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Relapse prevention in UK Stop Smoking Services: current practice, systematic reviews of effectiveness and cost-effectiveness analysis

T Coleman,[1]* S Agboola,[2] J Leonardi-Bee,[2] M Taylor,[3] A McEwen[4] and A McNeill[2]

[1]University of Nottingham, Division of Primary Care, Nottingham, UK
[2]University of Nottingham, Division of Epidemiology & Public Health, Nottingham, UK
[3]University of York, Health Economics Consortium, York, UK
[4]University College London, Department of Epidemiology & Public Health, London, UK

*Corresponding author

Declared competing interests of authors: Within the last 5 years Tim Coleman has undertaken consultancy work for Pierre Fabre Laboratories, France and also Johnson & Johnson. Both companies produce nicotine replacement therapy. Matthew Taylor has recently received funding from a company called Synergenz, which produces a diagnostic test for assessing patients' genetic risks of developing lung cancer. He evaluated the test's potential cost-effectiveness, based on its impact on stopping people smoking. Andy McEwan receives a personal income from Cancer Research UK via the University College London. He has received travel funding, honoraria and consultancy payments from manufacturers of smoking cessation products (Pfizer Ltd, Novartis UK and GSK Consumer Healthcare Ltd). He also receives payments for providing training to smoking cessation specialists and receives royalties from books on smoking cessation.

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Abstract

Relapse prevention in UK Stop Smoking Services: current practice, systematic reviews of effectiveness and cost-effectiveness analysis

T Coleman,[1]* S Agboola,[2] J Leonardi-Bee,[2] M Taylor,[3] A McEwen[4] and A McNeill[2]

[1]University of Nottingham, Division of Primary Care, Nottingham, UK
[2]University of Nottingham, Division of Epidemiology & Public Health, Nottingham, UK
[3]University of York, Health Economics Consortium, York, UK
[4]University College London, Department of Epidemiology & Public Health, London, UK

*Corresponding author

Background: Reducing smoking is a chief priority for governments and health systems like the UK National Health Service (NHS). The UK has implemented a comprehensive tobacco control strategy involving a combination of population tobacco control interventions combined with treatment for dependent smokers through a national network of NHS Stop Smoking Services (NHS SSS).

Objectives: To assess the effectiveness and cost-effectiveness of relapse prevention in NHS SSS. To (1) update current estimates of effectiveness on interventions for preventing relapse to smoking; (2) examine studies that provide findings that are generalisable to NHS SSS, and which test interventions that might be acceptable to introduce within the NHS; and (3) determine the cost-effectiveness of those relapse preventions interventions (RPIs) that could potentially be delivered by the NHS SSS.

Data sources: A systematic review of the literature and economic evaluation were carried out. In addition to searching the Cochrane Tobacco Addiction Group register of trials (2004 to July 2008), MEDLINE, the Cochrane Central Register of Controlled Trials, EMBASE, PsycINFO, the Science Citation Index and Social Science Citation Index were also searched.

Review methods: The project was divided into four distinct phases with different methodologies: qualitative research with a convenience sample of NHS SSS managers; a systematic review investigation the efficacy of RPIs; a cost-effectiveness analysis; and a further systematic review to derive the relapse curves for smokers receiving evidence-based treatment of the type delivered by the NHS SSS.

Results: Qualitative research with 16 NHS SSS managers indicated that there was no shared understanding of what relapse prevention meant or of the kinds of interventions that should be used for this. The systematic review included 36 studies that randomised and delivered interventions to abstainers. 'Self-help' behavioural interventions delivered to abstainers who had achieved abstinence unaided were effective for preventing relapse to smoking at long-term follow-up [odds ratio (OR) 1.52, 95% confidence interval (CI) 1.15 to 2.01]. The following pharmacotherapies were also effective as RPIs after their successful use as cessation treatments: bupropion at long-term follow-up (pooled OR 1.49, 95% CI 1.10 to 2.01); nicotine replacement therapy (NRT) at medium- (pooled OR 1.56, 95% CI 1.16 to 2.11) and long-term follow-ups (pooled OR 1.33, 95% CI 1.08 to 1.63) and one trial of varenicline also indicated effectiveness. The health economic analysis found that RPIs are highly cost-effective. Compared with 'no intervention'; using bupropion resulted in an incremental quality-adjusted life-year (QALY) increase of 0.07, with a concurrent NHS cost saving of £68; for NRT, spending £12 resulted in a 0.04 incremental QALY increase; varenicline resulted in a similar QALY increase as NRT, but at almost seven times the cost. Extensive sensitivity analyses demonstrated that cost-effectiveness ratios were more sensitive to variations in effectiveness than cost and that for bupropion and NRT, cost-effectiveness generally remained. Varenicline also demonstrated cost-effectiveness at a 'willingness-to-pay' threshold of £20,000 per QALY, but exceeded this when inputted values for potential

effectiveness were at the lower end of the range explored. For all drugs, there was substantial relapse to smoking after treatment courses had finished. Quit attempts involving NRT appeared to have the highest early relapse rates, when trial participants would be expected to still be on treatment, but for those involving bupropion and varenicline little relapse was apparent during this time.

