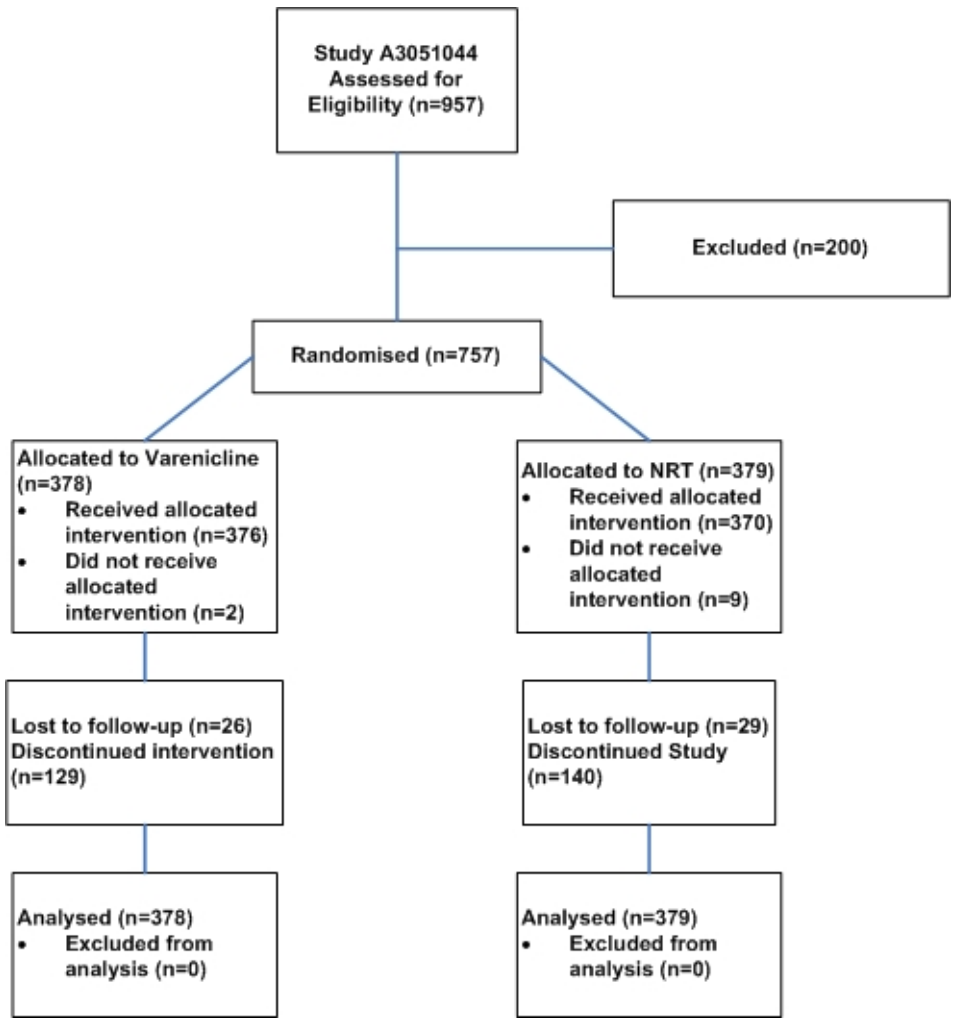


Table 10: Trial A3051044 Subject Disposition (Number (%) of Subjects)

	Varenicline		NRT	
Number screened = 957				
Assigned to treatment	378		379	
Treated[a]	376	(100.0)	370	(100.0)
Completed Study[b]	247	(65.7)	230	(62.2)
Discontinued Study	129	(34.3)	140	(37.8)
During Treatment Phase	65	(17.3)	75	(20.3)
Adverse events	13	(3.5)	6	(1.6)
Lack of efficacy	0		8	(2.2)
Protocol deviations	1	(0.3)	2	(0.5)
Refusal to participate further	25	(6.6)	34	(9.2)
Lost to follow-up	22	(5.9)	18	(4.9)
Other[c]	4	(1.1)	7	(1.9)
During Nontreatment Follow-up Phase	64	(17.0)	65	(17.6)
Lack of efficacy	0		1	(0.3)
Protocol deviations	0		1	(0.3)
Refusal to participate further	22	(5.9)	19	(5.1)
Lost to follow-up	26	(6.9)	29	(7.8)
Other[d]	16	(4.3)	15	(4.1)

[a]Percentages based on number of subjects treated.
[b]Subjects could discontinue study medication but remain in the study.
[c]Other reasons (treatment phase): varenicline – 2 subjects moved or went out of the city for an extended period, 2 Varenicline subjects were no longer motivated. NRT – 4 subjects moved or went out of the city; 1 subject was no longer motivated; 2 subjects continued to smoke cannabis or use codeine.
[d]Other reasons (non-treatment phase): Varenicline – 4 subjects moved; 3 subjects used Nicoderm patch and/or bupropion HCL; 4 subjects had other commitments; 4 subjects. were no longer motivated/started smoking again; 1 subject started another trial. NRT – 1 subject housebound; 4 subjects moved or went out of the city; 3 subjects had other commitments; 6 subjects were no longer motivated; 1 subject used bupropion.

5.3.4 Outcomes

Provide details of the outcomes investigated and the measures used to investigate those outcomes. Indicate which outcomes were specified in the trial protocol as primary or secondary, and whether they are relevant with reference to the specification of the decision problem. This should include therapeutic outcomes, as well as patient-related outcomes such as assessment of quality of life and social outcomes, and any arrangements to measure concordance. Data provided should be from pre-specified outcomes rather than post-hoc analyses. Where appropriate, also provide details of the principal outcome measure(s), including details of length of follow-up, timing of assessments, scoring methods, evidence of reliability/validity, and current status of the measure (such as approval by professional bodies or licensing authority).

The Primary Endpoint

- A3051028 and A3051036 - Continuous Abstinence Rate last four weeks of treatment, Week 9 through to Week 12.
- A3051035 - Continuous Abstinence Rate from Week 13 through to week 24.
- A3051044 - Continuous Abstinence Rate for the last 4 weeks of treatment.

The Key Secondary Efficacy Measure was:

- A3051028 and A3051036 - Continuous Abstinence Rate from Week 9 through Week 52
- A3051035 - Continuous Abstinence Rate from Week 13 through Week 24.
- A3051044 - Continuous Abstinence Rate from last 4 weeks of treatment through Week 52.

5.3.5 Statistical analysis and definition of study groups

State the primary hypothesis or hypotheses under consideration and the statistical analysis used for testing hypotheses. Also provide details of the power of the study and a description of sample size calculation, including rationale and assumptions. Provide details of how the analysis took account of patients who withdrew (for example, a description of the intention-to-treat analysis undertaken, including censoring methods; whether a per-protocol analysis was undertaken). Provide details of any subgroup analyses that were undertaken and specify the rationale and whether they were pre-planned or post-hoc.

Hypotheses, statistical analysis, the definition of study groups and sample size calculations are summarised in Table 11 below.

Table 11: Summary of statistical methodology, power calculation, study conduct

	Hypothesis	Statistical analysis	Interim analysis	Changes in conduct of Study or planned analyses	Datasets analysed	Sample calculation
A3051028 **&** **A3051036**	Varenicline is superior to bupropion and Placebo for promoting smoking cessation in adult smokers.	All measures of abstinence were analysed as binary data. Subjects were classified as responders or non-responders for each parameter and time-point, and analyses were of responder rates (n responders/N treated). In the analyses of these parameters, subjects who withdrew from the study and therefore did not have data for subsequent visits were assumed to be smokers (non-responders) for the remainder of the study, regardless of their smoking status at the last recorded visit. That is, in calculation of abstinence rates at any time-point, subjects who discontinued from the study continued to be represented in the denominator but not in the numerator, regardless of their last reported smoking status. Binary data were analyzed using logistic regression including treatment and centre in the primary model. Hypothesis testing was carried out using the likelihood ratio chi-squared statistic. The model was examined for goodness of fit using both the deviance score statistic and an analysis of the residuals. All significance tests were 2-tailed using an overall level of significance of alpha = 0.05. A step-down procedure was employed for the analysis of the primary and key secondary endpoints, as described below. Pooling of data for small centres was not necessary.	Interim analyses were not performed for these studies	All efficacy measures and planned analysis methods were defined in the statistical analysis plan, which were finalised before the treatment blinds were broken	The primary population for all efficacy and safety analyses was the All Subjects population, defined as randomised subjects who took at least one dose of study medication. An analysis was conducted on all patients randomised, irrespective of treatment received for publication. The results of the published analyses are presented here .	Sample sizes were approximated based on the comparison of varenicline 1 mg BID with bupropion, using a two-group continuity-corrected Chi-Squared test with a 0.050 two-sided significance level. Three hundred and thirty five (335) subjects per group had at least 90% power to detect a difference between bupropion and varenicline, assuming the true bupropion response rate for the 4-week CQR is 0.286 and an odds ratio = 1.721. These studies were intended to be powered to detect differences in both the primary (4-week CQR) and the key secondary endpoints (Continuous Abstinence rate from Week 9 through Week 52 and the LTQR at Week 52). The 4-week CQR and Continuous Abstinence rates used in estimating this sample size were extracted from the varenicline initial proof of concept efficacy study (A3051002) results, which compared three doses of varenicline to placebo and incorporated a bupropion arm, and are believed to represent clinically meaningful differences
A3051035	An additional 12 weeks of therapy in patients who have completed an initial 12 week course of varenicline therapy will result in a higher maintenance of abstinence than with placebo.	All measures of abstinence were analysed as binary data. Subjects were classified as responders or non-responders for each parameter and time-point summarised, and analyses were of responder rates (n responders/N treated). In the analyses for all of these parameters, subjects who withdrew from the study and therefore did not have data for subsequent visits were assumed to be smokers (non-responders) for the remainder of the study, regardless of their smoking status at the last recorded visit. That is, in calculation of abstinence rates at any time-point, subjects who discontinued from the study continued to be included in the denominator but not in	No interim analysis was performed for this study	The planned sample size for randomisation to double-blind treatment was 410 subjects per treatment group. It was estimated that an enrolment of 2000 subjects in the open-label treatment phase would provide the necessary 820 eligible subjects (subjects who did not smoke during the last 7 days of open-label treatment). In reality, the smoking cessation rate at Week 12 was higher than anticipated. Due to the 12-week lag period between subject enrolment in the open-label phase and determination of eligibility for continuation in the	The primary population for all efficacy and safety analyses was the All Subjects population, defined as randomised subjects who took at least one dose of study medication. An analysis was conducted on all patients randomised, irrespective of treatment received for publication. The results of the published analyses are	This study was powered to show differences between varenicline and placebo for the primary efficacy endpoint, Continuous Abstinence rate in the double-blind phase (from Week 13 to Week 24), in subjects who had stopped smoking at Week 12 (end of open-label phase). Sample size estimates were based on data for continuous abstinence from Week 7 to Week 24 published for bupropion. Response rates were 52.3% bupropion versus 42.3% placebo. Assuming treatment differences similar to those reported for bupropion in this study the number of subjects per treatment group required to provide 80%

Table 11: Summary of statistical methodology, power calculation, study conduct

	Hypothesis	Statistical analysis	Interim analysis	Changes in conduct of Study or planned analyses	Datasets analysed	Sample calculation
		the numerator, regardless of their last reported smoking status. Binary data were analysed using logistic regression including treatment and centre in the primary model. The comparison between varenicline and placebo was made using the type III analysis for the term treatment group. Hypothesis testing was carried out using the likelihood ratio chi-squared statistic. The model was examined for goodness of fit using both the deviance score statistic and an analysis of the residuals.		double-blind period, the planned sample size was exceeded (1210 subjects randomised) even with reduction of open-label enrolment to 1928 subjects	presented here.	power to detect a treatment difference using a two-group continuity-corrected Chi-Squared test with a 0.050 two-sided significance level was estimated to be 410 subjects
A3051044	Varenicline is superior to NRT for promoting smoking cessation in adults	All measures of abstinence were analyzed as binary data. Subjects were classified as responders or non-responders for each parameter and time-point, and analyses were of responder rates (n responders/N treated). In the analyses of these parameters, subjects who withdrew from the study and therefore did not have data for subsequent visits were assumed to be smokers (nonresponders) for the remainder of the study, regardless of their smoking status at the last recorded visit. That is, in calculation of abstinence rates at any time-point, subjects who discontinued from the study continued to be represented in the denominator but not in the numerator, regardless of their last reported smoking status. Binary data were analyzed using logistic regression including treatment and centre in the primary model. Hypothesis testing was carried out using the likelihood ratio chi-squared statistic. The model was examined for goodness of fit using the deviance score statistic. The additional effect of treatment-by –enter interaction was included in exploratory models. Moreover, sensitivity analyses for the four-week CQR from Weeks 8 to 11 and Weeks 9 to 12 for both treatment groups were conducted using logistic regression. Similarly, summary of the continuous abstinence rate starting from Week 8 and Week 9 for both treatment groups were also conducted.	No interim analysis was performed for this study	All efficacy measures and planned analysis methods were defined in the statistical analysis plan, which were finalised before the treatment blinds were broken	The primary population for all efficacy and safety analyses was the All Subjects population, defined as randomised subjects who took at least one dose of study medication. A pre-specified analysis was conducted on all patients randomised, irrespective of treatment received. The results of both analyses are presented here.	The sample size was approximated based on the comparison of varenicline versus NRT, using a two-group continuity-corrected Chi-Square test with a 0.05 two sided significance level. The study was powered at 90% or greater to detect differences in both the primary endpoint and secondary endpoints of long-term efficacy. Estimates for the NRT 4-week Continuous Quit Rate for the last 4 weeks of treatment and Continuous Abstinence Rate from the last 4 weeks of treatment through Week 52 were based on a review of the literature. Expected varenicline rates were based on the results of varenicline studies A3051002 and A3051007. Three hundred sixty five (365) subjects per group provided at least 90% power to detect a difference in the primary endpoint between the varenicline and NRT groups, assuming a true 4-week CQR at the end of study treatment of 0.24 for NRT and an odds ratio of at least 1.75 for varenicline (varenicline rate of at least 0.356). This sample size also provided at least 90% power to detect a difference in Continuous Abstinence Rate from the last 4 weeks of treatment through Week 52, assuming an NRT rate of 0.115 and an odds ratio of at least 2.0 (varenicline rate of 0.206

5.3.6 Critical appraisal of relevant RCTs

Each RCT should be critically appraised. If there is more than one RCT, tabulate the responses, highlighting any 'commercial in confidence' data. The critical appraisal will be validated by the Evidence Review Group. The following are suggested criteria for critical appraisal, but the list is not exhaustive.

- *How was allocation concealed?*
- *What randomisation technique was used?*

Table 12: Summary of evidence provided in submission for critical appraisal

	Study 1028	**Study 1036**	**Study 1035**	**Study 1044**
Allocation concealment adequate	Yes Table 13	Yes Table 13	Yes Table 13	No – open-label Table 13
Randomisation technique appropriate	Yes Table 13	Yes Table 13	Yes Table 13	Yes Table 13
Sample size justification provided	Yes Table 13	Yes Table 13	Yes Table 13	Yes Table 13
Follow-up adequate	Yes Table 2	Yes Table 2	Yes Table 2	Yes Table 2
Individuals undertaking outcomes assessment aware of allocation	No	No	No	Yes - open-label
Parallel group or cross-over design	N/A	N/A	N/A	N/A
Study groups comparable	Yes Tables 3,4,5	Yes Tables 3,4,5	Yes Tables 3,4,5	Yes Tables 3,4,5
Statistical analysis appropriate	Yes Table 11	Yes Table 11	Yes Table 11	Yes Table 11
ITT analysis undertaken	Yes Table 11	Yes Table 11	Yes Table 11	Yes Table 11
Drug dose in study comparable to that recommended in SmPC	Yes Table 2	Yes Table 2	Yes Table 2	Yes Table 2
Potential confounders	None known	None known	None known	[redacted]

The analysis of allocation concealment, blinding and sample size justification is presented in Table 13 below.

	Table 13: Summary of allocation concealment, blinding and sample size justification		
	Allocation concealment	**Blinding**	**Sample size justification**
A3051028 **&** **A3051036**	The studies used a single, centralised randomisation sequence (block size = 6) assigning subjects to varenicline, bupropion, or placebo in a ratio of 1:1:1 (varenicline: bupropion: placebo). Prior to the start of the study, a randomisation list was produced indicating treatment assignment for each ordered subject number. This randomisation was created by a computer-generated pseudo-random code using the method of randomly permuted blocks, and was stratified by centre. Investigators obtained subject identification numbers and study drug assignments via a drug management system employing web-based and telephone technology. The investigator assigned numbers to the subjects at the baseline visit in the order that they were deemed eligible for treatment. The subject then received study medication assigned to the corresponding number	Knowledge of treatment assignments was withheld from those directly involved with the operation of the study. This included study subjects, study investigators and their staffs, and the sponsor personnel involved in clinical operations.	Sample sizes were approximated based on the comparison of varenicline 1 mg BID with bupropion, using a two-group continuity-corrected Chi-Squared test with a 0.050 two-sided significance level. Three hundred and thirty five (335) subjects per group had at least 90% power to detect a difference between bupropion and varenicline, assuming the true bupropion response rate for the 4-week CQR is 0.286 and an odds ratio = 1.721. These studies were intended to be powered to detect differences in both the primary (4-week CQR) and the key secondary endpoints (Continuous Abstinence rate from Week 9 through Week 52 and the LTQR at Week 52). The 4-week CQR and Continuous Abstinence rates used in estimating this sample size were extracted from the varenicline initial proof of concept efficacy study (A3051002) results, which compared three doses of varenicline to placebo and incorporated a bupropion arm, and are believed to represent clinically meaningful differences
A3051035	All subjects received varenicline in the open-label phase of the study. For subjects who qualified for double-blind treatment the study used a single, centralised randomisation sequence (block size = 4) assigning subjects to varenicline or placebo in a ratio of 1:1. Prior to the start of the study, a randomisation list was produced indicating treatment assignment for each ordered subject number. This randomisation was created by a computer-generated pseudo-random code using the method of randomly permuted blocks, and was stratified by centre. Investigators obtained subject identification numbers and study drug assignments via a drug management system employing web-based and telephone technology. The investigator assigned numbers to the subjects in the order that they were deemed eligible for entry into the double-blind phase. The subject then received study medication assigned to the corresponding number.	Knowledge of treatment assignments was withheld from those directly involved with the operation of the study. This included study subjects, study investigators and their staffs, and the sponsor personnel involved in clinical operations.	This study was powered to show differences between varenicline and placebo for the primary efficacy endpoint, Continuous Abstinence rate in the double-blind phase (from Week 13 to Week 24), in subjects who had stopped smoking at Week 12 (end of open-label phase). Sample size estimates were based on data for continuous abstinence from Week 7 to Week 24 published for bupropion. Response rates were 52.3% bupropion versus 42.3% placebo. Assuming treatment differences similar to those reported for bupropion in this study the number of subjects per treatment group required to provide 80% power to detect a treatment difference using a two-group continuity-corrected Chi-Squared test with a 0.050 two-sided significance level was estimated to be 410 subjects
A3051044	This was an open-label study that used a single, centralized randomisation sequence (block size = 4) assigning subjects to varenicline or NRT in a ratio of 1:1. Prior to the start of the study, a randomisation list was produced indicating treatment assignment for each subject number. This randomisation was created by a computer-generated pseudo random code using the method of randomly permuted blocks, and was stratified by centre. Investigators obtained subject identification numbers and study drug assignments via a drug management system employing web-based and telephonic technology. The investigator assigned numbers to the subjects at the baseline visit in the order that they were deemed eligible for treatment. The subject then received study medication assigned to that number.	This was an open-label study	The sample size was approximated based on the comparison of varenicline versus NRT, using a two-group continuity-corrected Chi-Square test with a 0.05 two-sided significance level. The study was powered at 90% or greater to detect differences in both the primary endpoint and secondary endpoints of long-term efficacy. Estimates for the NRT 4-week Continuous Quit Rate for the last 4 weeks of treatment and Continuous Abstinence Rate from the last 4 weeks of treatment through Week 52 were based on a review of the literature. Expected varenicline rates were based on the results of varenicline studies A3051002 and A3051007. Three hundred sixty-five (365) subjects per group provided at least 90% power to detect a difference in the primary endpoint between the varenicline and NRT groups, assuming a true 4-week CQR at the end of study treatment of 0.24 for NRT and an odds ratio of at least 1.75 for varenicline (varenicline rate of at least 0.356). This sample size also provided at least 90% power to detect a difference in Continuous Abstinence Rate from the last 4 weeks of treatment through Week 52, assuming an NRT rate of 0.115 and an odds ratio of at least 2.0 (varenicline rate of 0.206).

5.4 Results of the relevant comparative RCTs

Provide the results for all relevant outcome measure(s) pertinent to the decision problem. If there is more than one RCT, tabulate the responses, highlighting any 'commercial in confidence' data. The information may be presented graphically to supplement text and tabulated data. Data from intention-to-treat analyses should be presented wherever possible and a definition of the included patients provided. If patients have been excluded from the analysis, the rationale for this should be given.

For each outcome for each included RCT the following information should be provided.

• The unit of measurement.
• The size of the effect; for dichotomous outcomes, the results ideally should be expressed as both relative risks (or odds ratios) and risk (or rate) differences. For time-to-event analysis, the hazard ratio is an equivalent statistic. Both absolute and relative data should be presented.
• A 95% confidence interval.
• The number of patients included in the analysis.
• The median follow-up time of analysis
• State whether intention-to-treat was used for the analysis and how data were imputed if necessary.
• Discuss and justify definitions of any clinically important differences.

• Where interim RCT data are quoted, this should be clearly stated, along with the point at which data were taken and the time remaining until completion of that RCT. Analytical adjustment should be described to cater for the interim nature of the data.
• If the RCT measures a number of outcomes, discuss whether and how an adjustment was made for multiple comparisons in the analysis.
• Other relevant data that may assist in interpretation of the results may be included, such as adherence to medication and/or study protocol.

The Double-blind Comparative Trials

The primary outcome measure was the Continuous Abstinence Rate for the last 4 weeks of study treatment. The key secondary endpoint was the Continuous Abstinence Rate for Weeks 9 through to 52.

Primary End Point Results

For the Continuous Abstinence Rate Weeks 9 through 12, varenicline demonstrated statistical superiority to both bupropion and placebo.

Table 14: Continuous Abstinence Rate Weeks 9 through 12 (%)

	Varenicline	**Bupropion**	**Placebo**
A3051028	44.0	29.5	17.7
A3051036	43.9	29.8	17.6

Table 15: A3051028 Continuous Abstinence Rate Weeks 9 through 12

	n/N	CQR %	Odds Ratio (95% CI) (Varenicline versus:)	p-Value (Varenicline versus:)
Varenicline	155/349	44.4		
Placebo	61/344	17.7	3.85 (2.70-5.50)	<0.001
Bupropion	97/329	29.5	1.93 (1.40-2.68)	<0.001

Table 16: A3051036 Continuous Abstinence Rate Weeks 9 through 12

	n/N	CQR %	Odds Ratio (95% CI) (Varenicline versus:)	p-Value (Varenicline versus:)
Varenicline	151/343	43.9		
Placebo	60/340	17.6	3.85 (2.69-5.50)	<0.001
Bupropion	102/340	29.8	1.90 (1.40-2.68)	<0.001

Odds Ratios for Primary Endpoint

Patients have about double the odds of quitting with varenicline than with bupropion

Study A3051028 Odds Ratio 1.93, (95% CI 1.40-2.68; p<0.001)
Study A3051036 Odds Ratio 1.90, (95% CI, 1.38-2.62; p<0.001)

Patients have about four times greater odds of quitting with varenicline than with placebo

Study A3051028 Odds Ratio 3.85, (95% CI, 2.70-5.50; p<0.001)
Study A3051036 Odds Ratio 3.85, (95% CI, 2.69-5.50; p<0.001)

Secondary endpoint results

For the Continuous Abstinence Rate Weeks 9 through to 52 varenicline demonstrated superiority to bupropion and statistical superiority to placebo

Table 17: Continuous Abstinence Rate Weeks 9 through 52 (%)

	Varenicline	Bupropion	Placebo
A3051028	21.9	16.1	8.4
A3051036	23	14.6	10.3

Odds Ratios for Secondary Endpoint

Patients have about one and a half times greater odds of quitting with varenicline than with bupropion

Study A3051028 Odds Ratio 1.46, (95% CI, 0.99-2.17; p<0.057)
Study A3051036 Odds Ratio 1.77, (95% CI, 1.19-2.63; p=0.004)

Patients have about three times greater odds of quitting with varenicline than with placebo

Study A3051028 Odds Ratio 3.09, (95% CI, 1.95-4.91; p<0.01)
Study A3051036 Odds Ratio 2.66, (95% CI, 1.72- 4.11; p<0.01)

In a pooled analysis of the two comparative trials, the odds of quitting smoking with varenicline were almost four times that of quitting with placebo, and almost twice that of quitting with bupropion.

The Maintenance of Abstinence Trial (A3051035)
The primary endpoint was the Continuous Abstinence Rate from Week 13 through Week 24. The key secondary endpoint was the Continuous Abstinence Rate from Week 13 through week 52.

Primary Endpoint Results
As measured by the Continuous Abstinence Rate Week 13 through to Week 24 (Double-blind phase), 71% of patients who received an additional 12 weeks of varenicline were still abstinent, compared with 50% of patients who received placebo.

Table 18: Continuous Abstinence Rate from Week 13 through to Week 24 Varenicline versus double-blind placebo).

	n/N	CQR %	Odds Ratio (95% CI)	p-Value
Varenicline	425/602	70.6		
Placebo	301/604	49.8	2.47 (1.95-3.15)	<0.0001

Odds Ratio for Primary Endpoint
At week 24, patients who received varenicline had an Odds Ratio of 2.48 (95% CI, 1.95-3.16; p<0.001) of maintaining abstinence compared to patients who received placebo.

Secondary Endpoint Results
As measured by the Continuous Abstinence Rate, Week 13 through to Week 52, 43.6% of patients who received an additional 12 weeks of varenicline were still abstinent, compared with 36.9% of patients who received placebo.

Table 19: Continuous Abstinence Rate from Week 13 through to Week 52

	n/N	CQR %	Odds Ratio (95% CI) Varenicline vs. placebo	p-Value Varenicline vs. placebo
Varenicline	265/602	44.0		
Placebo	224/604	37.1	1.35 (1.07-1.70)	<0.0126

Odds Ratio for Secondary Endpoint
At week 52, patients who received varenicline had an Odds Ratio of 1.34 (95% CI, 1.06-1.69; p<0.02) of maintaining abstinence compared to patients who received placebo

The open-label Varenicline versus NRT transdermal patch trial (A3051044)
The primary endpoint was the Continuous Abstinence Rate for the last 4 weeks of treatment (Weeks 9 through 12 for varenicline and Weeks 8 through 11 for NRT). The key secondary endpoint was the Continuous Abstinence Rate from the last 4 weeks of treatment through Week 52.

[redacted]

[redacted]

5.5 Meta-analysis

Where more than one study is available and the methodology is comparable, a meta-analysis should be undertaken. If a meta-analysis is not considered appropriate, the rationale should be given and a qualitative overview provided. The overview should summarise the overall results of the individual studies with reference to their critical appraisal. If any of the relevant RCTs listed in response to section 5.2.3 are excluded from the meta-analysis, the reasons for doing so should be explained. The impact that each exclusion has on the overall meta-analysis should be explored. The following steps should be used as a minimum.

• Perform a statistical assessment of heterogeneity. If the visual presentation and/or the statistical test indicate that the RCT results are heterogeneous, try to provide an explanation for the heterogeneity.
• Statistically combine (pool) the results for both relative risk reduction and absolute risk reduction using both the fixed effects and random effects models (giving four combinations in all).
• Provide an adequate description of the methods of statistical combination and justify their choice.
• Undertake sensitivity analysis where appropriate.
• Tabulate and/or graphically display the individual and combined results.

[Meta-analysis methods/ results table/graph]

Data Analysis

In order to assess inter-rater reliability on inclusion of articles, the *Phi* statistic (φ) was calculated. This provides a measure of inter-observer agreement independent of chance (Meade et. al. 2001) Odds Ratios [OR] and appropriate 95% Confidence Intervals [CIs] of outcomes were calculated according to the number of events of abstinence reported in the original studies or sub-studies. In circumstances of zero outcome events in one arm of a trial, 1 was added to each arm, as suggested by Sheehe (1966). All NRT interventions versus all controls were pooled using the DerSimonian-Laird (1986) random effects method, which recognises and anchors studies as a sample of all potential studies, and incorporates an additional between-study component to the estimate of variability. Table 17 below records odds ratios and relative risk reductions using both random and fixed effects. The I2 statistic was calculated for each analysis as a measure of the proportion of the overall variation that is attributable to between-study heterogeneity (Higgins and Thompson, 2002). Forest plots are displayed for each primary analysis, showing individual study effect measures with 95% CIs, and the overall DerSimonian-Laird pooled estimate.

A meta-regression analysis on the NRT studies was then conducted with predictors of heterogeneity including the following covariates: placebo control; reporting of sequence generation; reporting of allocation concealment; use of gum or patch; and, method of chemical confirmation of abstinence. When the meta-regression indicated heterogeneity, alternative sensitivity tests using z-tests were conducted to determine differences between the studies, reporting the covariates to the pooled all-studies effect size. Separate pooled analyses of NRT versus placebo, gum versus control and patch versus control were conducted. All analyses at 1 year and also at 3 months were conducted. For bupropion

trials, all bupropion trials versus all controls were pooled and a meta-regression analysis was conducted using the following covariates: placebo control; reporting of sequence generation; reporting of allocation concealment; method of chemical confirmation of abstinence; and plans to quit.

Separate meta-regression analyses were conducted and the relevant ORs for the covariates as the exponent of the point estimates were calculated (Thompson and Higgins, 2002). All placebo-controlled trials were pooled and effect sizes at 1 year and at 3 months were evaluated. For head-to-head trials of bupropion versus NRT, pooled random-effects analyses at 1 year and at three months were conducted. For varenicline trials, pooled random-effects analyses of varenicline versus placebo were conducted at 1 year and at three months and for head-to-head trials of varenicline versus bupropion at 1 year and at three months.

Results

70 RCTs examining NRT versus control interventions were found, 49 of which compared NRT to placebo. Thirty one studies compared NRT to other controlled groups, and one study used both placebo and no intervention as a control group. Thirty-three studies evaluated NRT gum, and 23 evaluated NRT patch. The remaining studies evaluated the efficacy of nicotine inhalers, nasal spray or lozenges. All of the studies provided sufficient details to evaluate NRT versus control at 1 year. Fifty-nine provided sufficient details to evaluate NRT versus control at or about 3 months.

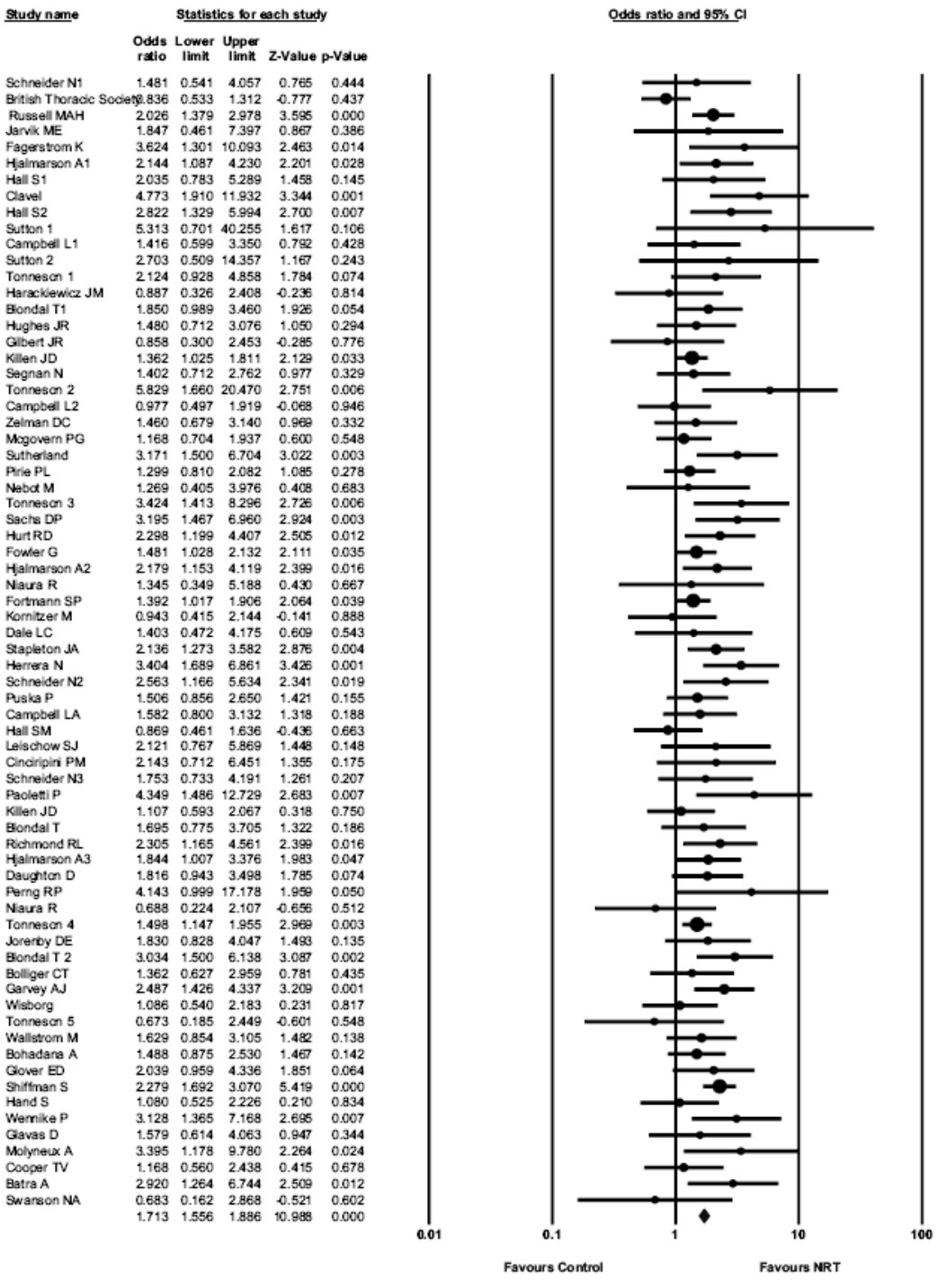
There were11 studies evaluating bupropion versus placebo and one RCT evaluating bupropion with no intervention. A further two of these evaluated bupropion versus NRT. Finally, 4 studies evaluating varenicline versus placebo were identified. Two of these also evaluated varenicline versus bupropion.

Meta-Analysis

NRT

70 trials (total n=28,343) assessing NRT versus controls at 1 year were combined. The pooled OR of smoking cessation favoured NRT over controls (OR 1.71, 95% CI, 1.55-1.88; P=<0.0001, I^2=26.5%, Heterogeneity P=0.02,) (Figure 5). This was consistent when evaluating only placebo controlled NRT trials (49 trials, n=21,512, OR 1.78, 95% CI, 1.60-1.99; P=<0.0001, I^2 27.4%, Heterogeneity P=0.04) or when evaluating with cessation as sustained abstinence (52 trials, total n=22,704, OR 1.72, 95% CI, 1.54-1.93; P=<0.0001, I^2= 29.4%, Heterogeneity P=0.02) or point prevalence (31 trials, n=10,686, OR 1.53, 95% CI, 1.30-1.81; P=0.01, I^2= 46%, Heterogeneity P=0.01). This was also consistent whether one evaluated NRT gum (33 trials, total n=12,245, OR 1.60, 95% CI, 1.37-1.86; P=<0.0001, I^2= 35.8%, Heterogeneity P=0.02) or NRT patch (23 trials, total n=11,108, OR 1.63, 95% CI, 1.41-1.89; P=<0.0001, I^2=12.3%, Heterogeneity P=0.24).

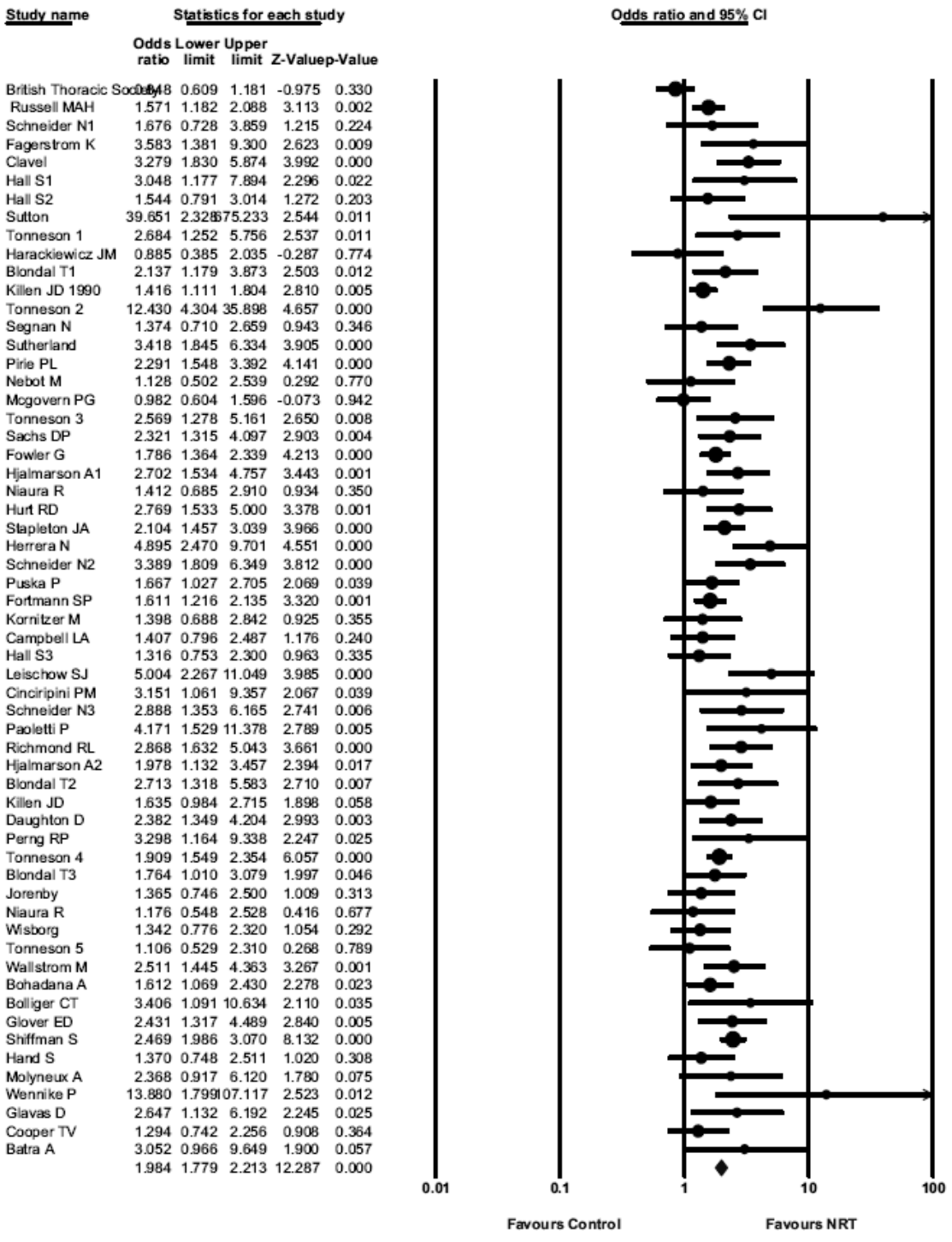
Figure 5: NRT versus Controls at 12 Months



Fifty-nine trials (total n=25,294) provided sufficient details to determine short-term effects of NRT on smoking cessation, as determined at 3 months. The pooled OR of the

59 trials was 1.98 (95% CI, 1.77-2.21; P=<0.0001, I2= 55.5%, Heterogeneity P=<0.0001, See Figure 6). The superiority of NRT over controls was consistent whether one evaluated placebo-controlled trials (42 trials, total n=19,216, OR 2.11, 95% CI, 1.86-2.40; P=<0.0001, I2= 57.6%, Heterogeneity P=<0.001), sustained abstinence (41 trials, total n=19,854, OR 2.04, 95% CI, 1.80-2.31; P=<0.0001, I2= 58%, Heterogeneity P=<0.0001) or point prevalence at 3 months (21 trials, total n=6,453, OR 1.78, 95% CI,1.47-2.14; P=<0.0001, I2=42.4, Heterogeneity P=0.004). Studies assessing gum versus controls at 3 months (24 trials, total n= 9,347) yielded an OR of 1.71 (95% CI, 1.41-2.07; P=<0.0001, I2= 62%, Heterogeneity P=<0.0001) and studies assessing patch versus controls (21 trials, total n=10,957) yielded an OR of 1.93 (95% CI, 1.67-2.24, P=<0.0001; I2= 35%, Heterogeneity P=0.05).

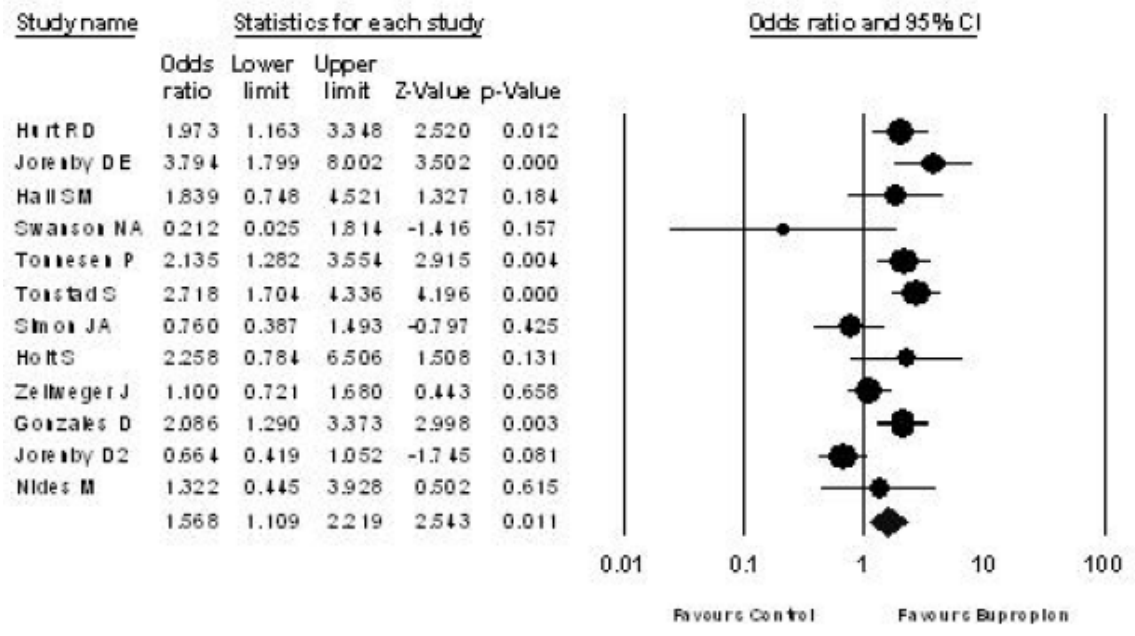
Figure 6: NRT versus Controls at 3 Months



Bupropion

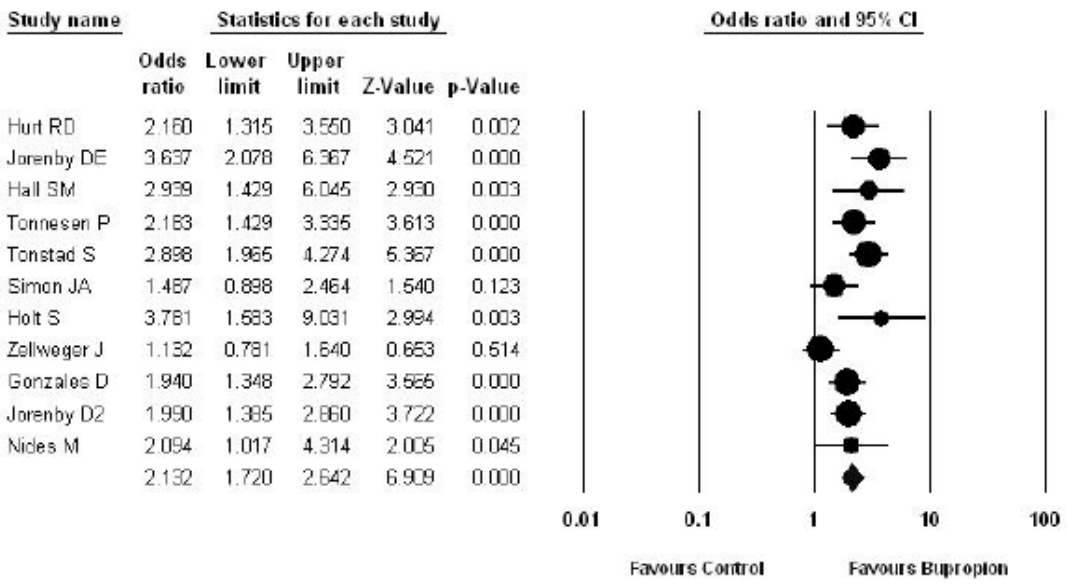
The effect of bupropion on smoking cessation relative to adequate controls at 1 year in 12 trials (total n = 5,228, See Figure 7). The pooled OR was 1.56 (95% CI, 1.10–2.21; P = 0.01, I^2 = 71.5%, Heterogeneity P =< 0.001). This effect was consistent whether examining placebo-controls (11 trials, total n = 5,148, OR 1.64, 95% CI, 1.16–2.30; P =< 0.001, I^2 = 72%, Heterogeneity P = 0.001), sustained abstinence (11 trials, total n = 4,613, OR 1.52, 95% CI, 1.04–2.23; P =< 0.0001, I^2 = 73.6%, Heterogeneity P = 0.0001), or point prevalence (10 trials, total n = 4,845, OR 1.56, 95% CI, 1.13–2.16; P =< 0.0001, I^2 = 75.1%, Heterogeneity P =< 0.0001).

Figure 7: Bupropion versus Controls at 12 Months



In evaluating the effect of bupropion on placebo at 3 months (11 trials, total n = 5,148), the OR was 2.13 (95% CI, 1.72–2.64; P =< 0.0001, I^2 = 53.6%, Heterogeneity P = 0.01, See Figure 8). This effect was consistent across sustained abstinence measures (8 trials, total n = 4,143, OR 2.18, 95% CI, 1.67–2.86; P =< 0.0001, I^2 = 63.5%, Heterogeneity P = 0.008) and point prevalence measures (9 trials, total n = 4,765, OR 2.11, 95% CI, 1.77–2.52, P =< 0.0001; I^2 = 38.8%, Heterogeneity P = 0.10).

Figure 8: Bupropion versus Controls at 3 Months



Varenicline

Four studies assessing the effect of varenicline versus placebo at 1 year were pooled (total n=2,528, See Figure 9). The pooled OR is 2.96 (95% CI, 2.12-4.12; P=<0.0001, I2=20.5%, Heterogeneity P=0.20). This effect was consistent with short-term cessation effects (4 trials, total n=2,528, OR 3.75, 95% CI, 2.65-5.30; P=<0.0001, I2=57.7%, Heterogeneity P=0.06, (See Figure 10)).