Limitations: The qualitative research sample was small.

Conclusions: Based on the totality of evidence, RPIs are expected to be effective and cost-effective if incorporated into routine treatment within the NHS SSS. While staff within the NHS SSS were largely favourably inclined towards providing RPIs, guidance would be needed to encourage the adoption of the most effective RPIs, as would incentives that focused on the importance of sustaining quit attempts beyond the currently monitored 4-week targets.

Contents

List of abbreviations

BNF	*British National Formulary*
CHD	coronary heart disease
CI	confidence interval
COPD	chronic obstructive pulmonary disease
CRD	Centre for Reviews and Dissemenation
DoH	Department of Health
EQ-5D	European Quality of Life-5 Dimensions
ICER	incremental cost-effectiveness ratio
LC	lung cancer
MI	myocardial infarction
NHS SSS	NHS Stop Smoking Service
NICE	National Institute for Health and Clinical Excellence
NNT	number needed to treat
NRT	nicotine replacement therapy
OR	odds ratio
PCT	primary care trust
p.p.m.	parts per million
QALY	quality-adjusted life-year
QoL	quality of life
RCT	randomised controlled trial
RPI	relapse prevention intervention/ treatment
RR	relative risk
SCSC	Smoking Cessation Service Co-ordinator

All abbreviations that have been used in this report are listed here unless the abbreviation is well known (e.g. NHS), or it has been used only once, or it is a non-standard abbreviation used only in figures/tables/appendices, in which case the abbreviation is defined in the figure legend or in the notes at the end of the table.

Executive summary

Background

Smoking remains a major, international cause of death and disease, and killed approximately 80,000 people in England in 2007. Reducing smoking is a major priority for governments and health systems like the UK National Health Service (NHS). The UK has implemented a comprehensive tobacco control strategy over recent years, involving a combination of population tobacco control interventions (such as price rises, advertising ban, smoke-free legislation) combined with treatment for dependent smokers through a national network of NHS Stop Smoking Services (NHS SSS). The NHS SSS provide evidence-based smoking cessation treatment, which is highly cost-effective. In England, over 4 million people have set a quit date through the services since their inception in 2000, with over 4 million of these having stopped smoking 4 weeks after their quit date. However, it is estimated that approximately 75% of these '4-week quitters' will have subsequently relapsed back to smoking ('relapsers') 6 months after their quit date. This project aimed to investigate whether and how the NHS SSS could reduce this proportion of relapsers, by providing relapse prevention interventions (RPIs) or treatments in order to improve the effectiveness of services in helping smokers to stop.

Objectives

1. To survey NHS SSS managers across the UK in order to:
   i. Describe and categorise RPIs that are currently used in the NHS SSS.
   ii. Describe the current treatment provided by NHS SSS for smokers who are trying to stop.
   iii. Ascertain barriers to the trialling or introduction of RPIs within current clinical practice.
2. To update estimates of effectiveness in the Cochrane review on interventions for preventing relapse to smoking, altering analysis methods, as appropriate, to enhance interpretation of findings.
3. To assess which studies, included in (2) above, provide findings that are generalisable to NHS SSS and which test interventions that might be acceptable to introduce within the UK.
4. To determine the cost-effectiveness of those RPIs, identified in (3) above, which could potentially be delivered by the NHS SSS.
5. To derive 'relapse to smoking' curves for smoking cessation attempts made with the support of evidence-based cessation treatments, such as those delivered by NHS SSS, using (1) prolonged and (2) point abstinence from smoking as outcome measures.
6. To identify deficiencies in the evidence base concerning the use of RPIs for smoking cessation and to identify priorities for future research.