Figure 9: Varenicline versus Placebo at 12 Months

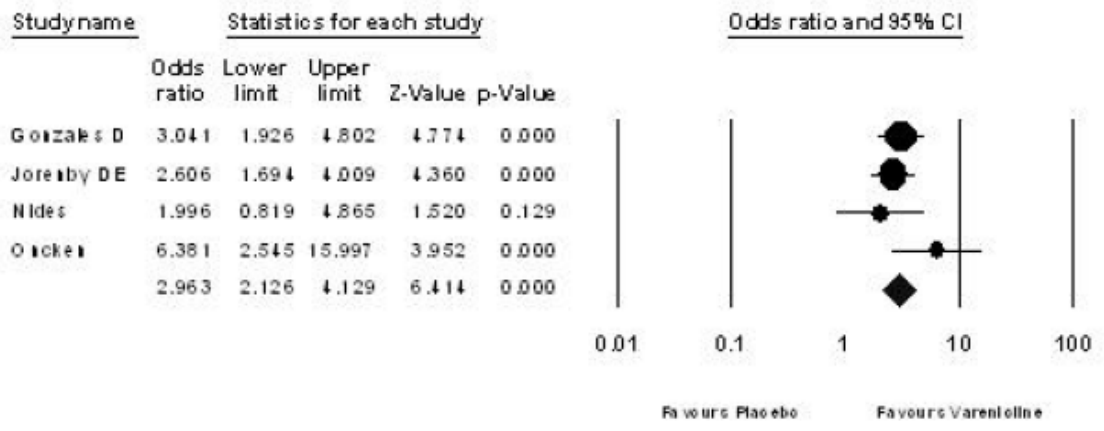
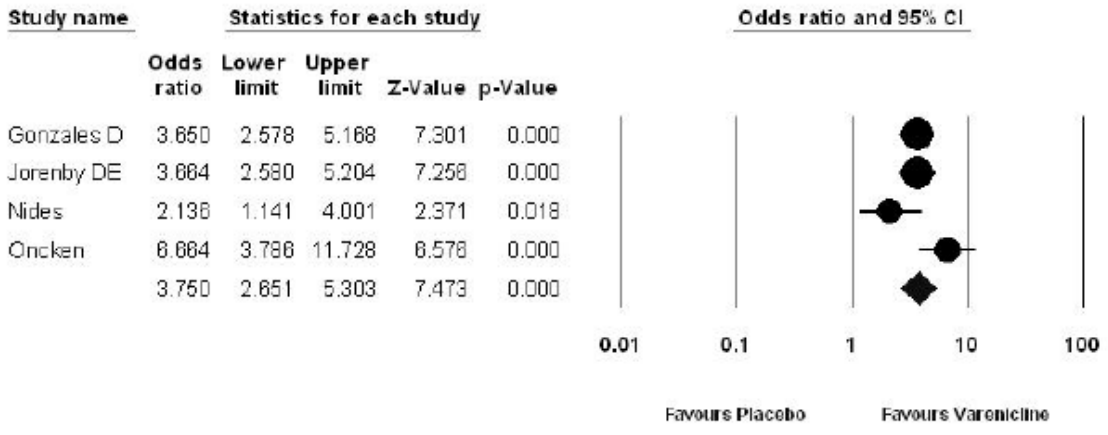


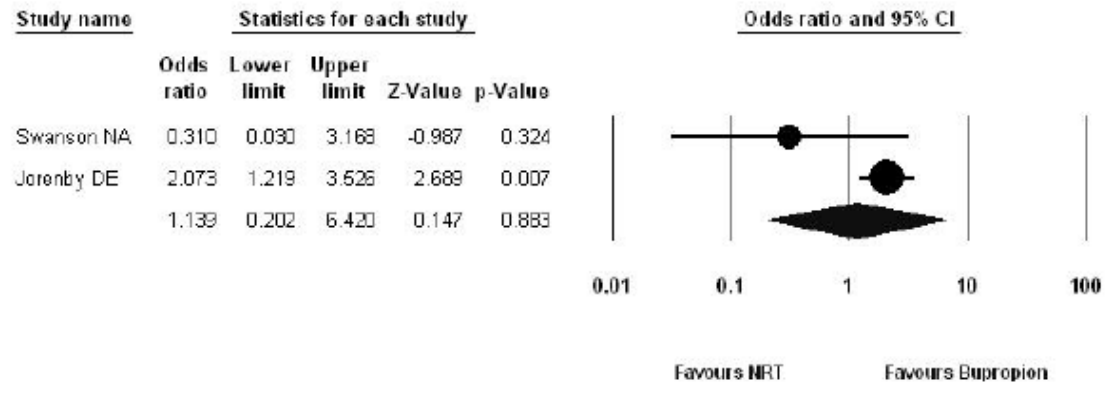
Figure 10: Varenicline versus Placebo at 3 Months



Comparisons

Two trials evaluated the superiority of NRT versus bupropion at 1 year (total n=548, See Figure 11) and found a pooled OR of 1.14 (95% CI, 0.20-6.42: P=0.88, I_2=59%, Heterogeneity P=0.11. Only 1 trial provided details on cessation rates at 3 months and favoured bupropion (OR 2.66, 95% CI 1.70-4.15; P=<0.001).

Figure 11: NRT versus Bupropion at 12 Months



Three trials evaluated the effectiveness of varenicline versus bupropion at 1 year and yielded a pooled OR of 1.58 (95% CI, 1.22-2.05; P=0.001, I_2=0%, Heterogeneity P=0.81, (See Figure 12)) in favour of varenicline. These same trials provided consistent data at 3 months (OR 1.61, 95% CI, 1.16-2.21; P=<0.0004, I2=56.1%, Heterogeneity P=0.10, (See Figure 13)).

Figure 12: Varenicline versus Bupropion at 12 Months

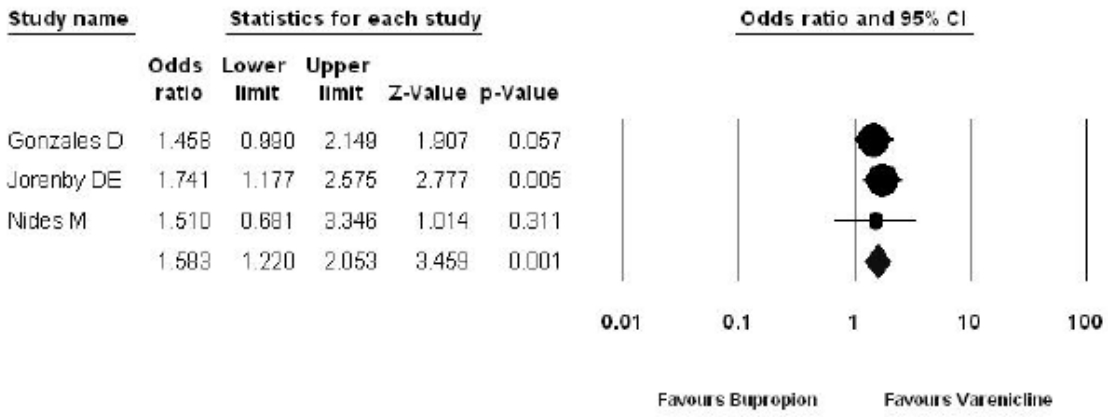
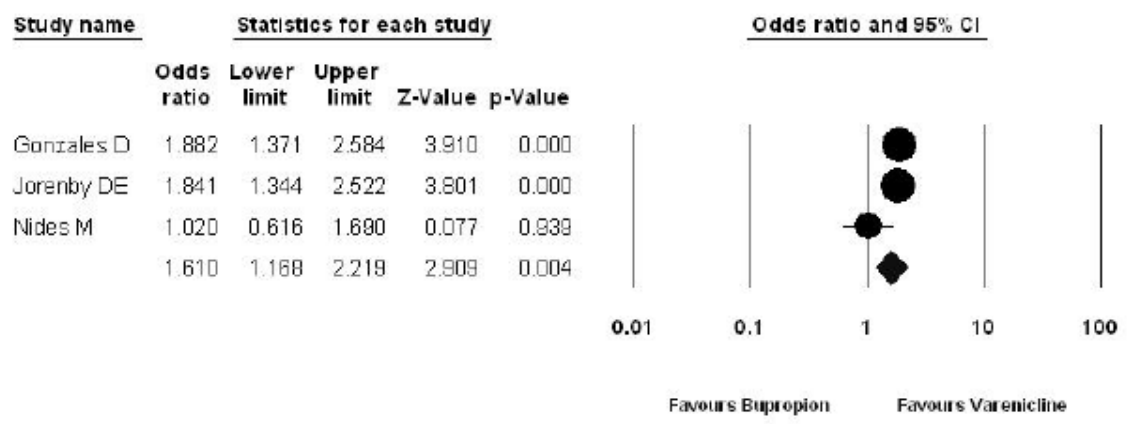


Figure 13: Varenicline versus Bupropion at 3 Months



Using indirect comparisons (Bucher et al. 1997) it was found that bupropion was not superior to NRT when compared to a placebo control at 1 year (OR 0.92, 95% CI 0.64-1.32;test for difference, P=0.65). This was similar for 3- month data (OR 1.01, 95% CI 0.79-1.29; test for difference 0.94). It was found that varenicline was superior to NRT when compared to placebo controls (OR 1.66., 95% CI 1.17-2.36; test for difference, P=0.004 (See Figure 14)) or to all controls at 1 year (OR 1.73, 95% CI 1.22-2.45, test for difference P=0.001). This was also the case when examining 3-month data for placebo controls (OR 1.78, 95% CI 1.23-2.57, test for difference P=0.002, See Figure 15) or all controls (OR 1.89, 95% CI 1.31-2.73, test for difference P=<0.0006).

Figure 14: Indirect Comparison between Varenicline and NRT versus Placebo at 12 Months (Bucher et al. indirect comparison methods)

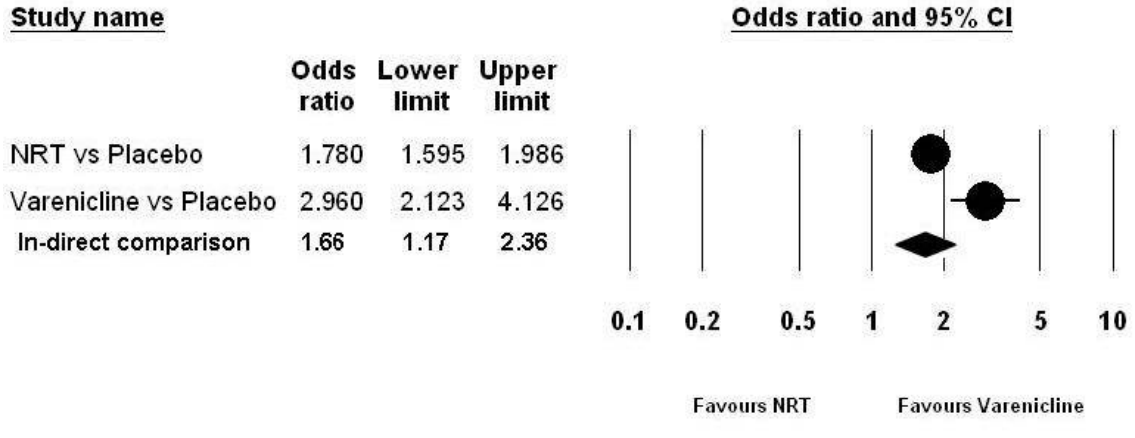
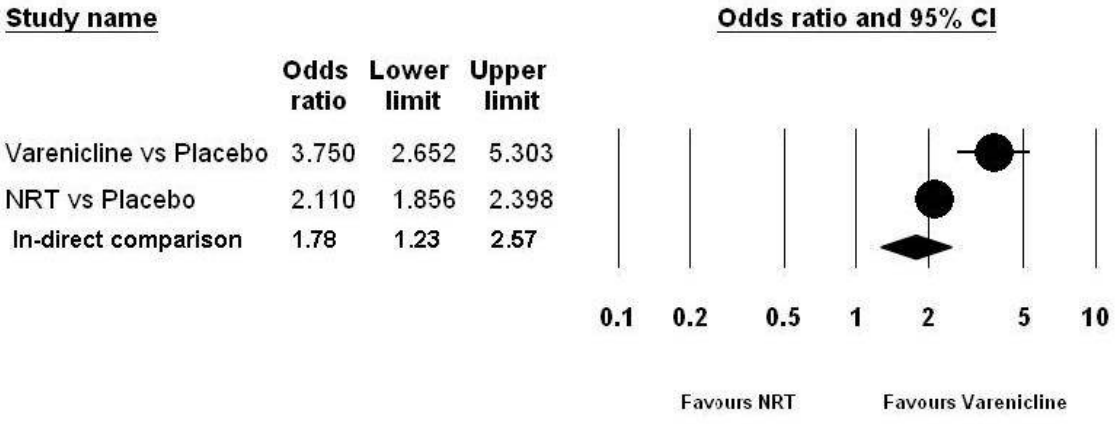


Figure 15: Indirect Comparison between Varenicline and NRT versus Placebo at 3 Months (Bucher et al. indirect comparison methods)



Meta-regression

Variability between study heterogeneity, considering the interventions, the methodological issues and the measurement tools was anticipated. Table 26 displays the covariates predicting heterogeneity in the primary outcomes of the NRT analysis using meta-regression. In this analysis, significant predictors of heterogeneity included: allocation concealment, use of NRT gum; and, methods of chemical confirmation (CO, cotinine, and urine markers). Using sensitivity analysis, only studies (n=3) using urine as a marker were significantly different from the pooled estimate (P=0.03), however, all but one of these studies also used CO as a chemical marker (P=0.5).

When examining covariates in the bupropion trials (See Table 24), only the sequence generation was a significant contributor to heterogeneity. Chemical covariates neared significance (P=0.06). Using sensitivity analyses, chemical confirmation and sequence generation did not predict heterogeneity. A meta-regression on the varenicline studies was not conducted, given the small number of studies.

Table 24: Univariable Meta-regression of Bupropion Studies

Covariates	Point estimate	Lower 95% limit	Upper 95% limit	OR	Lower 95% limit	Upper 95% limit	p-value
Placebo	2.00	-0.14	4.15	7.38	0.86	63.4	0.07
Sequence generation	-0.46	-0.84	-0.08	0.63	0.43	0.92	0.01
Allocation concealment	-0.20	-0.55	0.14	0.81	0.57	1.15	0.25
CO	0.76	0.06	1.46	2.13	1.06	4.30	0.03
Cotinine	-0.76	-1.46	-0.06	0.46	0.23	0.94	0.03
Planned to quit	0.13	-0.22	0.48	1.13	0.80	1.61	0.46

Legend. The point estimate and 95% CIs estimate the unit change in the effect size, whenever the predicted covariate is present. The OR for the point estimates and 95% CI denote the likelihood of covariate affecting the trial effect size.

Adverse events

For NRT trials, the following adverse events were reported significantly more often in active groups than control groups: mouth or throat irritation (n=12); skin irritation (n=11); nausea/vomiting (n=10); coughing (n=9); hiccoughs (n=6); dyspepsia (n=4); watering of eyes (n=3); headaches (n=3); heart palpitations (n=3); sneezing (n=3); sleep disturbances and dream abnormalities (n=2); insomnia (n=2); rhinitis (n=2); vertigo (n=1); taste disturbances (n=1) and muscle aches (n=1).

For bupropion trials, the following adverse events were reported significantly more in the active groups than control groups: dry mouth (9 trials), n=5,065, OR 1.86, 95% CI, 1.49-2.31, P=<0.0001); insomnia (9 trials), n=4,955, OR 1.93, 95% CI, 1.66-2.25, P=<0.0001); gastrointestinal upset (7 trials), n=4,206, OR 1.36, 95% CI, 1.07-1.73, P=0.01) and constipation (5 trials), n=3,373, OR 2.2, 95% CI, 1.53-3.16, P=<0.0001). Other severe events associated with trial participants in the active arms were: septic shock; grand mal seizure; sleep disorders; and anxiety. These were single cases and did not achieve significance.

For varenicline trials, the following adverse events were reported significantly more often than in the placebo groups: nausea (2 trials), n=1,379, OR 3.6, 95% CI, 2.75-4.71P=<0.0001); flatulence (2 trials), n=1,379, OR 2.18, 95% CI, 1.29-3.68, P=<0.0001); and, constipation (2 trials), n=1,379, OR 2.66, 95% CI, 1.63-4.32, P=<0.0001). Other, severe events that occurred in the active group included: atrial fibrillation, pneumonia, possible stroke, chest pain, and elevated blood pressure. These were, however, single cases and did not achieve significance.

5.6 Indirect/mixed treatment comparisons

In circumstances where there are no RCTs that directly compare the technology with the comparator(s) of interest, consideration should be given to using indirect/mixed treatment comparisons. This analysis indirectly compares the proposed technology with the main comparator by comparing one set of RCTs in which participants were randomised to the intervention/common reference with another set of RCTs in which participants were randomised to the main comparator/common reference. The common reference is often placebo, but may be an alternative technology.

Before comparing the proposed technology with the main comparator, the comparability of the two sets of RCTs must be established. If the RCTs have not been described in the previous sections the methodology and results from the RCTs included in the analysis should be summarised using the format described in sections 5.3 and 5.4 Highlight any potential sources of heterogeneity between the RCTs included in the analysis.

Give a full description of the methodology used and provide a justification for the approach.

The indirect treatment comparison used in the meta-analysis was between NRT and varenicline using placebo as a reference. The results of this comparison have been discussed and presented in the previous section; the methodology is presented below.

Head-to-head trials provide the strongest inferences regarding intervention superiority (McAlister et al 1999). However, in the absence of head-to-head trials of varenicline versus NRT, indirect comparisons of these interventions versus placebo were conducted using methods described by Bucher et al (1999) and conducted z-tests to confirm. This method maintains the randomisation from each trial and compares the summary estimates of pooled interventions with CIs. Adverse events were calculated, where reported, using Peto's Odds Ratio [OR] with 95% CIs (Yusuf et al 1985). Analyses were conducted using StatsDirect (version 2.5.2, www.statsdirect.com) and Comprehensive Meta-analysis (version 2, www.meta-analysis.com).

5.7 Safety

This section should provide information on the safety of the technology in relation to the decision problem. Evidence from comparative RCTs and regulatory summaries is preferred; however, findings from non-comparative trials may sometimes be relevant. For example, they may demonstrate that the technology shows a relative lack of adverse effects commonly associated with the comparator, or the occurrence of adverse effects not significantly associated with other treatments.

If any of the main trials are designed primarily to assess a safety outcome (for example, they are powered to detect significant differences between treatments with respect to the incidence of an adverse effect), these should be reported here in the same detail as described in the previous sections relating to the efficacy trials. Give a brief overview of the safety of the technology in relation to the decision problem. Give incidence rates of adverse effects if appropriate.

First Comparative Trial A3051028

Patients Completing the Study

Completion rates for this one-year study were 61.0% (n=213) in the varenicline group, 55.9% (n=184) in the bupropion group, and 54.4% (n=187) in the placebo group. More subjects (25.8 %, n=90) varenicline, (37.5% n=129) placebo, (31.6 % n=104) bupropion, discontinued in the 12-week treatment phase than in the non-treatment follow-up phase (13.2%, n=46) varenicline, (8.1%, n=28) placebo, and 12.5% n=41) bupropion). The most common reasons for drop-outs in the treatment phase were 'lost to follow-up' (12.3% n=43 varenicline, 14.2% n=49 placebo, 10.9% n=36 bupropion), and 'refusal to participate further' (6.6% n=23 varenicline, 12.2% n=42 placebo, 9.4% n=31 bupropion), and these were also the most frequent reasons for drop-outs in the non-treatment phase.

Withdrawals due to Lack of Efficacy

The rates of withdrawal due to lack of efficacy were less than 1.3% in all groups; varenicline (0.6%, n=2), bupropion (0.3% n=1) and placebo (1.2% n=4).

Treatment Emergent Adverse Events

The incidence of all-causality treatment-emergent adverse events was similar among treatment groups: 78.8% (n=275) for varenicline, 78.4% (n=258) for bupropion and 74.7% (n=257) for placebo.

Treatment Related Adverse Events

The incidence of adverse events considered related to study medication was higher in the active treatment groups than in the placebo group; (69.1% (n=241) for varenicline, 61.4% (n=202) for bupropion, and 53.2% (n=183) for placebo.

Severe Treatment Related Adverse Events

The incidence of severe events considered related to study medication was 4.0% (n=14) for varenicline, 5.5% (n=18) for bupropion, and 4.7% (n=16) for placebo.

Adverse Events Resulting in Discontinuation of Study Treatments
More bupropion-treated subjects (15.2%, n=50) permanently discontinued study medication as a result of adverse events than did subjects treated with varenicline (8.6%, n=30) or placebo (9.0% n=31). However, the percentage of subjects who temporarily discontinued study medication or had dose reductions due to adverse events was similar among the groups (4.6% (n=16), 3.3% (n=11), 4.1% (n=14) for the varenicline, bupropion, and placebo treatment groups, respectively. There were no deaths during the study.

Other Serious Adverse Events
Thirteen subjects experienced non-fatal serious adverse events while receiving treatment or within seven days of the last dose in this study: three subjects from the varenicline treatment group, three subjects from the bupropion treatment group, and seven subjects from the placebo treatment group.

Second Comparative Trial A3051036
Patients Completing the Study
Completion rates for this one-year study was 70.0% (n=240) in the varenicline group, 65.0% (n=221) in the bupropion group, and 60.0% (n=204) in the placebo group. More subjects (24.2 %, n=83) varenicline, (29.4 % n=100) bupropion, (34.7% n=118) placebo discontinued in the 12-week treatment phase than in the non-treatment follow-up phase (5.8%, n=20 varenicline, 5.6% n=19 bupropion and 5.3%, n=18 placebo). The most common reasons for drop-outs in the treatment phase were 'lost to follow-up' (9.6% n=33 varenicline, 11.5% n=39 bupropion 12.6% n=43 placebo), and 'refusal to participate further' (8.2% n=28 varenicline, 9.1% n=31 bupropion15.0% n=51 placebo), and these were also the most frequent reasons for drop-outs in the non-treatment phase.

Withdrawals due to Lack of Efficacy
The rates of withdrawal due to lack of efficacy were less than 1% in all groups; varenicline (0.3%, n=1), bupropion (0.0% n=0) and placebo (0.9% n=3).

Treatment Emergent Adverse Events
The incidence of all-causality treatment-emergent adverse events was similar among treatment groups: 79.6% (n=273) for varenicline, 77.1% (n=262) for bupropion and 75.9% (n=258) for placebo.

Treatment Related Adverse Events
The incidence of adverse events considered related to study medication was higher in the active treatment groups than in the placebo group; (67.6% (n=232) for varenicline, 61.5% (n=209) for bupropion, and 55.3% (n=188) for placebo.

Severe Treatment Related Adverse Events
The incidence of severe events considered related to study medication was 6.7% (n=23) for varenicline, 9.4% (n=32) for bupropion, and 3.2% (n=11) for placebo.

Adverse Events Resulting in Discontinuation of Study Treatments
More bupropion-treated subjects (12.6%, n=43) permanently discontinued study medication as a result of adverse events than did subjects treated with varenicline (10.5%, n=36) or placebo (7.4% n=25). However, the percentage of subjects who temporarily discontinued study medication or had dose reductions due to adverse events were (1.2% (n=4), 4.1% (n=14), 2.6% (n=9) for the varenicline, bupropion, and placebo treatment groups, respectively. There were no deaths during the study.

Other Serious Adverse Events
Seventeen subjects experienced non-fatal serious adverse events while receiving treatment or within seven days of the last dose in this study: six subjects from the varenicline treatment group, six subjects from the bupropion treatment group, and five subjects from the placebo treatment group.

Maintenance of Abstinence Trial A3051035
Patients Completing the Study
Of the 1927 subjects who took study medication (varenicline) 1210 (62.8%) entered the double-blind phase. Subjects who did not enter the double-blind phase were discontinued from the study. The most common reason for withdrawal from the open-label treatment phase was adverse events (10.4%, n=200), followed by a refusal to participate further (7.8%, n=150), other reasons (7.0%, n=134) and lost to follow-up (6.9%, n=132).

During the double-blind treatment phase 82.1% (n=494) of varenicline treated patients, and 76.7% (n=463) of placebo-treated patients completed the study. The most common reasons for withdrawal from the double-blind treatment phase was refusal to participate further (varenicline 3.2%, n=19; placebo 7.3% n=44), followed by lost to follow-up (varenicline 2.0%, n=12; placebo 5.1% n=31). During the non-treatment follow-up phase, 61 (10.1%) varenicline treated patient and 47 (7.8%) placebo-treated patients withdrew from the study. The most common reasons for withdrawal from the non-treatment phase was refusal to participate further (varenicline 4.5%, n=27; placebo 3.1% n=19), followed by lost to follow-up (varenicline 4.7%, n=28; placebo 4.0% n=24).

Withdrawals due to Lack of Efficacy
During the open-label treatment phase 29 varenicline treated patients (1.5%) withdrew from the study due to lack of efficacy. The rates of withdrawal due to lack of efficacy were less than 1% in both groups; varenicline (0.7%, n=4), and placebo (0.8% n=5) during the double-blind treatment phase. During the non-treatment follow-up phase a further two (0.3%) placebo-treated subjects withdrew due to lack of efficacy.

Treatment Emergent Adverse Events
The incidence of all-causality treatment-emergent adverse events during the open-label treatment phase for varenicline was 80% (n=1541). However, the drop-out rate during this phase was less than 12%. The incidence of all-causality treatment-emergent adverse events during the double-blind treatment phase for varenicline was 46.0% (n=277), and for placebo was 45.0% (n=272).

Treatment Related Adverse Events
The incidence of adverse events considered related to study medication during the open-label treatment phase for varenicline was 70.3% (n=1354). The incidence of adverse events considered related to study medication during the double-blind treatment phase for varenicline was 16.9% (n=102), and for placebo was 15.4% (n=93).

Adverse Events Resulting in Discontinuation of Study Treatments
The incidence of adverse events leading to discontinuation of treatment during the open-label treatment phase for varenicline was 11.9% (n=229). The incidence of adverse events leading to discontinuation of study treatment during the double-blind treatment phase for varenicline was 1.7% (n=10), and for placebo was 1.3% (n=8).

Severe Treatment Related Adverse Events
The incidence of severe events considered related to study medication during the open-label treatment phase (varenicline) was 6.6% (n=128). The incidence of severe adverse events considered related to study medication during the double-blind treatment phase was 1.3% (n=8) for varenicline and 1.7% (n=10) for placebo treated patients.

Other Serious Adverse Events
Twenty subjects experienced non-fatal serious adverse events during the open-label treatment phase (varenicline), only two of which were treatment related. During the double-blind treatment phase, ten subjects (1.7%) from the varenicline treatment group (one of which was treatment related), and five subjects (0.8%) of the placebo-treated group experienced a non-fatal serious adverse event.

Open-label Varenicline/NRT Trial A3051044
Patients Completing the Study
Completion rates for this one-year study were 65.7% (n=247) in the varenicline group, and 62.2% (n=230) in the NRT group. More subjects (37.8 %, n=140) in the NRT group (37.5% n=129) discontinued the study compared with the varenicline group (34.3%, n=129). The most common reasons for drop-outs in the treatment phase were ‘refusal to participate further’ (6.6% n=25 varenicline, 9.2% n=34 NRT) and ‘lost to follow-up’ (5.9% n=22 varenicline, 4.9% n=18), and these were also the most frequent reasons for drop-outs in the non-treatment phase.

Withdrawals due to Lack of Efficacy
The rates of withdrawal due to lack of efficacy were less than 2.2% in all groups; varenicline (0.0%, n=0) and NRT (2.5% n=9).

Treatment Emergent Adverse Events
The incidence of all-causality treatment-emergent adverse events was 84.8% (n=319) for varenicline and 70.3% (n=260) for NRT.

Treatment Related Adverse Events
The incidence of adverse events considered related to study medication was 75.8% (n=285) for varenicline and 47.6% (n=176) for NRT.

Adverse Events Resulting in Discontinuation of Study Treatments
More varenicline-treated subjects (6.9%, n=26) permanently discontinued study medication as a result of adverse events than did subjects treated with NRT (3.5%, n=13) or placebo (9.0% n=31). There were no deaths during the study.

Non-fatal Serious Adverse Events
Eleven subjects experienced non-fatal serious adverse events while receiving treatment or within seven days of the last dose in this study: three subjects from the varenicline treatment group and eight subjects from the NRT treatment.

5.8 Non-RCT evidence

In the absence of valid RCT evidence, evidence from other study designs will be considered, with reference to the inherent limitation inferred by the study design. The level of detail provided should be the same as for RCTs and where possible more than one independent source of data should be examined to explore the validity of any conclusions. Inferences about relative treatment effects drawn from observational evidence will necessarily be more circumspect from those from RCTs.

5.8.1 Summary of methodology of relevant non-RCTs

All the evidence provided in this submission is from randomised controlled trials.

5.8.2 Critical appraisal of relevant non-RCTs

Not applicable to this submission.

5.8.3 Results of the relevant non- RCTs

Not applicable to this submission.

5.9 Interpretation of clinical evidence

5.9.1 Provide a brief statement of the relevance of the evidence base to the decision problem. Include a discussion of the relevance of the outcomes assessed in clinical trials to the clinical benefits experienced by patients in practice.

Existing therapies for smoking cessation include Nicotine Replacement Therapy and bupropion. A systematic review and meta-analysis has assessed the relative efficacy of varenicline compared to these existing therapies using direct and indirect comparisons (Bucher et. al. 1997; Song et. al. 2003). A copy of the full systematic review and meta-analysis has been published on BMC Public Health. A summary of the main findings has been presented above.

Varenicline, NRT and bupropion all provide therapeutic effects in assisting with smoking cessation. The current evidence indicates varenicline has a superior therapeutic effect over the other interventions.

5.9.2 Identify any factors that may influence the applicability of study results to patients in routine clinical practice; for example, how the technology was used in the trial, issues relating to the conduct of the trial compared with clinical practice, or the choice of eligible patients. State any criteria that would be used in clinical practice to select suitable patients based on the evidence submitted. What proportion of the evidence base is for the dose(s) given in the Summary of Product Characteristics?

Two of the four randomised controlled trials examining varenicline in smoking cessation (A3051028 and A3051036) were conducted exclusively in the United States. The third (A3051035) was an international study conducted in 24 centres, including two centres in the United Kingdom, which recruited 253 patients. The fourth (A1044) was an international study conducted in 24 centres, including 4 centres in the United Kingdom which recruited 231 patients. There is no reason to suggest that the study results would not be applicable to patients in routine clinical practice in the United Kingdom

6 Cost effectiveness

6.1 Published cost-effectiveness evaluations

6.1.1 Identification of studies

Describe the strategies used to retrieve relevant cost-effectiveness studies from the published literature and from unpublished data held by the manufacturer or sponsor. The methods used should be justified with reference to the decision problem. Sufficient detail should be provided to enable the methods to be reproduced, and the rationale for any inclusion and exclusion criteria used should be provided. The search strategy used should be provided in appendix 3, section 9.3.

Search Strategy for Published Literature

In consultation with a medical librarian a search strategy of published literature was established. Searches were conducted independently, in duplicate, using the following ten databases (from inception to December 1, 2006): MEDLINE, EMBASE, Cochrane, AMED, NHS Economic Evaluation Database, CINAHL, TOXNET, Development and Reproductive Toxicology, Hazardous Substances Databank, Psych-info and Web of Science. Databases that included the full text of journals (*OVID, ScienceDirect,* and *Ingenta)*, including articles in full text from approximately 1700 journals, since 1993, were searched. In addition, the bibliographies of published systematic reviews (Silagy et

al. 2000, 2001, 2002, 2004; Hughes et al 2002, 2004; Lancaster et al 2000; Silagy 2000), and health technology assessments were searched (Nice. 2002). Searches were not limited by language, sex or age.

The Pfizer clinical trials database, Documentum, was searched.

6.1.2 Description of identified studies

Provide a brief overview of each study, stating the aims, methods, results and relevance to decision-making in England and Wales. Each study's results should be interpreted in light of a critical appraisal of its methodology. Where studies have been identified and not included, justification for this should be provided.

No studies involving a cost-effectiveness analysis of, or involving, varenicline were retrieved.

6.2 De novo economic evaluation(s)

I*n the absence of a relevant published economic evaluation, manufacturers or sponsors should submit their own economic evaluation. When estimating cost effectiveness, particular emphasis should be given to adhering to the 'reference case' (see the NICE document 'Guide to the methods of technology appraisal'). Reasons for deviating from the reference case should be clearly explained. Particularly important features of the reference case include those listed in the table below.*

Attribute	***Reference case***	***Section in 'Guide to the methods of technology appraisal'***
Comparator(s)	*The comparator that has been specified in the decision problem*	*5.3.2*
Perspective costs	*NHS and Personal Social Services*	*5.3.3*
Perspective benefits	*All health effects on individuals*	*5.3.3*
Form of economic evaluation	*Cost-effectiveness analysis*	*5.3.4*
Time horizon	*Sufficient to capture differences in costs and outcomes*	*5.3.5*
Synthesis of evidence	*Systematic review*	*5.4.1*

Outcome measure	*Quality-adjusted life years (QALYs)*	*5.5*
Health states for QALY measurement	*Described using a standardised and validated instrument*	*5.5*
Benefit valuation	*Time trade-off or standard gamble*	*5.5*
Source of preference data	*Sample of public*	*5.5*
Discount rate	*Health benefits and costs – both 3.5%*	*5.7.2*
Equity	*No additional weighting to QALYs*	*5.9.7*
Sensitivity analysis	*Probabilistic sensitivity analysis*	*5.9.3*

6.2.1 Technology

How is the technology (assumed to be) used within the economic evaluation? For example, give indications, and list concomitant treatments, doses, frequency and duration of use. The description should also include assumptions about continuation and cessation of the technology.

The use of varenicline within the economic evaluation is in line with the recommendations for use within the Summary of Product Characteristics (SmPC).

Indication: Smoking cessation in adults (>18years) motivated to quit smoking.

Dosing:

Initial titration

Days 1 to 3	0.5mg once daily
Days 4 to 7	0.5mg twice daily

Remainder of treatment course

Day 8 to end of treatment (either 12 or 24 weeks)	1.0 mg twice daily

6.2.2 Patients

6.2.2.1 What group(s) of patients is/are included in the economic evaluation? Do they reflect the licensed indication? If not, how and why are there differences? What are the implications of this for the relevance of the evidence base to the specification of the decision problem?

The patient groups included within the economic evaluation are in line with the recommendations for use within the Summary of Product characteristics (SmPC):

Group 1

Adults (>18years) motivated to quit smoking.

Group 2

Adults (>18years) abstinent at the end of a 12 week course of varenicline therapy

6.2.2.2 Was the analysis carried out for any subgroups of patients? If so, how were these subgroups identified, what clinical information is there to support the biological plausibility of this approach, and how was the statistical analysis undertaken?

No subgroup analyses other than by age and gender were undertaken.

6.2.2.3 Were any obvious subgroups not considered? If so, which ones, and why were they not considered?

Subgroup analyses in patients with significant co-morbidities were considered to be of interest but not conducted in the absence of clinical data.

6.2.2.4 At what points do patients 'enter' and 'exit' the evaluation? Do these points differ between treatment regimens? If so, how and why?

Patient entry:
When attempting to quit smoking.

Patient exit:
At death, calculated according to the statistics of smokers in UK, or reaching 100 years, whichever comes first.

Entry and exit points do not differ between treatment regimens.

6.2.3 Comparator technology

What comparator(s) was/were used and why was it/were they chosen? The choice of comparator should be consistent with the summary of the decision problem (Section A).

For group 1 the evaluation compares varenicline against:

- NRT

- Bupropion
- Placebo

For group two the evaluation considers the cost-effectiveness of a further 12 week course of varenicline versus placebo.

NRT and bupropion have been selected as the active comparators since they are the two other therapies available on prescription in the UK for smoking cessation.

6.2.4 Study perspective

If the perspective of the study did not reflect NICE's reference case, provide further details and a justification for the approach chosen.

It has not proved possible to quantify the PSS resources relevant to smoking and therefore the perspective of the study is one of the NHS only.

6.2.5 Time horizon

What time horizon was used in the analysis, and what was the justification for this choice?

A lifetime horizon was used in the analysis. This was selected because the health impacts of smoking and the consequent benefit of smoking cessation extend throughout the entire lifetime of an individual.

6.2.6 Framework

The purpose of this section is to provide details of the framework of the analysis. Section a) below relates to model-based evaluations, and section b) below relates to evaluations conducted alongside clinical trials. Please complete the section(s) relevant to the analysis.

a) Model-based evaluations

6.2.6.1 Please provide the following. 1• A description of the model type.

• A schematic of the model. For models based on health states, direction(s) of travel should be indicated on the schematic on all transition pathways.
• A list of all variables that includes their value, range (distribution) and source.
• A separate list of all assumptions and a justification for each assumption.

Model overview

The BENESCO (Benefits of Smoking Cessation on Outcomes) model is an update of the HECOS model (Orme 2001). The additions to the HECOS model are highlighted below in Table 25

Table 25: Summary of BENESCO features beyond the HECOS model

New feature	Rationale
Directly compares two interventions simultaneously - the HECOS model could only look at results for one strategy at a time.	Allows for instantaneous incremental/ comparative analysis.
Includes utilities	Allows for calculation of QALYs
Projects beyond a 20-year time frame (to death) and includes all cause mortality death rates.	For younger age groups, benefits of quitting smoking may not be realised until more than 20 years post-quitting. A lifetime model will capture all consequences.
Updates relapse rate projection to three stages of relapse, compared to the two stages of HECOS, to reflect markedly reduced risk of relapse in long term quitters	In a review of the previous model the relapse rate was regarded as conservative given it was a fixed (linear) rate throughout the model.
Specifies cohort: age/ gender and pre-existing conditions	Allows for sub-group analysis and more flexibility.
Allows for a degree of co-existence of conditions	Treatment and management of some of the chronic diseases considered in the model (i.e. CHD) are such that if a patient survives the acute event, their probability of survival in the long-term is good. This means patient has the potential to develop and die from another smoking-related disease (i.e. lung cancer or COPD).
Splits costs into the cost of treating acute events (i.e. first CHD event) and the cost of long-term disease management (i.e. post CHD event management)	More accurate calculation of treatment costs.

The model follows over time a hypothetical cohort of smokers who make a single attempt to quit smoking at the beginning of the simulation.

This cohort is followed from the time the smokers start their attempt to quit smoking until all members of the cohort have either died or reached the maximum age of 100.

In the first year of the simulation, the cohort of patients receiving the intervention attempt to quit according to efficacy values described later in this section.

At the end of each year, the members of the cohort are distributed into various smoking states (i.e. smoker, recent quitter, long term quitter), each of which can be associated with co-morbidities (COPD, lung cancer, CHD, stroke, and asthma exacerbations).

The probability for a subject to transition from one health state to another depends upon the subject's smoking status and health state in the previous year.

Each health state is associated with a specific cost and utility value.

Patients accumulate costs and outcomes through their transition to the different states, until death.

Model structure

Smoking status

Smokers that enter the model may transition to the different smoking states according to the length of time since they quit smoking.

State 1 – Smoker attempting to Quit:

- The patient is attempting to quit and make the transition from smoker to quitter.
- This state takes place in the first year and the probability of successfully quitting (moving to the recent quitter state from the smoker state) is dependent upon the smoking cessation method that is used.

State 2 – Recent Quitter:

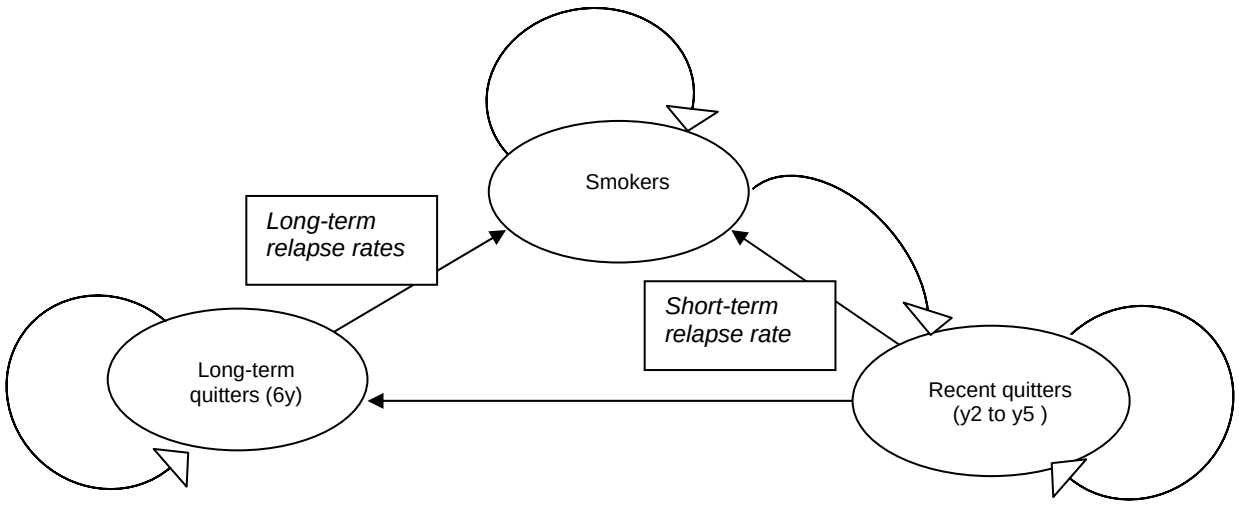
- If abstinent after one year, the subject will be considered a recent quitter. At this time, the health benefits from not smoking will begin, although there is still a risk of relapse.
- The rate at which the recent quitters relapse to smoking is independent of the smoking cessation method that was initially used and does not differ between treatment groups (Wetter et al. 2004).
- In the framework of the BENESCO model, this stage lasts through year 5 providing that there is no relapse to smoking.

State 3 – Long-term Quitter:

- If after 5 years the subject is still abstinent, then the risk of relapsing to smoking is further reduced for the next 5 years (years 6-10 in the model)
- If the subject maintains abstinence through 10 years following their quit attempt, the relapse rate is further reduced again, and the subject remains in this stage until death providing that there is no relapse back to smoking.

Transitions to the different smoking states are described in figure 16.

Figure 16: Smoking status transitions



Health states

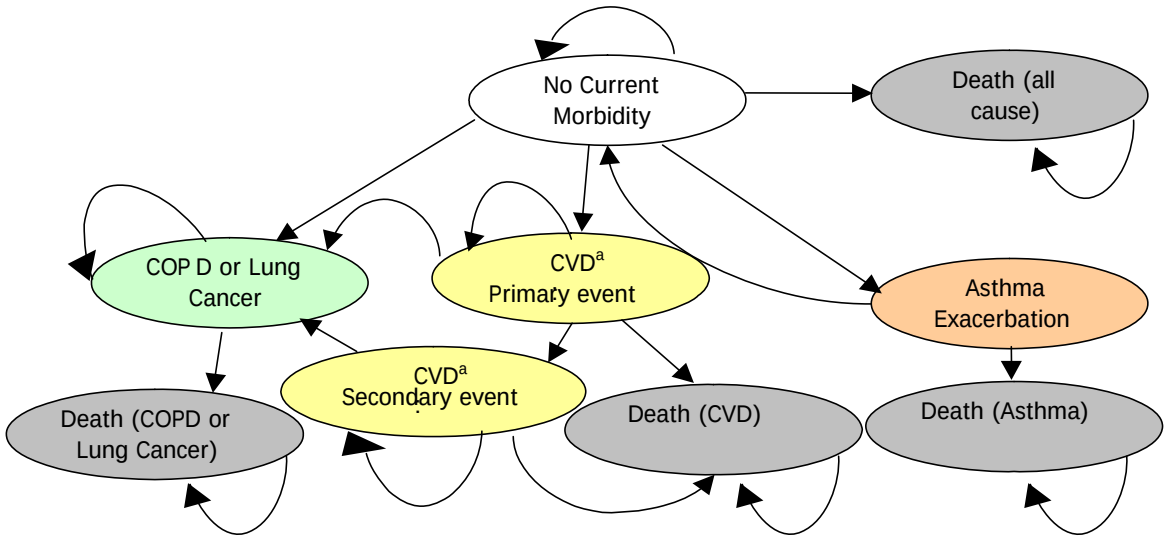
The BENESCO model health states correspond to those diseases that account for the greatest mortality, morbidity and cost associated with smoking. Transitions to the different health states are described in Figure 20. As in any Markov model, health states are mutually exclusive (i.e. a patient can not have COPD and CHD in the same cycle). Markov cycle length is of one year.

Figure 20 illustrates the order in which the smoking related conditions can occur in the model. By modelling the morbidities in this way, a patient can have, for example, one or more asthma exacerbations, followed by CHD or stroke with one or more acute events, followed by lung cancer or COPD. Death can occur at any time, and is classified according to the state experienced prior to death.

If a subject has one of the two acute morbidities (CHD or Stroke (CVD in the schematic)) they cannot develop the other. Similarly if a subject develops one of the two chronic morbidities (Lung Cancer or COPD) they cannot develop the other. Subjects can progress from an acute morbidity to a chronic morbidity, but not the other way (from a chronic to an acute). If a subject does progress from an acute morbidity to a chronic one, their acute morbidity is ignored from that point forward.

A schematic of the model health states and transition pathways is represented below (Figure 17).

Figure 17: Health states transitions



aCVD = either CHD or stroke

The acquisition of morbidities is influenced by the patients' smoking status. The probability of acquiring a smoking related disease decreases as a function of time in a smoker who has quit. Therefore the relative risk of acquiring a smoking related disease or death is lower the longer a patient has remained abstinent (see appendix 1).

The acquisition of morbidities is also influenced by the age of the patients; not only because it is used as a proxy to the duration of smoking, but also because the risk of acquiring certain morbidities (see Table 48: key model assumptions) increases with age.

Model parameters

Demographic parameters

Demographic characteristics of the population
As smoking behaviour and morbidity risks vary according to age and gender, the model requires the input of men and women age groups' specific data.

General demographics

Latest estimates of the size of the UK population by gender and age were provided from routine Office for National Statistics (ONS) data (ONS 2006) (Table 28). These were aggregated to the age-bands required for the model.

Mortality rates by age and gender were taken from the latest interim life tables calculated by the UK Government Actuary's Department (GAD 2006) (Table 26), which were for 2002-4. Rates were weighted by population size and averaged to produce the values for the age-bands required for the model.

Table 26: General Demographics

Data Item	Data source	M age 18-34	M age 35-64	M age 65+	F age 18-34	Females age 35-64	Females age 65+
Population by age, gender	ONS (2006) Population trends. Version 124	6,727,400	11,843,600	4,040,000	6,660,700	12,140,100	5,189,300
All cause death	GAD (2006). UK Interim Life Table 2002-04	0.09%	0.47%	4.88%	0.04%	0.30%	3.87%

Data relating to the prevalence of smoking comes predominantly from the ONS General Household Survey (ONS 2005a) and it is illustrated in Table 27. Again, these were aggregated into the age-bands required for the model.

Table 27: Smoking prevalence by age and gender

Data Item	Data source	Males age 18-34	Males age 35-64	Males age 65+	Females age 18-34	Females age 35-64	Females age 65+
Smoking prevalence by age, gender	Sources: General Household Survey, Office for National Statistics Smoking, drinking and drug use among young people in England in 2004, National Centre of Social Research/National Foundation for Education Research for Department of Health	32.6%	27.7%	12.7%	28.0%	28.5%	26.7%

Prevalence

This section describes the prevalence of the diseases included in the model.

The prevalence of COPD in Britain was estimated from a study utilising the General Practice Research Database (Soriano 2000).

In England and Wales around 25% of patients are alive one year after diagnosis and this falls to 7% at five years (Cancer Research UK 2006). Coleman et al. (2004) suggest a life expectancy of 0.7 years after diagnosis with lung cancer, assuming an exponential distribution. We therefore estimate the prevalence of lung cancer is 0.7 times the incidence, at all ages.

Inputs relating to the prevalence of CHD were based on longstanding illness data provided in the ONS General Household Survey 2004 (ONS 2005a).

Prevalence of stroke in the UK was taken from the ONS General Household Survey 2004 (ONS 2005a)

In 2004, the estimated number of people with asthma in the UK was 5.2m (Asthma UK 2004). The estimated population of the UK at this time was 59,834,300 (ONS 2004), and given the ratio of males to females is 1:1(Hoskins 2000), the prevalence was estimated at 4.3% for males and females. Adjusted for the UK population size assumed in the model, the current prevalence is estimated at 5.3m. The prevalence was required to be broken down into age-bands of 18-34, 35-64 and 65+. This was estimated using proportions observed during a survey by Hoskins et al(Hoskins 2000). Hoskins estimated that 35% of patients were aged 16 to 45, 28% 45 to 75 and 4% 75 and over. By assuming that within these age bands prevalence is constant by age, we are able to estimate prevalence in the three age bands of 1,079,346 for the 18-34 age-band, 1,616,903 for the 35-64 age-band and 701,424 for the 65+ group.

Inputs for the prevalence of the co-morbidities are shown in the tables below for the general population and for smokers. The calculations used to obtain these values are described in the Appendix 1. In the absence of evidence for a difference in asthma prevalence in smokers the prevalence for the general population has been substituted.

Table 28: Prevalence in general population by age and gender (%)

Data Item	Data source	M age 18-34	M age 35-64	M age 65+	F age 18 - 34	F age 35-64	F age 65+
COPD	Soriano JB, Maier WC, Egger P, Visick G, Thakrar B, et al. (2000) Recent trends in physician diagnosed COPD in women and men in the UK. Thorax. 55(9): 789-794.		1	3		1	2
Lung cancer	Cancer Research UK. (2006) .Forman D. et al. (2003) Cancer prevalence in the UK: results from the EUROPREVAL study		0.1	0.7		0.06	0.24
History of CHD	ONS. (2005a) General Household Survey 2004. Version 124		1.6	8		1	5.9
History of Stroke	ONS. (2005a) General Household Survey 2004. Version 124		0.5	3		0.3	2
Asthma exacerbations	Asthma UK. (2004) Where do we stand? Asthma in the UK today. http://www.asthma.org.uk/document.rm?id=18 Hoskins G, McCowan C, Neville RG, Thomas GE, Smith B, et al. (2000) Risk factors and costs associated with an asthma attack. Thorax. 55(1): 19-24.	6	5	6.5	6.4	5.3	5.3

Table 29: Prevalence in smoker population by age and gender (%)

Data Item	Data source	M age 18-34	M age 35-64	M age 65+	F age 18 -34	F age 35-64	F age 65+
COPD	Soriano JB, Maier WC, Egger P, Visick G, Thakrar B, et al. (2000) Recent trends in physician diagnosed COPD in women and men in the UK. Thorax. 55(9): 789-794.		2.4	5.5		2.9	4.8
Lung cancer	Cancer Research UK. (2006) .Forman D. et al. (2003) Cancer prevalence in the UK: results from the EUROPREVAL study		0.3	2.1		0.2	0.6
History of CHD	ONS. (2005a) General Household Survey 2004. Version 124		2.6	10.7		2.1	7.9
History of Stroke	ONS. (2005a) General Household Survey 2004. Version 124		0.8	4.5		0.6	2.6
Asthma	Asthma UK. (2004) Where do we stand? Asthma in the UK today. http://www.asthma.org.uk/document.rm?id=18 Hoskins G, McCowan C, Neville RG, Thomas GE, Smith B, et al. (2000) Risk factors and costs associated with an asthma attack. Thorax. 55(1): 19-24.	6	5	6.5	6.4	5.3	5.3

Incidence

Table 30 shows the incidence split for different age bands for different categories (general population, smokers and quitters).

There is a lack of incidence data for COPD and therefore incidence levels equal to the mortality values were adopted (see mortality section below).

Rates of incidence of lung cancer were taken from the latest ONS MB1 publication (ONS 2005b). For this calculation, we have used the ICD-10 definition “malignant neoplasm of trachea, bronchus or lung” (C33-34).

The annual incidence of fatal CHD events was calculated from rates of mortality due to ischaemic heart disease (ICD 10 codes I20-25) (British Heart Foundation 2006).

Incidence for stroke was taken from the ONS Health Statistics quarterly 12 (ONS 2001), which provided a split between first event and all events. Due to a lack of mortality data, the same split was assumed for first/subsequent for mortality as for incidence.

Incidence in general population is split by age and gender.

As a proxy for calculating the incidence of Asthma episodes the incidence of hospital admissions estimated from the Asthma UK report (Asthma UK 2004) are broken down into different age bands according to the proportions estimated by Hoskins et al (2000). This is deemed to be conservative because a significant number of asthma exacerbations are managed in the Accident & Emergency Department, without the need for hospitalisation.

Table30: Incidence in general population (%)

Data Item	Data source	M age 18-34	M age 35-64	M age 65+	F age 18-34	F age 35-64	F age 65+
COPD	*Assumption*. Incidence levels equal to the mortality value calculated		0.01	0.3		0.01	0.2
Lung cancer	ONS. (2005b) Registrations of cancer diagnosed in 2003, England. Version MB1 no. 34		0.05	0.4		0.03	0.2
CHD (first non fatal event)	British Heart Foundation. (2006) .Coronary Heart Disease Statistics fact sheet.		0.08	0.8		0.02	0.6
Stroke (first non fatal event)	ONS. (2001) Health Statistics Quarterly 12.		0.15	0.65		0.10	0.6
CHD (any non-fatal)	Volmink JA, Newton JN, Hicks NR, Sleight P, Fowler GH, et al. (1998) Coronary event and case fatality rates in an English population: results of the Oxford myocardial infarction incidence study. The Oxford Myocardial Infarction Incidence Study Group. Heart. 80(1): 40-44.		0.12	1.4		0.03	0.9
Stroke (any non-fatal)	ONS. (2001) Health Statistics Quarterly 12.		0.20	1		0.14	1
Asthma	Asthma UK. (2004) Where do we stand? Asthma in the UK today. http://www.asthma.org.uk/document.rm?id=18 [Accessed 14/09/06],	0.06	0.05	0.06	0.06	0.05	0.05

Table 31: Incidence in smoker population by age and gender (%)

Data Item	Data source	M age 18-34	M age 35-64	M Age 65+	F age 18-34	F age 35-64	F age 65+
COPD	*Assumption:* Incidence levels equal to the mortality value calculated		0.02	0.55		0.02	0.44
Lung cancer	ONS. (2005b) Registrations of cancer diagnosed in 2003, England. Version MB1 no. 34		0.1	1.0		0.08	0.5
CHD (first non fatal event)	British Heart Foundation. (2006) .Coronary Heart Disease Statistics fact sheet.		0.1	1		0.05	0.86
Stroke (first non fatal event)	ONS. (2001) Health Statistics Quarterly 12.		0.26	0.92		0.2	0.74
CHD (any non-fatal)	Volmink JA, Newton JN, Hicks NR, Sleight P, Fowler GH, et al. (1998) Coronary event and case fatality rates in an English population: results of the Oxford myocardial infarction incidence study. The Oxford Myocardial Infarction Incidence Study Group. Heart. 80(1): 40-44.		0.19	1.74		0.05	1.18
Stroke (any non-fatal)	ONS. (2001) Health Statistics Quarterly 12.		0.35	1.55		0.28	1.33
Asthma	Asthma UK. (2004) Where do we stand? Asthma in the UK today. http://www.asthma.org.uk/document.rm?id=18 [Accessed 14/09/06],	0.08	0.05	0.07	0.08	0.05	0.06

Table 32: Incidence in 'Recent Quitters' by age and gender (%)

Data Item	Data source	M age 18-34	M age 35-64	M age 65+	F age 18-34	F age 35-64	F age 65+
COPD	Assumption. Incidence levels equal to the mortality value calculated		0.02	0.40		0.01	0.32
Lung cancer	ONS. (2005b) Registrations of cancer diagnosed in 2003, England. Version MB1 no. 34		0.04	0.43		0.03	0.20
CHD (first non fatal event)	British Heart Foundation. (2006) .Coronary Heart Disease Statistics fact sheet.		0.08	0.81		0.02	0.71
Stroke (first non fatal event)	ONS. (2001) Health Statistics Quarterly 12.		0.11	0.61		0.08	0.55
CHD (any non-fatal)	Volmink JA, Newton JN, Hicks NR, Sleight P, Fowler GH, et al. (1998) Coronary event and case fatality rates in an English population: results of the Oxford myocardial infarction incidence study. The Oxford Myocardial Infarction Incidence Study Group. Heart. 80(1): 40-44.		0.12	1.39		0.02	0.97
Stroke (any non-fatal)	ONS. (2001) Health Statistics Quarterly 12.		0.14	1.03		0.11	1.00
Asthma	Asthma UK. (2004) Where do we stand? Asthma in the UK today. http://www.asthma.org.uk/document.rm?id=18 [Accessed 14/09/06],	0.05	0.05	0.06	0.06	0.05	0.05

Table 33: Incidence in 'long-term quitters' by age and gender (%)

Data Item	Data source	M age 18-34	M age 35-64	M Age 65+	F age 18-34	F age 35-64	F age 65+
COPD	*Assumption:* Incidence levels equal to the calculated mortality value		0.02	0.05		0.00	0.04
Lung cancer	ONS. (2005b) Registrations of cancer diagnosed in 2003, England. Version MB1 no. 34		0.04	0.43		0.03	0.20
CHD (first non fatal event)	British Heart Foundation. (2006) .Coronary Heart Disease Statistics fact sheet.		0.05	0.68		0.01	0.50
Stroke (first non fatal event)	ONS. (2001) Health Statistics Quarterly 12.		0.11	0.61		0.05	0.46
CHD (any non-fatal)	Volmink JA, Newton JN, Hicks NR, Sleight P, Fowler GH, et al. (1998) Coronary event and case fatality rates in an English population: results of the Oxford myocardial infarction incidence study. The Oxford Myocardial Infarction Incidence Study Group. Heart. 80(1): 40-44.		0.07	1.16		0.02	0.69
Stroke (any non-fatal)	ONS. (2001) Health Statistics Quarterly 12.		0.0014	0.0103		0.0007	0.0083
Asthma	Asthma UK. (2004) Where do we stand? Asthma in the UK today. http://www.asthma.org.uk/document.rm?id=18 [Accessed 14/09/06],	0.05	0.05	0.06	0.06	0.05	0.05

Mortality, disease specifics

Tables 34, 35, 36 and 37 below refer to mortality figures for the general population, smokers, recent quitters and long-term quitters.

To obtain annual mortality figures for COPD, the mortality rates observed for these ICD 10 codes in the latest ONS mortality rate statistics (ONS 2006) were applied to the age and gender specific population values used in this analysis and then aggregated according to the age-bands required for the model.

Mortality for lung cancer has been estimated from the mortality statistics (ONS 2006).

The annual incidence of fatal CHD events has been calculated from rates of mortality due to ischaemic heart disease (ICD 10 codes I20-25) (British Heart Foundation 2006).

All fatal stroke events have been taken from ONS cause of death data, defining stroke deaths as “intracranial and subarachnoid haemorrhages, cerebral infarctions and other unspecified strokes” (ICD 10 codes I60-I64) (ONS 2006).

Table 34: Mortality General Population (%)

Data Item	Data source	M age 18-34	M age 35-64	M age 65+	F age 18-34	F age 35-64	F age 65+
COPD	ONS. (2006) Mortality Statistics. Cause		0.98	10		0.70	9.16
Lung cancer	ONS. (2006) Mortality Statistics. Cause		26	47		40	75
CHD (incidence of first fatal event)	British Heart Foundation. (2006) .Coronary Heart Disease Statistics fact sheet		0.06	0.64		0.02	0.51
Stroke (incidence of first fatal event)	Assumption. The same split between first event and all events is assumed for first/subsequent for mortality as for incidence.		0.01	0.21		0.01	0.28
CHD (incidence of all fatal events)	ONS. (2006) Mortality Statistics. Cause. ICD 10 codes I20-25		0.09	1.09		0.02	0.70
Stroke (incidence of all fatal events)	ONS. (2006) Mortality Statistics. Cause. ICD 10 codes I60-I64. British Heart Foundation.		0.02	0.35		0.01	0.42

Table 35: Mortality smokers (%)

Data Item	Data source	M age 18-34	M age 35-64	M age 65+	F age 18-34	F age 35-64	F age 65+
COPD	ONS. (2006) Mortality Statistics. Cause		0.98	10.12		0.70	9.16
Lung cancer	ONS. (2006) Mortality Statistics. Cause		26.89	47.69		40.48	75.35
CHD (incidence of first fatal event)	British Heart Foundation. (2006) .Coronary Heart Disease Statistics fact sheet		0.10	0.81		0.04	0.69
Stroke (incidence of first fatal event)	Assumption. The same split between first event and all events is assumed for first/subsequent mortality as for incidence.		0.02	0.30		0.02	0.38
CHD (incidence of all fatal events)	ONS. (2006) Mortality Statistics. Cause. ICD 10 codes I20-25		0.15	1.39		0.04	0.94
Stroke (incidence of all fatal events)	ONS. (2006) Mortality Statistics. Cause. ICD 10 codes I60-I64. British Heart Foundation.		0.03	0.50		0.03	0.56

Table 36 Mortality – 'Recent Quitters' (%)

Data Item	Data source	M age 18-34	M age 35-64	M age 65+	F age 18-34	F age 35-64	F age 65+
COPD	ONS. (2006) Mortality Statistics. Cause		0.98	10.12		0.70	9.16
Lung cancer	ONS. (2006) Mortality Statistics. Cause		26.89	47.69		40.48	75.35
CHD (incidence of first fatal event)	British Heart Foundation. (2006) .Coronary Heart Disease Statistics fact sheet		0.06	0.65		0.02	0.56
Stroke (incidence of first fatal event)	Assumption. The same split between first event and all events is assumed for first/subsequent mortality as for incidence.		0.01	0.20		0.01	0.28
CHD (incidence of all fatal events)	ONS. (2006) Mortality Statistics. Cause. ICD 10 codes I20-25		0.09	1.12		0.02	0.78
Stroke (incidence of all fatal events)	ONS. (2006) Mortality Statistics. Cause. ICD 10 codes I60-I64. British Heart Foundation.		0.01	0.33		0.01	0.42

Table 37: Mortality 'Long Term Quitters (%)

Data Item	Data source	M age 18-34	M age 35-64	M age 65+	F age 18-34	F age 35-64	F age 65+
COPD	ONS. (2006) Mortality Statistics. Cause		0.98	10.12		0.70	9.16
Lung cancer	ONS. (2006) Mortality Statistics. Cause		26.89	47.69		40.48	75.35
CHD (incidence of first fatal event)	British Heart Foundation. (2006) .Coronary Heart Disease Statistics fact sheet		0.04	0.54		0.01	0.40
Stroke (incidence of first fatal event)	Assumption. The same split between first event and all events is assumed for first/subsequent mortality as for incidence.		0.01	0.20		0.01	0.24
CHD (incidence of all fatal events)	ONS. (2006) Mortality Statistics. Cause. ICD 10 codes I20-25		0.06	0.93		0.01	0.55
Stroke (incidence of all fatal events)	ONS. (2006) Mortality Statistics. Cause. ICD 10 codes I60-I64. British Heart Foundation.		0.01	0.33		0.01	0.35

Utilities

Table 38 and Table39 show respectively the utility values for the general population by age bands and for disease specific co-morbidities.

To avoid the potential of overestimating the effect of the utility in smokers with and without smoking-related morbidity, we have assumed that the baseline utility weight for smokers and long-term quitters is equivalent, and any changes to utility are the result of a smoking related disease. Values have been taken from published data (Fiscella 1996) according to the different age bands. This is a conservative approach as it has been shown that smokers' HrQoL is significantly lower than that of non-smokers (Kind P, 1998)

Utility weights were for mild, moderate and severe COPD have been taken from published data (Spencer et al. 2005). Estimates of health status by disease stage were generated from the Health Survey for England (HSE 1996). A weighted average utility score was calculated for COPD from the mild, moderate and severe utility scores using data for COPD severity as reported in the literature (Mannino et al. 2003).

For lung cancer EuroQoL self classifier data was extracted from the literature (Trippoli et al. 2001).

The utilities for myocardial infarction (MI) and angina were taken from the Beaver Dam Health Outcomes Study (Hay et al. 2005).

For stroke, data was taken from a meta-analysis of quality of life estimates in minor, moderate and severe stroke (Tengs et al. 2003). A separate study by Duncan et al. (2000) reports the Proportions of individuals with each stroke severity were taken from the Kansas City Stroke Study Cohort (Duncan et al. 2000). A weighted average utility for all strokes was calculated based on the proportions of individuals with each stroke severity. For utility following a second stroke data was taken directly from a study by Gage et al. (1998)

The utility for asthma exacerbation was taken from a study providing a comparison of (HR-QoL) instruments in cohort of 228 adult inpatients/outpatients (Szende 2004). The data we have used in the model is the EQ-5D utility value for 'poor control' group.

Table 38: Utility for the general population

Data Item	Data source	M age 18-34	M age 35-64	M age 65+	F age 18 -34	F age 35-64	F age 65+
Utility for No co-morbidity	Fiscella (1996)	0.93	0.88	0.80	0.91	0.85	0.77

Table 39: Utilities for disease states

Utility	Data source	First year/ first event	Second year	Subsequent event
COPD	Spencer M, Briggs A, Grossman R, Rance L. Development of an economic model to assess the cost effectiveness of treatment interventions for chronic obstructive pulmonary disease. Pharmacoeconomics 2005; 23(6): 619-637. Mannino DM, Buist AS, Petty TL, Enright PL, Redd SC. Lung function and mortality in the United States: data from the First National Health and Nutrition Examination Survey follow up study. Thorax. 2003 May; 58(5): 388-93.	0.76	0.76	N/A
Lung Cancer	Trippoli S, Vaiani M, Lucioni C, et al. Quality of life and utility in patients with non-small cell lung cancer. Pharmacoeconomics 2001; 19(8): 855-863.	0.61	0.51	N/A
CHD	Hay JW, Sterling KL. Cost effectiveness of treating low HDL-cholesterol in the primary prevention of coronary heart disease. Pharmacoeconomics. 2005; 23(2): 133-41 citing: Fryback DG, Dasbach EJ, Klein R, et al. The Beaver Dam Health Outcomes Study: initial catalog of health-state quality factors. Med Decis Making 1993; 13: 89–102	0.76	N/A	0.76
Stroke	Tengs T, Lin T. A meta-analysis of quality of life estimates for stroke. Pharmacoeconomics 2003; 21(3): 191-200. Duncan PW, Lai SM, Keighley J. Defining post-stroke recovery: implications for design and interpretation of drug trials. Neuropharmacology. 2000 Mar 3; 39(5): 835-41. Gage BF, Cardinalli AB, Owens DK. Cost-effectiveness of preference-based antithrombotic therapy for patients with nonvalvular atrial fibrillation. Stroke. 1998 Jun; 29(6): 1083-91.	0.74	N/A	0.15
Asthma	Szende A, Svensson K, Stahl E, Meszaros A, Berta GY. Psychometric and utility-based measures of health status of asthmatic patients with different disease control level. Pharmacoeconomics. 2004;22(8):537-47.	0.52	N/A	N/A

Cost of co-morbidities

Table 40 below shows the cost of co-morbidities.

A review of studies of the economic impact of COPD was recently undertaken (Halpin 2006). This study cited data from the UK arm of the International Confronting COPD

survey (Britton 2003), which provided estimates of direct and indirect costs of COPD treatment according to COPD severity. The average direct costs were £819.42 per patient and this is the value that has been used within the model.

The cost of lung cancer to the NHS has been estimated as £127m per year (Parrott 2004). The cost per incident case has then been estimated by dividing this figure by the incidence value already estimated (after first uprating one year by the Hospital and Community Health Services Pay and Prices Index inflation index (Curtis 2005)).

The cost of CHD to the NHS was estimated to be £628.6m in 1993 (McMurray J 1993). We have inflated this figure to 2005 and then divided by the prevalent population of diseased patients to estimate current annual costs of CHD.

The estimated annual total direct healthcare cost of stroke in 2005 was estimated by the National Audit Office to be £2.8b (National Audit Office, 2005). This equates to approximately £22,000 per event (110,000 stroke events in England and Wales). The estimate for an individual stroke patient calculated in 2003 was approximately £9,000 per year (Youman 2003). Adjusting for inflation, we take the average of these two to provide an estimated direct cost to the NHS of £16,000 per event.

The estimated cost due to A&E attendance for asthma was £78 in 2000 (Hoskins 2000). The cost of an in-patient admission for asthma in 2006 was taken from the NHS reference cost at £792. To derive the number of patients that required A&E and hospital admission by age-band, the following steps were undertaken. The rate for the 18-34 age-group was assumed the same as for the 16-44 band from Hoskins, the 35-64 age-group was weighted across 16-44 and the 45-74 age-groups from Hoskins at a ratio of 3:2, and the 65+ age band was weighted across 45-74 and 75+ age-groups from Hoskins at a ratio of 2:3. The ratio of A&E visits to hospital admission observed by Hoskins across all age groups was 0.958:1, which is in close agreement with that observed using the hospital episode statistics (HES 2005) from 2005 of 0.967:1. Using the HCHS inflation index from PSSRU (Curtis et al. 2005) to inflate the costs, we were able to derive the cost per patient in 2006 as £888.

Table 40: Cost of co-morbidities

Cost	Data source	First event (£)	Second event (£)
COPD	Britton M. (2003) The burden of COPD in the U.K.: results from the Confronting COPD survey. Respir.Med. 97 Suppl C, S71-S79	819	N/A
Lung cancer	Parrott S, Godfrey C. (2004) Economics of smoking cessation. BMJ. 328(7445): 947-949.	3731	N/A
CHD	McMurray J, Hart W., Rhodes G. (1993) An evaluation of the cost of heart failure to the National Health Service in the UK. British Journal of Medical Economics. 6, 99-110.	980	980
Stroke	Youman P, Wilson K, Harraf F, Kalra L. (2003) The economic burden of stroke in the United Kingdom. Pharmacoeconomics. 21 Suppl 1, 43-50.	16000	16000
Asthma	Hoskins G, McCowan C, Neville RG, Thomas GE, Smith B, et al. (2000) Risk factors and costs associated with an asthma attack. Thorax. 55(1): 19-24.	888	N/A

Efficacy rates

The smoking cessation strategies that have been included as options within the BENESCO model are varenicline, NRT, bupropion and placebo. The efficacy values utilised in the model are listed in Table 41 below. These efficacies represent the quit rates seen at one year following the initiation of a quit attempt.

Varenicline and bupropion efficacy rates have been obtained from direct, head-to-head clinical trial data from the varenicline clinical trial program and comprise the pooled continuous abstinence rates from weeks 9 to 52. The same source was used to provide an estimate of the efficacy of Placebo.

The efficacy rate for NRT was derived through indirect comparison methods as described in 5, from a recently published systematic review and meta-analysis (Wu et al. 2006). As previously noted the methodology used (Bucher et al. 1997, Song et al. 2003) preserves the randomisation of the original trials. The choice of this efficacy rate rather than that from the open-label varenicline/NRT study was driven by the higher than expected efficacy rates in that study for varenicline compared with the results from the double-blind randomised trials (A3051028 and A3051036) and NRT compared with the results from robust systematic reviews and meta-analyses of the wealth of NRT data available (Silagy et a. 2004, Wu et al. 2006).

Table 41: Efficacy rates for Base Case treatment

Data Item	Data source	Efficacy rate
Varenicline	Pooled Gonzales D, Rennard S, Nides M, et. al. Varenicline, an {alpha) 4 beta 2 Nicotinic Acetylcholine Receptor Partial Agonist, vs. Sustained-Release Bupropion and Placebo for Smoking Cessation: A Randomised Controlled Trial. JAMA 2006; 296 47-55. Jorenby D, Taylor Hays J, Rigotti N, et. al. Efficacy of Varenicline, an {alpha}4 beta2 Nicotinic Acetylcholine Receptor Partial Agonist, vs. Placebo or Sustained-Release Bupropion for Smoking Cessation: A Randomised Controlled Trial. JAMA 2006; 296 56-63.	**22.5%**
Bupropion	Pooled Gonzales D, Rennard S, Nides M, et. al. Varenicline, an {alpha) 4 beta 2 Nicotinic Acetylcholine Receptor Partial Agonist, vs. Sustained-Release Bupropion and Placebo for Smoking Cessation: A Randomised Controlled Trial. JAMA 2006; 296 47-55. Jorenby D, Taylor Hays J, Rigotti N, et. al. Efficacy of Varenicline, an {alpha}4 beta2 Nicotinic Acetylcholine Receptor Partial Agonist, vs. Placebo or Sustained-Release Bupropion for Smoking Cessation: A Randomised Controlled Trial. JAMA 2006; 296 56-63.	**15.7%**
NRT	Wu reference	**14.9%**
Placebo	Pooled Gonzales D, Rennard S, Nides M, et. al. Varenicline, an {alpha) 4 beta 2 Nicotinic Acetylcholine Receptor Partial Agonist, vs. Sustained-Release Bupropion and Placebo for Smoking Cessation: A Randomised Controlled Trial. JAMA 2006; 296 47-55. Jorenby D, Taylor Hays J, Rigotti N, et. al. Efficacy of Varenicline, an {alpha}4 beta2 Nicotinic Acetylcholine Receptor Partial Agonist, vs. Placebo or Sustained-Release Bupropion for Smoking Cessation: A Randomised Controlled Trial. JAMA 2006; 296 56-63.	**9.4%**

For the cost-effectiveness of a further 12 weeks of treatment with varenicline, versus placebo, in patients successfully treated with one 12-week course, the efficacy values have been taken from the maintenance of abstinence study (Tonstad 2006) and are shown in Table 42 below.

Table 42: Efficacy rates for Varenicline versus placebo in patients abstinent at end of a 12 week course of Varenicline (Group 2)

Data Item	Data source	Imputed Efficacy rate
Varenicline 12 weeks	Tonstad S, Tonnesen P, Hajek P, et. al. Effect of Maintenance Therapy with Varenicline on Smoking Cessation: A Randomised Controlled Trial. JAMA 2006; 296 64-71.	**43.6%**
Placebo 12 weeks		**36.9%**

These are the rates in the clinical study for Continuous Abstinence from the start of Double-blind treatment (Week 13) through to Week 52. i.e. the Week 40 follow-up values in a group of patients who are regarded as having successfully quit smoking.

The BENESCO model is designed to evaluate the efficacy of therapy in a cohort of subjects entering as *smokers.* The model can accommodate evaluating a cohort of subjects entering as *quitters* in that subjects entering the model do not accrue events until after the first year.

Costs of treatments

The cost of varenicline is £ 1.95 per day plus £0.93 cost of prescription treatment at the end of 2 weeks and 12 weeks.

Bupropion is costed at £ 81.56. The treatment consists of 150mg once daily for 6 days then 150mg twice daily for a total of 9 weeks (2 weeks before quit date and 7 weeks post quit date).

NRT at £117.68 is costed according to a 12 weeks treatment and the cost is based on a basket for all NRT products prescribed in the UK at 2006 prescribing costs weighted basket of treatments.

Table 43: Smoking Cessation Intervention Cost (£)

Data Item	SCI cost
Varenicline	165.66
Bupropion	81.56
NRT	117.68
Placebo	0

Table 44: Cost of treatment for Varenicline versus placebo in patients abstinent at end of a 12 week course of Varenicline (Group 2)

Data Item	SCI cost (£)
Varenicline 12 weeks	165.66
Placebo	0

Relapse rates

As discussed in Section 2.1, relapse to smoking was modelled as a 3 stage process.

- Stage 1: Attempting to quit.
  - In the first year, the smoking relapse rates are derived from the 1-year quit rate associated with the particular smoking cessation strategy selected.

- Stage 2: Recent quitter.
  - The annual relapse rate of 6% for recent quitters (2-5 years after initial cessation) was derived as follows using data obtained from Wetter 2004:
    - There were 1143 subjects in the study cohort, of whom 984 had been abstinent for a year or more and 718 subjects had been abstinent more than 5 years.
    - The percentage of the cohort who had quit for at least a year and were still abstinent at 5years: 718/984 = 72.97%
    - The percentage of the cohort who relapsed after 5 years = 100% -72.97% = 27.03%
    - Relapse rate *PER YEAR* after 5 yrs of quitting = (-Ln(1-27.03%))/5 = 6.3%.

- Stage 3: Long-term quitter
  - For the relapse rate occurring for the long-term quitters abstinent for 6-10 years, the Krall 2002 article cites 2% annually. This same article cites 1% annually for those abstinent for longer than 10 years.

All model values are shown below in Table 45 below.

Table 45: Relapse rates over time

	Relapse Rate
Relapse to smoking: annual rate for quitter up to 5 years after quitting	6.3%
Relapse to smoking: rate for quitter 6-10 years after quitting	2.0%
Relapse to smoking: rate for quitter 10 years+ after quitting	1.0%

Model assumptions

The BENESCO model is based on certain assumptions, which are outlined below.

Morbidities

- All patients entering the model are smokers, with co-morbidities according to the "baseline prevalence" inputs.
- As in any Markov model, states are mutually exclusive (e.g. a patient can not have COPD and CHD at the same time) (see fourth bullet point)
- As in any Markov model, transitions to states are independent of time spent in previous states (Markov assumption)
- If a subject progresses from having an acute co-morbidity (CHD or stroke) to having a chronic one (Lung cancer or COPD) they no longer accumulate the annual costs of treating the effects of the acute condition but start accumulating the costs of the chronic one. This is conservative, and maintains the history-less nature of the Markov model.
- Over the time horizon, patients may enter either the CHD or stroke state, but it is not possible to transition from one to the other, and the model follows whichever occurs first. This assumption is made because once a patient experiences one event (for example CHD), their risk of the other type of event (stroke) is generally increased. Modelling all the possible multiple-morbidity risks and scenarios would greatly increase the complexity of the BENESCO model and the quantity of local data needed to populate the model. This decision simplifies the model by not varying the risks of other morbidities based on subject's morbidity history, which is a conservative assumption.

Age

- In the model, age is used as a proxy to duration of smoking. For example, a smoker aged 45 is assumed to have been a smoker at the beginning of the model, and continues in this state unless a successful quit attempt was experienced in year 1.

- Risk of smoking-related morbidity varies with age and with smoking status. Subjects are classified by specified age bands and by smoking status, and the relevant risks applied to each group.
- The age bands in the model are 18 to 34 years, 35 to 64 years and 65 years and older. Males and females are modelled separately. These age bands reflect those applied in the Thun et al analysis of the Cancer Prevention Study (CPS) – II (Thun 2000).

Effect of Aging on Morbidity

Over time, the cohort of subjects will age. Thus, an increasing proportion of subjects who were initially in the 18 to 34 years age-band will move to the 35 to 64 years age band and experience the rates of disease for this age group. Similarly, as the cohort ages, all subjects eventually experience the rate of disease of those in the 65 years and older group. This allows for the model to account for the effect of aging on the risk of morbidity and mortality (see calc risks sheet in BENESCO model). The proportions of these events are assumed to increase at a constant rate over time (the default values are calculated using weightings from national population data).

- The model calculations have been set up so that after 17 years (i.e., model cycles), the rates for the 18 to 34 years old are no longer used (as no subject will remain under the age of 35). Similarly, after 29 years, all of the group who were 35 to 64 years old at baseline are now aged 65 years or older. The same principle applies to other age groups.

Effect of Aging on Mortality

Death rates have been adjusted in two ways:

- All subjects aged 85 years and older experience higher all cause mortality rates. Specifically, the all cause death rate in this age group was assumed to be the midpoint between 1.00 (all subjects die) and the 65+ mortality rates.

This is because the data source for mortality rates (National Vital Statistics Reports) does not provide data over the age of 85.

- Subjects alive in the model at age 99 are all assumed to die in the next cycle, using the all cause death rate.

Effect of Smoking on Morbidity

There is no morbidity or mortality in the under 35 age-group except for asthma exacerbations. Previous research has documented that chronic smoking-related disease is uncommon in the smokers under the age of 35 years old (Thun 2000). This is a conservative assumption.

Additionally, the relative risk of smoking-related morbidity for a person who has not maintained cessation for at least one-year duration (the attempting to quit stage) is assumed to be the same as that of a current smoker. The effect of this assumption in the model is that from baseline to year 1 the risks of developing smoking-related morbidity are the same in the smokers or quitters group. This assumption has also been used in the HECOS model (Orme, 2001) and the Dutch model reported by Feenstra and by van Genugten (Feenstra, 2005; van Genugten, 2003).

Chronic Morbidities

• The risk of developing COPD, lung cancer, CHD and stroke increases with age independent of smoking status.
• For former smokers, the relative risk of these smoking related-morbidities is reduced over time compared to current smokers of the same age.
• The number of deaths resulting from an asthma attack is assumed to be small and accounted for in the all cause mortality rate. This is a conservative assumption
• Disease events are assumed to be mutually exclusive. For example, a subject cannot acquire both CHD and lung cancer within same cycle.

Mortality - Asthma exacerbation

The number of deaths resulting from a smoking-related asthma attack is assumed to be small and accounted for in the all-cause mortality rate.

Utility

The baseline utility values are assumed to be the same for smokers and non-smokers. This is a conservative assumption that prevents the model over-estimating the benefits of smoking cessation in comparison with the disutility due to morbidities.

6.2.6.2 Why was this particular model used?

The BENESCO model has been developed to estimate the long-term health and economic benefits of smoking cessation.
It:

- Simulates the consequences of smoking on a population
- Reflects the health and economic benefits over various time horizons that can be achieved through a one-time smoking cessation attempt
- Determines the cost-effectiveness of varenicline relative to other smoking cessation interventions and to unaided cessation
- Maintains a high level of quality without oversimplification or under representation

6.2.6.3 What was the justification for the chosen structure? How was the course of the disease/condition represented? Please state why any possible other structures were rejected.

The structure selected was used as it forms the basis of the HECOS model which was developed with input from many stakeholders. The updating to the model described earlier in the submission was designed so as to enable the effective and credible modelling of the cost-effectiveness of pharmacological smoking cessation agents in an HTA environment.

6.2.6.4 What were the sources of information used to develop and inform the structure of the model?

The BENESCO model is an updated version of the HECOS model (Orme. 2001).
The BENESCO model development was guided by key learnings from the HECOS model (developed for the World Health Organisation with input from many stakeholders) used to evaluate the costs and life years gained from smoking cessation.

Table 46: Additional features in BENECO model compared with HECOS model.

Additional feature in BENESCO	**Rationale**
Directly compare 2 interventions simultaneously	Allows for instantaneous incremental/ comparative analysis; The HECOS model could only look at results for one strategy at a time
Include utilities	Allows for calculation of QALYs
Project beyond 20-year time frame (to death) and include all cause mortality death rates.	For younger age groups, benefits of quitting smoking may not be realised until more than 20 years post-quitting. A lifetime model will capture all consequences.
Update relapse rate projection to three stages of relapse compared to two stage to reflect markedly reduced risk of relapse in long term quitters	In a review of the previous model, relapse rate was regarded as conservative since it was a fixed (linear) rate throughout the model.
Specify cohort: pre-existing conditions	Allows for sub-group analysis and more flexibility.
Allow for some co-existence of conditions	Treatment and management of some of the chronic diseases considered in the model (CHD) are such that if a patient survives the acute event, their probability of survival in the long-term is good. This means patient has the potential to develop and die from another smoking-related disease (e.g. lung cancer or COPD).
Split costs into cost of treating acute event (i.e. first CHD event) and cost of long-term disease management (i.e. secondary prevention of CHD event)	More accurate calculation of treatment costs.

6.2.6.5 Does the model structure reflect all essential features of the condition that are relevant to the decision problem? If not, why not?

The model structure does not capture all the effects of smoking as there are approximately 30 conditions known to be causally related to smoking. The morbidities selected in the model are the major ones associated with smoking and are the most costly.

The other causally associated conditions are in general less prevalent and there inclusion would only add to the benefits seen with the provision of a more effective smoking cessation therapy.

6.2.6.6 For discrete time models, what was the model's cycle length, and why was this length chosen? Does this length reflect a minimum time over which the pathology or symptoms of a disease could differ? If not, why not?

The Markov cycle length is of one year.

The clinical trial follow-up was one year and therefore this time duration has been chosen for convenience. There was no reason to choose a different cycle length and the results would not have changed with a different length.

6.2.6.7 Was a half-cycle correction used in the model? If not, why not?

Yes

6.2.6.8 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about the longer-term difference in effectiveness between the technology and its comparator?

The costs and clinical outcomes are extrapolated beyond the duration of trial follow-up.

Rationale:

- All of the interventions are short term in nature.
- No long-term differences between any of the technologies modelled have been assumed. After the initial efficacy values are taken into account, all other assumptions in the model apply equally to each technology and placebo.

b) Non-model-based economic evaluations

6.2.6.9 Was the evaluation based on patient-level economic data from a clinical trial or trials?

No

6.2.6.10 Provide details of the clinical trial, including the rationale for its selection.

Not Applicable

6.2.6.11 Were data complete for all patients included in the trial? If not, what were the methods employed for dealing with missing data for costs and health outcomes?

Not Applicable

6.2.6.12 Were all relevant economic data collected for all patients in the trial? If some data (for example, resource-use or health-related utility data) were collected for a subgroup of patients in the trial, was this subgroup pre-specified and how was it identified? How do the baseline characteristics and effectiveness results of the subgroup differ from those of the full trial population? How were the data extrapolated to a full trial sample?

Not Applicable

6.2.6.13 Are costs and clinical outcomes extrapolated beyond the trial follow-up period(s)? If so, what are the assumptions that underpin this extrapolation and how are they justified? In particular, what assumption was used about any longer-term differences in effectiveness between the technology and its comparator?

Not Applicable

6.2.7 Clinical evidence

Where relevant, answers to the following questions should be derived from, and consistent with, the clinical evidence section of the submission (section 5). Cross-references should be provided. If alternative sources of evidence have been used, the method of identification, selection and synthesis should be provided and a justification for the approach provided.

6.2.7.1 How was the baseline risk of disease progression estimated? Also state which treatment strategy represents the baseline.

The baseline risk for Group 1 is the continuous abstinence rate (week 9 to week 52) from the pivotal clinical trials for placebo (A3051028 and A3051036).

The baseline risk for Group 2 is the continuous abstinence rate from the start of the double-blind period (week 13 through week 52) from the maintenance of abstinence trial for placebo (A3051035).

6.2.7.2 How were the relative risks of disease progression estimated?

In the case of smoking cessation what is of interest is the ‘progression’ of quitting over time as this drives the probability of incurring smoking related morbidity or mortality.

In the cost-effectiveness model, we use the efficacy rate at 1 year defined by the continuous abstinence rate from week 9 to week 52 from the pivotal clinical trials, with the exception of NRT where the efficacy is derived from an adjusted indirect comparison.

After one year, efficacy rates from the literature for recent quitter (up to year 5) and long term quitter (5 to 10 year) then (+10 years) are used to inform the progression of smoking status. The same relapse rates, discussed in the section above (6.2.6) are applied across different strategies.

The probability of an individual incurring a specific disease induced by smoking depends on the status of the patient: no smoker, smoker, recent quitter or long term quitter.

The relative risk of augmenting the probability of incurring a disease and dying from the disease is given in appendix 1.

The assumption is made that patients who are long term quitters have the same probability of incurring a specific disease or dying as the general population.

6.2.7.3 Were intermediate outcome measures linked to final outcomes (such as patient survival and quality-adjusted life years [QALYs])? If so, how was this relationship estimated, what sources of evidence were used, and what other evidence is there to support it?

The intermediate outcome of quit rates over time has been used to define the probability of incurring smoking related disease or dying. This fundamental principle underlies all assumptions made about the medical benefits of smoking cessation.

6.2.7.4 Were the health effects or adverse effects associated with the technology included in the economic evaluation? If not, would their inclusion increase or decrease the estimated cost effectiveness of this technology?

The adverse effects associated with the technology and comparators have not been included in the economic evaluation.

6.2.7.5 Was expert opinion used to estimate any clinical parameters? If so, how were the experts identified, to which variables did this apply, and what was the method of elicitation used?

Based on the robust development of the HECOS model with wide stakeholder input, there was no requirement to defer to expert opinion for any of the parameters of interest in the model.

6.2.7.6 What remaining assumptions regarding clinical evidence were made? Why are they considered to be reasonable?

N/A.

6.2.8 Measurement and valuation of health effects

6.2.8.1 Which health effects were measured and how was this undertaken? Health effects include both those that have a positive impact and those with a negative impact, such as adverse events.

We have used Quality adjusted life years as the main outcome from the literature. We take into account of Quality of life weights for the general population (distinguished by age-bands) and for smoking induced disease.

6.2.8.2 Which health effects were valued? If taken from the published literature, how and why were these values selected? What other values could have been used instead? If valued directly, how was this undertaken?

Health effects have been taken from literature. The preference was for quality of life values taken from data using validated score algorithms such as the EQ-5D and SF-36 whose weights for different health items are found through regression methods from questionnaires scored by the general public. If these were not available, we deferred to preference based-based index such as the time trade off or the standard gamble. If these were not available, we deferred to visual standard gamble scales.

6.2.8.3 Were health effects measured and valued in a manner that was consistent with NICE's reference case? If not, which approach was used?

Yes they were.

6.2.8.4 Were any health effects excluded from the analysis? If so, why were they excluded?

We have included all the major health effects of smoking, COPD, CHD, Stroke, Lung Cancer and Asthma exacerbations which are the most prevalent and have the highest cost.

The many other causally associated conditions are in general less prevalent and there inclusion would only add to the benefits seen with the provision of a more effective smoking cessation therapy. i.e. a negligible impact on the results in favour of varenicline.

6.2.8.5 If health effects were not expressed using QALYs, what health outcome measure was used and what was the justification for this approach?

As a secondary outcome, we have used life years gained, and we derived incremental estimates for the different strategies.

6.2.9 Resource identification, measurement and valuation

6.2.9.1 What resources were included in the evaluation? (The list should be comprehensive and as disaggregated as possible.)

The resources explicitly included in the model are the cost of the interventions and the disease costs.

6.2.9.2 How were the resources measured?

The model is structured in such a way that the costs of the different health states are collected at different points in time.

6.2.9.3 Were the resources measured using the same source(s) of evidence as the baseline and relative risks of disease progression?

Yes

6.2.9.4 Were resources used to treat the disease/condition included for all relevant years (including those following the initial treatment period)? Provide details and a justification for any assumptions that were made (for example, assumptions regarding types of subsequent treatment).

The cost of the intervention applies only to the first year.

The unit cost of each health state is taken from published sources that refer to current practice in the NHS in England Wales. Where we could not find an average cost of disease treatment, we have utilised a top down cost exercise. This approach consists in dividing a total cost made up of all the resources used to treat a particular disease, divided by the prevalence of that disease, to find the unit cost of the disease incurs. Details for the estimation of costs can be found in the cost section in 6.2.9.1.

6.2.9.5 What source(s) of information were used to value the resources?

N/A

6.2.9.6 What is the unit cost (excluding VAT) of the intervention(s) included in the analysis? Does this differ from the (anticipated) acquisition cost reported in section 1?

Costs of treatments

The cost of varenicline is £ 1.95 per day plus £0.93 cost of prescription treatment at the end of 2 weeks and 12 weeks.

Bupropion is costed at £ 81.56. The treatment consists of 150mg once daily for 6 days then 150mg twice daily for a total of 9 weeks (2 weeks before quit date and 7 weeks post quit date).

NRT at £117.68, is costed according to a 12 weeks treatment and the cost is based on a basket for all NRT products prescribed in the UK at 2006 prescribing costs weighted basket of treatments.

Table 47: Smoking Cessation Intervention Cost (£)

Data Item	SCI cost
Varenicline	165.66
Bupropion	81.56
NRT	117.68
Placebo	0

Table 48 shows the cost of treatment for the varenicline 12 week course versus placebo in patients abstinent at the end of a 12 week course of varenicline..

Table 48: Cost of treatments: Varenicline versus Placebo in patients abstinent at end of a 12-week course of Varenicline (Group 2)

Data Item	SCI cost (£)
Varenicline 12 weeks	165.66
Placebo	0

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6.2.9.7 Were the resources measured and valued in a manner consistent with the reference case? If not, how and why do the approaches differ?

Yes.

6.2.9.8 Were resource values indexed to the current price year?

Costs of each disease have been inflated to 2006 prices according to the inflation rates in the PSSRU.

6.2.9.9 Provide details of and a justification for any assumptions that were made in the estimation of resource measurement and valuation.

N/A

6.2.10 Time preferences

Were costs and health benefits discounted at the rates specified in NICE's reference case?

Yes, costs and outcomes were discounted using an annual discount rate of 3.5%.

6.2.11 Sensitivity analysis

Sensitivity analysis should be used to deal with sources of main uncertainty other than that related to the precision of the parameter estimates.

For technologies whose final price/acquisition cost has not been confirmed, sensitivity analysis should be conducted over a plausible range of prices.

6.2.11.1 Which variables were subject to sensitivity analysis? How were they varied and what was the rationale for this?

The variables subject to the sensitivity analysis were:

- Discount rates for cost and QALYs
- baseline risk (quit rate in the placebo arm),
- Cost of NRT at 25% of its original cost.

The discount rates taken for the sensitivity analysis are 6% for costs and 1.5% for QALYs. As for the baseline risk, the upper and lower values of the 95% confidence interval around the rate have been taken to estimate the cost effectiveness estimates. 25% of the cost of NRT has been taken into account in the analysis to consider the possibility that this product can be offered at a high discount or can be subsidised at point of delivery and also considering that NRT cost is calculated according a basket of different types of NRT treatments.

Exploration of the uncertainty surrounding baseline risk - main analysis

We explored the sensitivity of the main analysis results to baseline risk (efficacy rate in the placebo arm).

We were interested in the changes in cost-effectiveness estimates with different levels of baseline risk in the population. This is represented in clinical trials by the efficacy rate of the placebo arm. To undertake this analysis we calculated the confidence interval for the efficacy rate according to the formula for a proportion as follows:

$p \pm 1.96*\sigma$

Where σ represent the standard deviation for a proportion

$p \pm 1.96* \sqrt{((p*(1-p)/N)}$

Giving a confidence interval around the placebo efficacy value of 9.4% of LCI 7% UCI 11%.

We then calculated the relative risk of each treatment against placebo and created a univariate sensitivity analysis by multiplying the Relative Risk of each treatment vs.

placebo by the upper and lower bound of the confidence interval. As an output variable we took the net benefit of each treatment calculated at a cost-effectiveness threshold of £30,000 per QALY according to the formula:

NET Benefit =30000* QALYs- cost

6.2.11.2 Was probabilistic sensitivity analysis (PSA) undertaken? If not, why not? If it was, the distributions and their sources should be clearly stated; including the derivation and value of 'priors'.

Yes, probabilistic sensitivity analysis was undertaken

The list of parameters which were assessed (Table 49) cover:

• Effectiveness of smoking cessation strategies

• Treatment costs for morbidities

• Utilities

Table 49: Parameters included in Probabilistic Sensitivity analysis

Parameters	Data source	Methodology	Distribution used with parameters
Efficacy			
Varenicline vs. Placebo	Varenicline trials: Gonzales (2006) & Jorenby (2006)	The log Odds ratio is sampled from a Normal distribution according to mean and SD found in the trials. It is then converted back to the Odds with the exponential transformation. We then work out the efficacy rate of the treatment by combining the odds ratio with the sampled efficacy rate in the placebo arm.	Normal (1.05,0.16)
Bupropion vs. Placebo	Varenicline trials: Gonzales (2006) & Jorenby (2006)		Normal (0.67,0.09)
NRT vs. Varenicline	Wu et al. (2006)	As above, but we work out the efficacy of NRT by combining the odds ratio of NRT vs. varenicline with the sampled value for odds of varenicline vs. NRT estimate is found through indirect estimates	Normal (0.56, 0.19)
Placebo	Varenicline trials: Gonzales (2006), and Jorenby (2006)	Numbers of events (first parameter) and non events (second parameter) comes from the pooled varenicline trials	Beta (62,620)
Costs			
COPD	Britton (2003)	The standard error is assumed to be 10% of the mean value.	Lognormal (6.69,0.20)
Lung Cancer	Parrott, S et al. (2004)		Lognormal (8.20,0.20)

CHD	McMurray J. et al. (1993)		Lognormal (6.87,0.20)
Stroke	Youman et al. (2003)		Lognormal (9.66,0.20)
Asthma	Hoskins G. et al. (2000)		Lognormal (6.77,0.20)
<u>Utilities</u>			
Males 18-34	Fiscella (1996)	The standard error is assumed to be 10% of the mean values	Beta(6.07,0.46)
Males 35-64			Beta(11.42,1.60)
Males 65+			Beta(19.20,4.80)
Females 18-34			Beta(8.09,0.80)
Females 35-64			Beta(13.58,2.39)
Females 65+			Beta(22.23,6.64)
COPD	Spencer et al. (2005)	Weighted average of three Beta distributions respectively for mild, moderate and severe disease	0.10*Beta_sev(58, 28)+0.42*Beta_mod(160,62) +0.47*Beta_mild(310,73)
Lung Cancer	Trippoli et al. (2001)		Beta(0.65,0.41)
CHD	Hay et al. (2005) Fryback et al. (1993)	Weighted average of two betas respectively for Myocardial infarction and Angina	0.53*Beta(53,19)+ 0.47* Beta(158,43)
Stroke	**Ist** Tengs et al. (2003) Duncan et al. (2000)	Weighted average of three betas respectively for mild, moderate and severe stroke.	0.39*Beta_mild(42,6) +0.50* Beta_mod(25,11)+ 0.11*Beta_sev(50, 47)
	2nd Gage et al. (1998)		Beta(1.95,11.05)
Asthma	Szende et al. (2004)		Beta(118,109)

6.2.11.3 Has the uncertainty associated with structural uncertainty been investigated? To what extent could/does this type of uncertainty change the results?

We did not investigate structural uncertainty because the model chosen being based on the HECOS model was the most appropriate for measuring the cost-effectiveness of pharmacological therapies for smoking cessation.

6.2.12 Statistical analysis

6.2.12.1 How were rates or probabilities based on intervals transformed into (transition) probabilities?

We assume that the interval is a 95% confidence interval (when it is not stated) and impose a normal distribution and we work out the mean of the range from the lower and upper bound of the range and we assume that this is the transition rate.

6.2.12.2 Is there evidence that (transition) probabilities should vary over time for the condition or disease? If so, has this been included in the evaluation? If there is evidence that this is the case, but it has not been included, provide an explanation of why it has been excluded.

Yes. In this case the transition probability of interest is the abstinence rate. The rates we have used for relapse rate over 1 year (i.e. relapse rate up to 5 years, relapse rate 6 to 10 year and relapse rate over 10 years) are all declining as a function of time and this reflects the realistic assumption that patients who are abstinent over a prolonged period of time are less likely to relapse in the future years

6.2.13 Validity

Describe the measures that have been undertaken in order to validate and check the model.

The steps listed below have been carried out successfully with the model to ensure that the calculations in the model are performing as expected. Cell by cell verification has also been undertaken.

Set both treatments to be the same (e.g. varenicline vs.varenicline) and check for differences between final results, and intermediate values/totals.

- Ensure all values in every cell of Populations, Costs and QALYs sheets are identical, using a comparison sheet.
- Ensure differences in totals in Populations, Costs and QALYs sheets are zero
- Ensure all differences in CE calculations are zero, and CE ratios are n/a.
  This test demonstrates that the two treatment arms have the same logic and calculations, and hence will come to the same results with the same data.

Check transition probabilities sum to 1.000, for each year.

- Check that the sum of each years risks (in calc risks sheet) sum to 1.000
- This test ensures that patients are neither entering nor leaving the model – only changing from one state to another.

Check (number alive) + (number dead) = (number starting model) at all times.

- Total number alive, and numbers dead, each year in the populations' sheets.
- Check that each year these two total to the number entering the model.

This test demonstrates that patients are neither entering nor leaving the model - only changing from one state to another.

Set all mortality to 0.

- Set background mortality to zero, by overtyping existing values in the INPUT Fixed Point Data sheet.
- Set disease mortalities to zero, by overtyping existing values in the INPUT Fixed Point Data sheet.
- Ensure the two treatments being compared are different (e.g. varenicline vs. NRT)
- Check that the number alive and dead at the end of each year is the same for both treatments.

This test demonstrates that differences in patient numbers alive and dead between treatments are due to differences in mortality due to smoking and its co-morbidities.
Note:
In this test, death still occurs in the model because a proportion of elderly still die each year, to ensure everyone is dead at 100 years old. This effect is the same in each arm and hence the numbers alive/dead will be the same each year for each arm of the model.

Set all utility to 1.00.

- Set all utility values to 1.00 by overtyping the values in the INPUT Fixed Point Data sheet.
- Set outcomes discounting to 0%
- Check that the number alive at the end of each year is the same as the number of Life Years each year, and the number of QALYs.

This test demonstrates that all patients alive are being counted in the LYG and QALY calculations.

Set the treatment cost of every morbidity to £0

- Set the treatment cost for each morbidity to £0 by over-typing the values in the INPUT Fixed Point Data.
- Set outcomes discounting to 0%
- Check that the total cost for each disease (in the Results Cost Table) is £0 at each time point.
- Check that the total cost of each treatment arm is equal to the total cost of the Smoking Cessation treatment for that arm (i.e. no morbidity cost, just initial treatment cost) and that this figure matches the Smoking Cessation Strategy Cost in the Results Cost Table.

This test demonstrates that the disease costs are derived from the values in the INPUT Fixed Point Data sheet, and that without these (i.e. with them set to £0) the cost of each strategy is purely the cost of the initial SC intervention.

Set each Smoking Cessation strategy cost to £0

- Set the treatment cost for each Smoking Cessation strategy to £0 by overtyping the values in the INPUT Fixed Point Data.
- Set outcomes discounting to 0%
- Check that the Smoking Cessation Strategy Cost (in the Results Cost Table) is £0 for both treatment arms.
- THEN set the treatment cost for each morbidity to £0 by over-typing the values in the INPUT Fixed Point Data.
- THEN Check that the total costs for both treatment arms are 0 every year.

This test demonstrates that all the costs are derived from the values in the INPUT Fixed Point Data sheet, and that without these (i.e. with them set to £0) the cost of each strategy is £0.

6.3 Results

Provide details of the results of the analysis. In particular, results should include, but are not limited to, the following:

• costs, QALYs and incremental cost per QALY
• disaggregated results such as life years gained, costs associated with treatment, costs associated with adverse events, and costs associated with follow-up/subsequent treatment
• a statement as to whether the results are based on a probabilistic sensitivity analysis
• cost-effectiveness acceptability curves
• scatterplots on cost-effectiveness quadrants.

6.3.1 Base-case analysis

6.3.1.1 What were the results of the base-case analysis?

6.3.1.1 Results for standard treatment regimen (Group 1)

In the analysis of varenicline vs. NRT, bupropion or placebo, comparing the effectiveness of an initial course of treatment, the lifetime results demonstrate that varenicline dominates, and compared with NRT produces cost savings of around £495,000,000 for England and Wales (Table 50).

Table 50: Lifetime Results; Costs QALYs and Life Years in a Life time

	Costs (£)	QALYs	Life Years	Incremental results
Varenicline	34,018,920,489	42,135,027	86,711,276	Dominant
Bupropion	34,347,878,880	42,063,665	86,540,790	
NRT	34,514,466,202	42,057,446	86,525,933	
Placebo	34,608,281,768	42,001,477	86,392,224	

The cost-effectiveness results for varenicline versus NRT (Table 51) demonstrate that varenicline dominates at 20 years and at Lifetime for both cost per QALY and cost per LYG. At 10 years, varenicline versus NRT has an ICER of £3,432 per additional QALY and of £3,378 per LYG.

Table 51: Incremental results - Varenicline vs. NRT

Model year	2	5	10	20	Lifetime
Varenicline Treatment Related Costs (Millions)	1,995	4,404	8,615	17,750	34,019
NRT Treatment Related Costs (Millions)	1,850	4,290	8,584	17,928	34,514
difference (Millions)	*144.7 [7.8%]*	*114.1 [2.7%]*	*31.2 [0.4%]*	*-177.5 [-1%]*	*-494.7 [-1.4%]*
Varenicline QALYs (Thousands)	5,059	11,677	20,411	31,782	42,135
NRT QALYs (Thousands)	5,059	11,674	20,402	31,752	42,058
difference (Thousands)	*0.4 [0%]*	*2.4 [0%]*	*9.1 [0%]*	*30.5 [0.1%]*	*77.5 [0.2%]*
Varenicline Life Years (Thousands)	6,204	15,041	28,346	50,530	86,711
NRT Life Years (Thousands)	6,204	15,039	28,337	50,488	86,526
difference (Thousands)	*0.1 [0%]*	*1.8 [0%]*	*9.2 [0%]*	*42 [0.1%]*	*185.1 [0.2%]*
Incremental Cost per additional QALY	382,025	47,283	3,432	Dominates	Dominates
Incremental Cost per LYG	1,159,187	62,514	3,378	Dominates	Dominates

The cost-effectiveness results for varenicline versus bupropion (Table 52) demonstrate that varenicline dominates at 20 years and at Lifetime for both cost per QALY and cost per LYG. At 10 years, varenicline versus bupropion has an ICER of £18,564 per additional QALY and of £18,272.

Table 52: Incremental results Varenicline vs. Bupropion

Model year	2	5	10	20	Lifetime
Varenicline Treatment Related Costs (Millions)	1,995	4,404	8,615	17,750	34,019
Bupropion Treatment Related Costs (Millions)	1,735	4,172	8,460	17,787	34,348
difference (Millions)	*260 [15%]*	*231.8 [5.6%]*	*155.4 [1.8%]*	*-36.8 [-0.2%]*	*-329 [-1%]*
Varenicline QALYs (Thousands)	5,059	11,677	20,411	31,782	42,135
Bupropion QALYs (Thousands)	5,059	11,675	20,403	31,754	42,064
difference (Thousands)	*0.3 [0%]*	*2.2 [0%]*	*8.4 [0%]*	*28.1 [0.1%]*	*71.4 [0.2%]*
Varenicline Life Years (Thousands)	6,204	15,041	28,346	50,530	86,711
Bupropion Life Years (Thousands)	6,204	15,039	28,337	50,492	86,541
difference (Thousands)	*0.1 [0%]*	*1.7 [0%]*	*8.5 [0%]*	*38.7 [0.1%]*	*170.5 [0.2%]*
Incremental Cost per additional QALY	745,046	104,283	18,564	Dominates	Dominates
Incremental Cost per LYG	2,260,712	137,874	18,272	Dominates	Dominates

The cost-effectiveness results for varenicline versus placebo (Table 53) demonstrate that varenicline dominates at 20 years and at Lifetime for both cost per QALY and cost per LYG. At 10 years varenicline versus placebo has an ICER of £20,240 per additional QALY and of £19,922 per LYG.

Table 53: Incremental results. Varenicline vs. Placebo

Model year	2	5	10	20	Lifetime
Varenicline Treatment Related Costs (Millions)	1,995	4,404	8,615	17,750	34,019
Placebo Treatment Related Costs (Millions)	1,482	3,944	8,298	17,793	34,608
difference (Millions)	*512.8 [34.6%]*	*460 [11.7%]*	*317.1 [3.8%]*	*-42.6 [-0.2%]*	*-589.4 [-1.7%]*
Varenicline QALYs (Thousands)	5,059	11,677	20,411	31,782	42,135
Placebo QALYs (Thousands)	5,058	11,673	20,396	31,729	42,001
difference (Thousands)	*0.7 [0%]*	*4.2 [0%]*	*15.7 [0.1%]*	*52.6 [0.2%]*	*133.6 [0.3%]*
Varenicline Life Years (Thousands)	6,204	15,041	28,346	50,530	86,711
Placebo Life Years (Thousands)	6,204	15,038	28,330	50,458	86,392
difference (Thousands)	*0.2 [0%]*	*3.1 [0%]*	*15.9 [0.1%]*	*72.5 [0.1%]*	*319.1 [0.4%]*
Incremental Cost per additional QALY	785,258	110,597	20,240	Dominates	Dominates
Incremental Cost per LYG	2,382,728	146,222	19,922	Dominates	Dominates

6.3.1.1b Results of analysis comparing 12 weeks of Varenicline therapy versus placebo in patients abstinent at end of a 12 week course of Varenicline (Group 2)

The Licence states that an additional 12 weeks of therapy may be considered for patients who have successfully quit after the initial 12 weeks of varenicline therapy.

Table 54 below demonstrates the cost-effectiveness results for 12 weeks of varenicline therapy compared with placebo. The varenicline treatment dominates, generating an additional 68,300 QALYs over the lifetime with a further cost-saving for England and Wales of £44,500,000.

Table 54: Incremental results Varenicline versus Placebo in patients abstinent at end of a 12-week course of Varenicline (Group 2)

Model year	2	5	10	20	Lifetime
Varenicline Treatment Related Costs (Millions)	1,974	4,298	8,279	16,835	32,223
Placebo Treatment Related Costs (Millions)	1,455	3,806	7,860	16,600	32,267
difference (Millions)	*519.2 [35.7%]*	*492.2 [12.9%]*	*419.1 [5.3%]*	*235.1 [1.4%]*	*-44.5 [-0.1%]*
Varenicline QALYs (Thousands)	5,060	11,684	20,437	31,867	42,350
Placebo QALYs (Thousands)	5,060	11,681	20,429	31,840	42,282
difference (Thousands)	*0.3 [0%]*	*2.1 [0%]*	*8 [0%]*	*26.9 [0.1%]*	*68.3 [0.2%]*
Varenicline Life Years (Thousands)	6,204	15,046	28,371	50,647	87,225
Placebo Life Years (Thousands)	6,204	15,044	28,363	50,610	87,062
difference (Thousands)	*0.1 [0%]*	*1.6 [0%]*	*8.1 [0%]*	*37.1 [0.1%]*	*163.2 [0.2%]*
Incremental Cost per additional QALY	1,554,429	231,370	52,302	8,735	Dominates
Incremental Cost per LYG	4,716,643	305,896	51,479	6,345	Dominates

6.3.2 Subgroup analysis

6.3.2.1 What were the results of the subgroup analysis/analyses if conducted?

Subgroup analyses were conducted for 3 different age bands, 18 years to 34 years (Table 55), 35 years to 64 years (Table 56) and 65 years and older (Table 57) and by gender.

Subgroup analysis by age

A subgroup analysis was conducted by the age-bands used to assure data accuracy within the model leaving all other parameters unchanged. The effect of this analysis is to examine the impact of the decreased opportunity to acquire smoking related diseases against the increased prevalence by age of those diseases and death. Cost and QALYs vary between the analyses as expected. varenicline maintains dominance in all subgroups over NRT, bupropion and placebo.

Table 55: Subgroup analysis 18 years to 34 years

	Costs (£)	QALYs	Incremental results
Varenicline	10,343,792,277	20,039,040	Dominant
Bupropion	10,512,167,919	20,018,094	
NRT	10,570,558,339	20,016,298	
Placebo	10,650,502,186	19,999,841	

Table 56: Subgroup analysis 35 years to 64 years

	Costs (£)	QALYs	Incremental results
Varenicline	21,585,624,366	20,604,194	Dominant
Bupropion	21,772,627,911	20,556,020	
NRT	21,861,671,972	20,551,891	
Placebo	21,921,647,129	20,514,040	

Table 57: Subgroup analysis 65 years and older

	Costs (£)	QALYs	Incremental results
Placebo	2,511,623,033	1,564,785	
Bupropion	2,539,417,159	1,566,852	Ext dominated by Varenicline
NRT	2,557,635,716	1,566,649	Dominated by bupropion
Varenicline	2,566,805,939	1,569,225	12426

Subgroup analysis by gender

A subgroup analysis was undertaken by gender leaving all other parameters unchanged (Tables 58 and 59). Varenicline maintains dominance over bupropion, NRT and placebo.

Males

Table 58: Analysis of Males

	Costs (£)	QALYs	ICER
Varenicline	17,602,987,449	20,835,463	Dominant
Bupropion	17,764,272,815	20,796,452	
NRT	17,842,948,101	20,793,109	
Placebo	17,892,439,324	20,762,458	

Table 59: Analysis of Females

	Costs (£)	QALYs	ICER
Varenicline	16,415,933,040	21,299,565	Dominant
Bupropion	16,583,606,066	21,267,213	
NRT	16,670,666,787	21,264,440	
Placebo	16,715,842,445	21,239,020	

6.3.3 Sensitivity analyses

6.3.3.1 What were the main findings of the sensitivity analyses?

Varying the discount rates (6% for costs and 1.5% for benefits) for the main analyses did not alter varenicline dominating (table 60).

Table 60: Cost-effectiveness results with Costs discounted at 6% & benefits at 1.5% - main analysis

	Costs (£)	QALYs	Incremental results
Varenicline	21,623,019,507	56,783,701	Dominant
Bupropion	21,724,132,324	56,664,718	
Placebo	21,785,984,069	56,561,033	
NRT	21,870,338,711	56,654,519	

Varying the discount rates (6% for costs and 1.5% for benefits) for varenicline 12 weeks versus placebo in patients abstinent at end of an initial course of varenicline, resulted in an incremental cost effectiveness ratio of £1,583 per additional QALY (table 61).

Table 61: Cost-effectiveness results with Costs discounted at 6% and benefits at 1.5% for Varenicline versus Placebo in patients abstinent at end of an initial course of Varenicline

	costs (£)	QALYs	ICER
Varenicline 12 weeks	20,514,000,000	57,142,000	1524
Placebo	20,340,000,000	57,,028,000	

Varying the cost of NRT to 25% of current price for the main analyses did not alter varenicline dominating (table 62).

Table 62: Cost-effectiveness results with the Cost of NRT reduced to 25%

	Costs (£)	QALYs	Incremental results
Varenicline	34018920489	42,135,028	Dominant
NRT	34233447728	42,057,548	
Bupropion	34347878880	42,063,665	
Placebo	34608281769	42,001,477	

The results of this sensitivity analysis led to the decision to evaluate the effectiveness of varenicline versus NRT, if NRT were only available as an Over The Counter (OTC) treatment (I.e. there were no costs to the NHS if NRT were the treatment option). As can be seen in Table 63, varenicline was still dominating over a lifetime.

Table 63: Cost-effectiveness results with the Cost of NRT reduced to 0%

Model year	2	5	10	20	Lifetime
Varenicline Treatment Related Costs (Millions)	1,995	4,404	8,615	17,750	34,019
NRT Treatment Related Costs (Millions)	1,477	3,916	8,211	17,555	34,141
difference (Millions)	*518.3 [35.1%]*	*487.6 [12.5%]*	*404.6 [4.9%]*	*195.6 [1.1%]*	*-122 [-0.4%]*
Varenicline QALYs (Thousands)	5,059	11,677	20,411	31,782	42,135
NRT QALYs (Thousands)	5,059	11,674	20,402	31,752	42,057
difference (Thousands)	*0.4 [0%]*	*2.4 [0%]*	*9.1 [0%]*	*30.6 [0.1%]*	*77.6 [0.2%]*
Varenicline Life Years (Thousands)	6,204	15,041	28,346	50,530	86,711
NRT Life Years (Thousands)	6,204	15,039	28,337	50,488	86,526
difference (Thousands)	*0.1 [0%]*	*1.8 [0%]*	*9.2 [0%]*	*42.1 [0.1%]*	*185.3 [0.2%]*
Incremental Cost per additional QALY	1,366,163	201,809	44,455	6,399	Dominates
Incremental Cost per LYG	4,145,384	266,813	43,755	4,648	Dominates

When varying the baseline risk, the highest net benefit of varenicline at a lower (healthier population) and higher level of the baseline risk (sicker population) demonstrates that varenicline is still the most cost effective strategy for a threshold of £30000 per QALY (Table 64).

Table 64: Results of varying baseline risk in the main analysis

	Point estimate 9.4%	lower bound CI 7%	upper bound CI 1.5%
Varenicline	£ 1,230,031,911,846	£ 1,227,785,903,923	£ 1,231,997,168,778
Bupropion	£ 1,227,562,071,509	£ 1,226,014,821,607	£ 1,228,915,915,174
NRT	£ 1,227,212,831,335	£ 1,225,725,474,978	£ 1,228,514,268,148
Placebo	£ 1,225,436,042,927	£ 1,224,497,710,728	£ 1,226,257,083,600

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Varying the utility value for an asthma exacerbation from 0.52 to 0.72 was undertaken to ensure the particularly high disutility value from the literature did not markedly modify the results in favour of varenicline. The cost-effectiveness results for varenicline versus NRT (Table 67) demonstrate that varenicline dominates at 20 years and at Lifetime for both cost per QALY and cost per LYG. At 10 years varenicline versus NRT has an ICER of £3,417 per additional QALY and of £3,356 per LYG. These results demonstrate that changing the utility value for an asthma exacerbation from 0.52 to 0.72 would not materially alter the results.

Table 67: Results of varying the utility value for an asthma exacerbation from 0.52 to 0.72

Model year	2	5	10	20	Lifetime
Varenicline Treatment Related Costs (Millions)	1,995	4,404	8,615	17,750	34,019
NRT Treatment Related Costs (Millions)	1,850	4,290	8,584	17,928	34,514
difference (Millions)	*144.7 [7.8%]*	*114 [2.7%]*	*31 [0.4%]*	*-177.9 [-1%]*	*-495.5 [-1.4%]*
Varenicline QALYs (Thousands)	5,060	11,678	20,414	31,786	42,140
NRT QALYs (Thousands)	5,059	11,676	20,405	31,756	42,063
difference (Thousands)	*0.4 [0%]*	*2.4 [0%]*	*9.1 [0%]*	*30.6 [0.1%]*	*77.6 [0.2%]*
Varenicline Life Years (Thousands)	6,204	15,041	28,346	50,530	86,711
NRT Life Years (Thousands)	6,204	15,039	28,337	50,488	86,526
difference (Thousands)	*0.1 [0%]*	*1.8 [0%]*	*9.2 [0%]*	*42.1 [0.1%]*	*185.3 [0.2%]*
Incremental Cost per additional QALY	386,633	47,433	3,417	Dominates	Dominates
Incremental Cost per LYG	1,157,584	62,404	3,356	Dominates	Dominates

Probabilistic Sensitivity analysis results

Figure 18. CEAC of all smoking cessation interventions

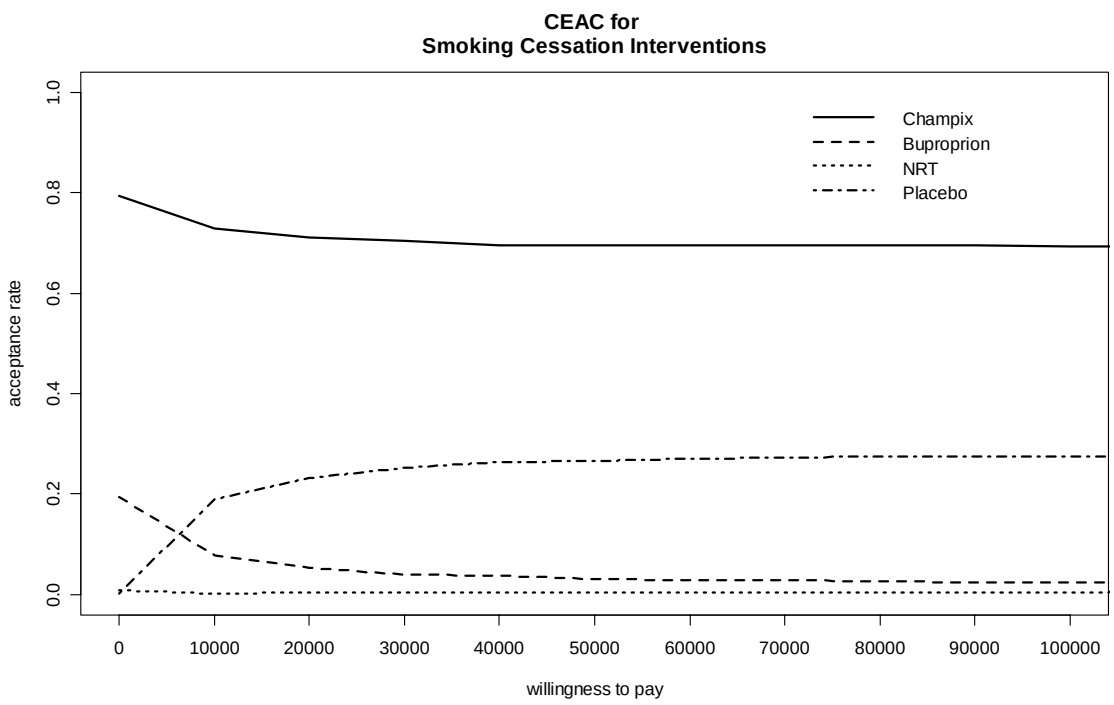
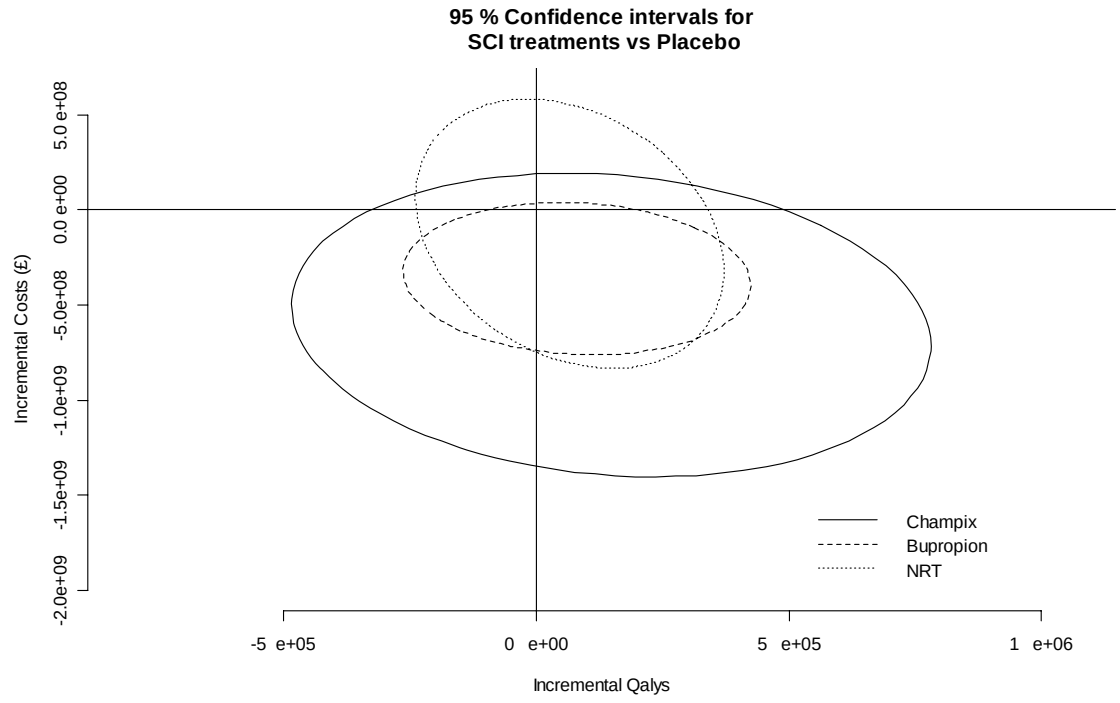


Table 68: Table to accompany Figure 19.

	Costs	QALYs	Incremental results
Varenicline	33,805,751,323	42,044,529	Dominant
Bupropion	34,050,122,263	41,976,554	Dominated
NRT	34,285,787,326	41,962,137	Dominated
Placebo	34,410,698,691	41,896,542	Dominated

Figure 19: Cost-Effectiveness Plane



This is a plot of all the individual 'runs', with increase in effect calculated on the X-axis and increase in cost on the Y-axis.

Pair wise analyses

The pair wise analyses all demonstrate that at a willingness to pay threshold of £30,000 it is 70% probable that varenicline is cost-effective

Figure 20: CEAC for Varenicline versus NRT

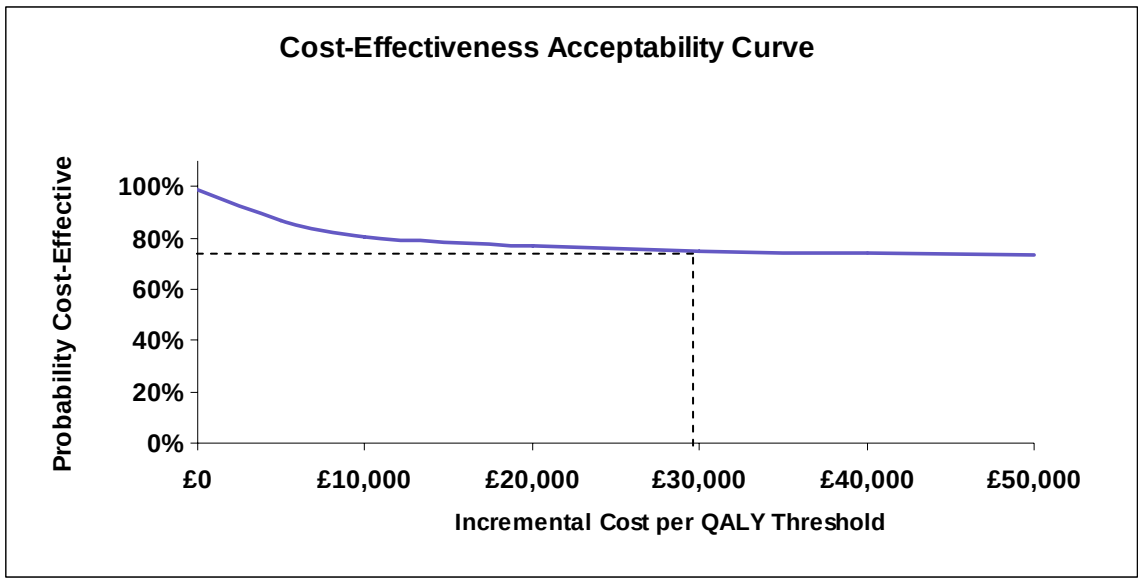


Figure 21: CEAC for Varenicline versus Bupropion

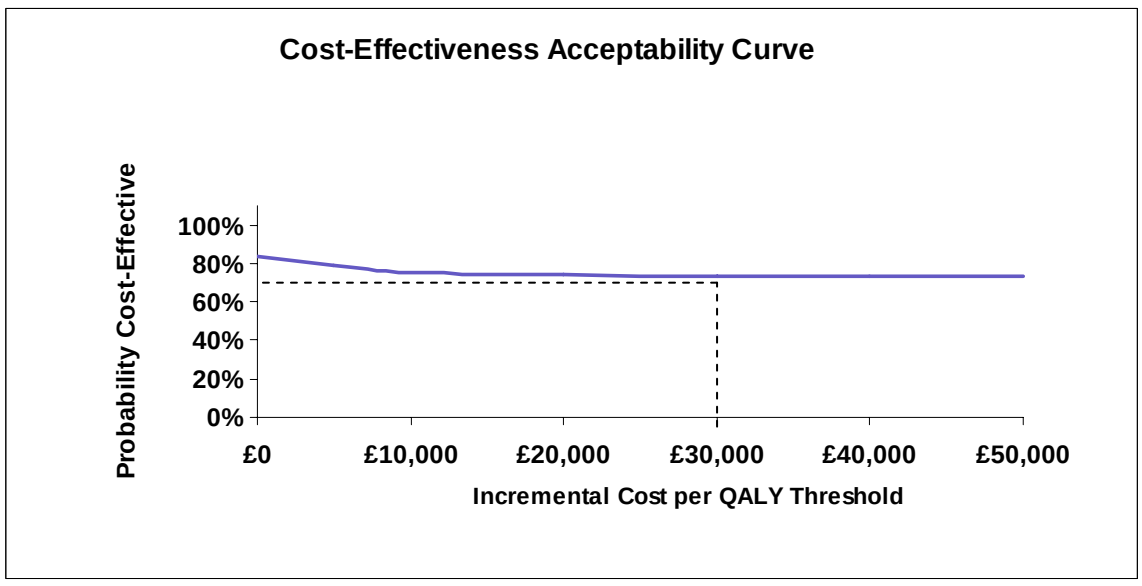
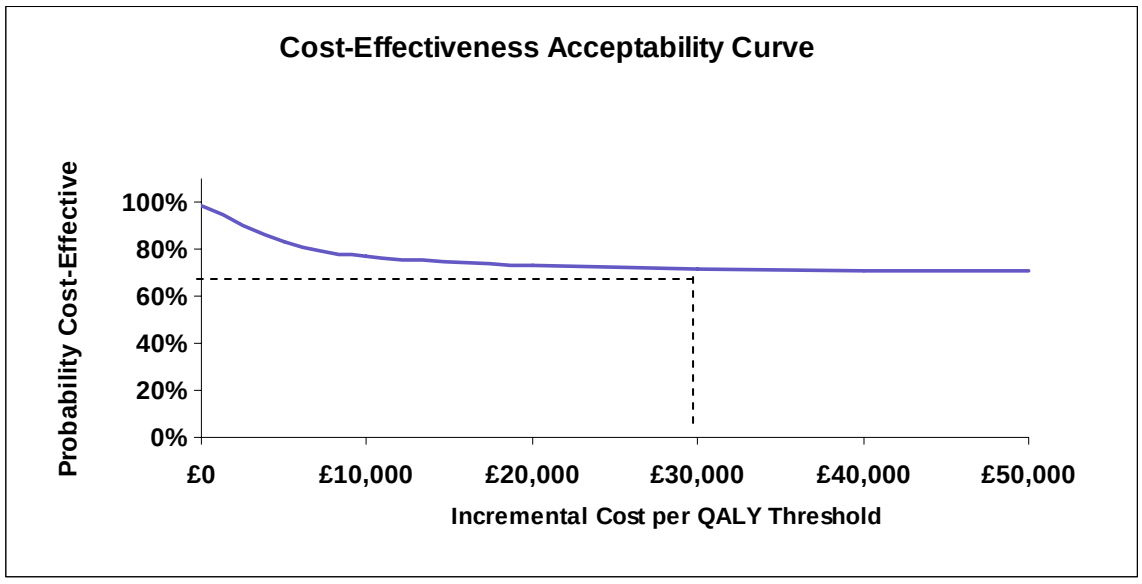
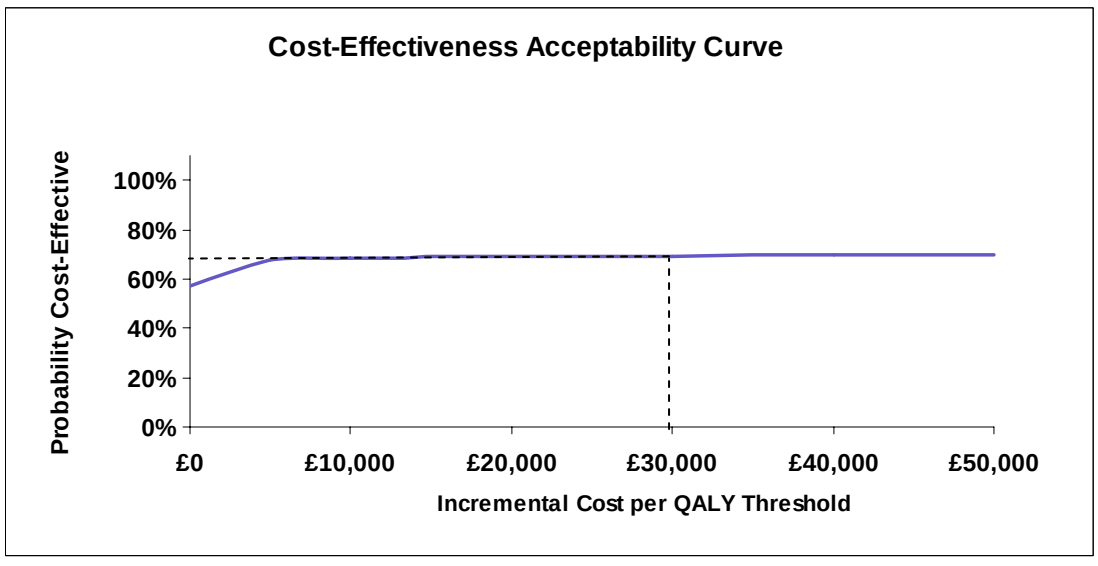


Figure 22: CEAC for Varenicline versus Placebo



For all these pair wise comparisons, at a willingness to pay threshold of £30,000, there is a greater than 70% probability that varenicline is cost-effective.

Figure 23: CEAC for Varenicline versus Placebo in patients abstinent at end of a 12-week course of Varenicline (Group 2)



For this pair wise comparison, at a willingness to pay threshold of £30,000, there is a greater than 70% probability that varenicline is cost-effective in patients abstinent at end of an initial course of varenicline.

6.3.4 Interpretation of economic evidence

6.3.4.1 Are the results from this economic evaluation consistent with the published economic literature? If not, why do the results from this evaluation differ, and why should the results in the submission be given more credence than those in the published literature?

Not applicable

6.3.4.2 Is the economic evaluation relevant to all groups of patients who could potentially use the technology?

Patients with significant smoking related co-morbidities were excluded from the pivotal clinical trials and no specific trials have occurred in patients with significant smoking related co-morbidities. It is therefore unknown if the benefits of smoking cessation, with *any* prescription therapy, will apply at the levels described in this submission.

6.3.4.3 What are the main strengths and weaknesses of the evaluation? How might these affect the interpretation of the results?

Strengths:

- The model used is based on a widely used and accepted model.
- The model is Excel based and totally transparent.
- The majority of the inputs and assumptions used in the modelling are from published sources and widely accepted.
- Assumptions are conservative.
- All assumptions in the model apply equally to all interventions after the initial, chemically confirmed, 9 to 52 week continuous abstinence rates are used.

Weaknesses:

- The effects of interventions varying in duration between 9 and 12 weeks on smoking cessation measured at one year, are the basis for a life-time model of the effects of smoking cessation on the chances of incurring smoking disease related diseases or death.
- In the absence of head to head data from randomised double-blind controlled trials, an adjusted indirect comparison from published data has been used to evaluate the effectiveness of NRT in relation to varenicline.

The evaluation is a robust comparison of the effect of short-term interventions on a behaviour that carries consequences over a lifetime. The strengths of the evaluation are clear and the weaknesses have been addressed as far as feasible whilst maintaining a conservative approach in all cases where evidence is weak or absent.

6.3.4.4 What further analyses could be undertaken to enhance the robustness/completeness of the results?

The sensitivity analyses comprising part of the evaluation are comprehensive. As is always the case, conducting further clinical trials (particularly in subgroups) and collecting/evaluating real world data would provide information that could be used in future economic evaluations that may result in changes in the magnitude of the effects seen in the current evaluation.

7 Assessment of factors relevant to the NHS and other parties

The purpose of this section is to provide an analysis of any factors relevant to the NHS and other parties that may fall outside the remit of the assessments of clinical effectiveness and cost effectiveness. This will facilitate the subsequent evaluation of the budget impact analysis. Such factors might include issues relating to service organisation and provision, resource allocation and equity, societal or ethical issues, plus any impact on patients or carers. Further examples are given in section 3.4 of the NICE document 'Guide to the methods of technology appraisal'.

7.1 What is the estimated annual budget impact for the NHS in England and Wales?

The estimated budget impact for England and Wales is projected to be £2,102,840 in 2007 rising to £5,051,520 in 2011.

This is the budget impact of the addition of varenicline to the range of smoking cessation therapies available on prescription in England and Wales. The significant cost savings associated with the reduction in smoking related diseases (section 6 – please note that the cost savings are projected for an adult UK population - the Budget Impact on prescribing costs here is estimated for an adult England and Wales population) dwarf the increased expenditure on smoking cessation therapies projected from the introduction of varenicline.

The introduction of varenicline is not expected to have an impact on the provision of smoking cessation services in England and Wales. Service configuration does not include pharmaceutical smoking cessation interventions as a primary approach and therefore the availability of an additional therapy is not predicted to result in an increased demand for services.

It should be noted that Pfizer has developed a structured behavioural support programme to provide smokers attempting to quit with varenicline, support in dealing with the psychological aspects of addiction and quitting. The programme is also designed to increase compliance. This programme is designed to run alongside existing services and is offered, at no additional to patient or the NHS, to patients prescribed varenicline to assist successful smoking cessation.

7.2 What number of patients was assumed to be eligible? How was this figure derived?

The adult (>18years) population for England and Wales has been calculated at 42,152,045. Table 69 shows the population broken down by age and gender.

Table 69: Adult population by gender and age (%)

Male 18-24	Male 25-44	Male 45-64	Male 65+	Female 18-24	Female 25-44	Female 45-64	Female 65+
6	18	15	9	6	18	16	12

Of these current and former smokers have been calculated (Table 70).

Table 70: Current and former smokers by age and gender (%)

	Male 18-24	Male 25-44	Male 45-64	Male 65+	Female 18-24	Female 25-44	Female 45-64	Female 65+
Current smoker	25	31	22	9	29	27	23	11
Former smoker	5	18	37	58	7	17	27	32

The percentage of smokers attempting to quit is projected from the Smoking Related Behaviour and Attitude survey (ONS 2004) and shown in Table 71.

Table 71: Percentage of current smokers attempting to quit (%)

	18-24 years	25-44 years	45-64 years	65+ years
2007	22	35	25	13
2008	23	37	26	14
2009	23	38	27	14
2010	24	39	28	15
2011	25	41	29	16
Annual increase	0.8	1.3	0.9	0.5

For each year, 25% of those attempting to quit are assumed to opt for treatment involving prescription pharmaceutical therapy. This assumption is applied to reflect current UK practice.

To reflect reality, successful quitters relapse at known rates derived from clinical trial data (see section 5) and a proportion of former smokers are also assumed to relapse and become eligible for therapy (Wetter et al. 2004).

7.3 What assumption(s) were made about current treatment options and uptake of technologies?

Current treatment options (NRT, bupropion + varenicline) are assumed to remain the same over the budget impact period and it is assumed that NRT will remain available on prescription as currently.

7.4 What assumption(s) were made about market share (where relevant)?

Market shares are based on market research (Pfizer data on file. 2006) and shown in table 72 below.

Table 72 Market share trends (%)

	Varenicline	Bupropion	Prescription NRT
2007	11	4	85
2008	16	4	80
2009	21	3	76
2010	26	3	71
2011	31	2	67

7.5 What unit costs were assumed? How were these calculated?

Unit costs are based on the cost of a course of treatment:

- Varenicline 12 weeks £165.66
- NRT (Cost is based on a basket of all NRT products prescribed in the UK at 2006 prescribing rates £117.68
- Bupropion 9 weeks £81.56

A prescription cost charge of £.0.93 is added for each prescription.

A percentage of patients prescribed each therapy are assumed to only receive an initial prescription because of failure to have quit smoking at the first follow-up visit after commencing therapy and this is costed as follows:

- Varenicline £28.23
- NRT £39.54
- Bupropion £39.54

The proportion was based on a calculation involving 6 month and 12 month efficacy values for each technology.

7.6 In addition to drug costs, consider other significant costs associated with treatment. What is the recommended treatment regime – for example, what is the typical number of visits, and does treatment involve daycase or outpatient attendance? Is there a difference between recommended and observed doses? Are there likely to be any adverse events or a need for other treatments in combination with the technology?

It is assumed that any additional costs associated with smoking cessation programs are equal irrespective of the technology used and have therefore not been included in this analysis.

The introduction of varenicline is not expected to have an impact on the provision of smoking cessation services in England and Wales. Service configuration does not include pharmaceutical smoking cessation interventions as a primary approach and therefore the availability of an additional therapy is not predicted to result in an increased demand for services.

It should be noted that Pfizer has developed a structured behavioural support programme to provide smokers attempting to quit with varenicline, support in dealing with the psychological aspects of addiction and quitting. The programme is also designed to increase compliance. This programme is designed to run alongside existing services and is offered, at no cost to patient or the NHS, to all patients prescribed varenicline to assist successful smoking cessation.

7.7 Were there any estimates of resource savings? If so, what were they?

This is the budget impact of the addition of varenicline to the range of smoking cessation therapies available on prescription in England and Wales.

The significant cost savings associated with the reduction in smoking related diseases (section 6 - please note that the cost savings are projected for an adult UK population - the Budget Impact on prescribing costs here is estimated for an adult England and Wales population) dwarf the increased expenditure on smoking cessation therapies projected from the introduction of varenicline.

The PSS cost savings associated with the decrease of smoking related diseases have also not been quantified but can also be expected to be significant.

A decrease in smoking will not necessarily be associated with a decrease in smoking cessation services. It is, in fact, possible that the effort expended will increase disproportionately as numbers decrease.

7.8 Are there any other opportunities for resource savings or redirection of resources that it has not been possible to quantify?

See above (Section 7.7).

8 References

Please use the Vancouver style (that is, consecutive numbering throughout the main text). In the reference list, the names of up to six authors should be given, followed by et al.; for example:

> *1. Chalmers TC, Smith H, Blackburn B, Silverman B, Schroeder B, Reitmen D et al. (1981) Method for assessing the quality of randomized controlled trials. Controlled Clinical Trials 2: 31–9.*

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9 Appendices

9.1 Appendix 1

Relative Risks of mortality/morbidity – split by age, gender, and smoking status (current smokers versus current smoker

COPD	**RR in smokers**	**RR in former smokers**	**RR in never smokers**	**Source**
Males age 18-34 yrs	1.0	1.0	1.0	Thun (2000)
Males age 35-64 yrs	10.8	7.8	1.0	
Males age 65+ yrs	10.8	7.8	1.0	
Females age 18-34 yrs	1.0	1.0	1.0	
Females age 35-64 yrs	12.3	8.9	1.0	
Females age 65+ yrs	12.3	8.9	1.0	
Lung cancer				
Males age 18-34 yrs	1.0	1.0	1.0	Thun (2000)
Males age 35-64 yrs	21.3	8.3	1.0	
Males age 65+ yrs	21.3	8.3	1.0	
Females age 18-34 yrs	1.0	1.0	1.0	
Females age 35-64 yrs	12.5	4.8	1.0	
Females age 65+ yrs	12.5	4.8	1.0	
CHD				
Males age 18-34 yrs	1.0	1.0	1.0	Thun (2000)
Males age 35-64 yrs	2.6	1.6	1.0	
Males age 65+ yrs	1.5	1.2	1.0	
Females age 18-34 yrs	1.0	1.0	1.0	
Females age 35-64 yrs	3.2	1.4	1.0	
Females age 65+ yrs	1.7	1.4	1.0	
Stroke				
Males age 18-34 yrs	1.0	1.0	1.0	Thun (2000)
Males age 35-64 yrs	2.4	1.0	1.0	
Males age 65+ yrs	1.5	1.0	1.0	
Females age 18-34 yrs	1.0	1.0	1.0	
Females age 35-64 yrs	3.8	1.5	1.0	
Females age 65+ yrs	1.6	1.2	1.0	
Asthma				
Males age 18-34 yrs	1.43	1.0	1.0	Cassino (1999)
Males age 35-64 yrs	1.01	1.0	1.0	
Males age 65+ yrs	1.11	1.0	1.0	
Females age 18-34 yrs	1.43	1.0	1.0	
Females age 35-64 yrs	1.02	1.0	1.0	
Females age 65+ yrs	1.11	1.0	1.0	

Let the number of incident cases of disease Z in the whole population be denoted IZ. This data is available from national datasets.
The proportion of incident cases that arise in never smokers is equal to
PNS = [(NNS x RRNS) / (NS x RRS + NFS x RRFS + NNS x RRNS)].
where
RRS = RR of disease Z in current smokers
RRFS= RR of disease Z in former smokers
RRNS = RR of disease Z in never smokers
NS = number of current smokers
NFS = number of former smokers
NNS = number of never smokers
The formula used calculates the proportion adjusting for the different relative risks that may exist in each population stratum.
The proportion of incident cases that arise in smokers is equal to
PS = [(NS x RRS) / (NS x RRS + NFS x RRFS + NNS x RRNS)].
The proportion of incident cases that arise in former smokers is equal to
PFS = [(NFS x RRFS) / (NS x RRS + NFS x RRFS + NNS x RRNS)].
Note that PNS+PS+PFS = 1 by definition and, generally, but depending on the precise definition used and the context, RRNS=1. These proportions are unrelated to the fractions of incidence that may be attributable to smoking or formerly smoking – the model does not attempt to calculate attributable fractions.
The number of incident cases that arise in never smokers is equal to
N Z NS = IZ x PNS
The number of incident cases that arise in smokers is equal to
N Z S = IZ x PS

9.2 Appendix 2: Search strategy for section 5

The following information should be provided.

9.2.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- *Medline*
- *Embase*
- *Medline (R) in-process*
- *The Cochrane Library*

In consultation with a medical librarian a search strategy of published literature was established. Searches were conducted independently, in duplicate, using the following ten databases (from inception to December 1, 2006): MEDLINE, EMBASE, Cochrane, AMED, CINAHL, TOXNET, Development and Reproductive Toxicology, Hazardous Substances Databank, Psych-info and Web of Science. Databases that included the full text of journals (*OVID, ScienceDirect,* and *Ingenta)*, including articles in full text from approximately 1700 journals, since 1993, were searched. In addition, the bibliographies of published systematic reviews (Silagy et al. 2000, 2001, 2002, 2004; Hughes et al 2002, 2004; Lancaster et al 2000; Silagy 2000), and health technology assessments were searched (Nice, 2002). Searches were not limited by language, sex or age.

9.2.2 The date on which the search was conducted.

1st December 2006

9.2.3 The date span of the search.

Database inception to 1st December 2006

9.2.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The above databases were searched using the following freetext and MeSH terms
Varenicline
Nicotine receptor partial agonist
'Nicotinic-Agonists'
'Receptors, Nicotinic'

9.2.5 Details of any additional searches, for example searches of company databases (include a description of each database).

Documentum - the company database (Holds records of all trials conducted by Pfizer) was searched.

9.2.6 The inclusion and exclusion criteria.

Searches were not limited by language, sex or age.

9.2.7 The data abstraction strategy.

All abstracts were reviewed for evidence relating to varenicline unknown to the developers of the submission.

The decision to utilise the systematic review (Wu et al. 2006) for efficacy values for NRT and to confirm the efficacy values for Placebo and Bupropion meant that no search or retrieval of comparator data was undertaken.

9.3 Appendix 3: Search strategy for section 6

The following information should be provided.

9.3.1 The specific databases searched and the service provider used (for example, Dialog, DataStar, OVID, Silver Platter), including at least:

- *Medline (Dialog Datastar)*
- *Embase (Dialog Datastar)*
- *Medline (R) in-process (Dialog Datastar)*
- *Health Economic Evaluation Database*
- *NHS Economic Evaluation Database (NHS EED).*

- Medline (Dialog Datastar)
- Embase (Dialog Datastar)
- Medline (R) in-process (Dialog Datastar)
- NHS Economic Evaluation Database (NHS EED).

9.3.2 The date on which the search was conducted.

18th November 2006

9.3.3 The date span of the search.

Database inception to 18th November 2006

9.3.4 The complete search strategies used, including all the search terms: textwords (free text), subject index headings (for example, MeSH) and the relationship between the search terms (for example, Boolean).

The above databases were searched using the following free text and MeSH terms
Varenicline
Nicotine receptor partial agonist
'Nicotinic-Agonists'
'Receptors, Nicotinic'

NHS EED was additionally searched using the term ‘smoking’ and all abstracts retrieved and reviewed.

9.3.5 Details of any additional searches, for example searches of company databases (include a description of each database).

Documentum - the company database (Holds records of all trials conducted by Pfizer) was searched.

9.3 Appendix 4: BENESCO economic model

Versions for Group 1 and Group 2 provided separately

9.3 Appendix 5: BENESCO model technical manual

Provided separately