Methods

The project was divided into four distinct phases with very different methodologies:

1. Qualitative research in a convenience sample of health professionals working in the NHS SSS, followed by an online survey of managers of the NHS SSS across the UK to assess current delivery of RPIs by cessation services and the feasibility of introducing such interventions if found to be effective. For the survey, the definition used for RPIs, based on our qualitative work and previous literature, was: 'behavioural or drug therapies delivered after acute smoking cessation treatment has ended and resulted in abstinence from smoking. RPIs, therefore, seek to reduce relapse to smoking among abstinent smokers'.
2. A systematic review to update and refine the previous Cochrane review of RPIs, using an identical search strategy to identify randomised trials of behavioural and pharmacological studies of smoking RPIs, published up to July 2008 in databases such as the Cochrane Tobacco Addiction Group register of trials, MEDLINE, EMBASE, etc. In contrast to the Cochrane review and to obtain estimates for treatment effects which

might reflect those obtained by use of RPIs in NHS SSS, our primary analyses examined the effectiveness of RPIs among recently-abstinent smokers (abstainers), pooling outcome data from similar follow-up time points (defined as short term (permitted range 1–3 months), medium term (range 6–9 months) and long term (range 12–18 months), with the long-term follow-up point considered as the primary end point time, and separating the studies by type of intervention and population group. We also analysed, using a similar methodology, the effectiveness of RPIs used alongside traditional smoking cessation treatments by assessing trials which randomised non-abstinent smokers and which delivered RPIs and cessation therapies simultaneously.

3. A health economic analysis to provide estimates for interventions' cost-effectiveness compared to 'no intervention' using a cohort simulation approach to model the costs of smoking and the quality-adjusted life-years (QALYs) gained by using RPIs. Model estimates for effectiveness of interventions were taken from the systematic review (in 2 above) and sensitivity analyses investigated the impacts of substantially varying background population quit rates, costs and effectiveness of interventions and the longevity of intervention effects.
4. A systematic review to describe rates of relapse to smoking amongst smokers stopping with the support of evidence-based treatment and from which relapse curves relevant to NHS SSS users could be drawn. We examined routinely-available NHS SSS data to assess their comprehensiveness for describing relapse patterns of smokers attending the NHS SSS. We searched for randomised controlled trials (RCTs) in which intervention group smokers received evidence-based interventions similar to those provided by the NHS SSS including trials of nicotine replacement therapy (NRT), bupropion and varenicline delivered with behavioural support. We then selected trials of adult smokers in which a clearly identified quit date was used and smoking status was recorded at least three times in the next month and at least 12 months after this. The smoking status data from the intervention groups were synthesised enabling relapse curves to be drawn.

Results

1. Qualitative research with 16 health professionals working in NHS SSS indicated that there was no shared understanding of what relapse prevention meant or the kinds of interventions that should be used for this, but a willingness to provide such treatments was apparent. In the online survey, 96 NHS SSS managers from across the UK returned completed survey questionnaires (52% response rate). Of these, 58.3% ($n = 56$) reported running services that provided RPIs for clients (RPI definition provided within survey). The most commonly provided RPIs were behavioural support: telephone (77%), group (73%) and individual (54%). Pharmacotherapy was less frequently used for relapse prevention, just under half (48%, $n = 27$) offered NRT and 21.4% ($n = 12$) bupropion. Over 80% of those reporting providing RPIs do so for over 6 months after smokers become abstinent. Nearly two-thirds of all respondents thought it was likely that they would either continue to provide or commence provision of RPIs in their services. Of the remaining respondents, it was believed that the government's focus on 4-week quit rates (66.7%, $n = 22$), and the inadequate funding for the provision of RPIs [42.9% (14 services)] were major barriers to introducing such interventions into routine care.
2. The systematic review included 36 studies which randomised and delivered interventions to abstainers. 'Self-help' behavioural interventions delivered to abstainers who had achieved abstinence unaided were effective for preventing relapse to smoking at long-term follow-up [odds ratio (OR) 1.52, 95% confidence interval (CI) 1.15 to 2.01]. The following pharmacotherapies were also effective as RPIs after their successful use as cessation treatments: bupropion at long-term follow-up (pooled OR 1.49, 95% CI 1.10 to 2.01); NRT at medium- (pooled OR 1.56, 95% CI 1.16 to 2.11) and long-term follow-ups (pooled OR 1.33, 95% CI 1.08 to 1.63) and one trial of varenicline also indicated effectiveness. Eighteen studies randomised smokers prior to quit attempts; although a few trials reported significant findings at some follow-ups, where pooled analyses were possible, there

was no evidence for the effectiveness of any interventions.

3. The health economic analysis found that, as with other interventions which reduce smoking, RPIs are highly cost-effective. Compared with 'no intervention'; using bupropion resulted in an incremental QALY increase of 0.07, with a concurrent NHS cost saving of £68; for NRT, spending £12 resulted in a 0.04 incremental QALY increase; varenicline resulted in a similar QALY increase as NRT but at almost seven times the cost; however, findings were derived from a single trial and require cautious interpretation. Extensive sensitivity analyses demonstrated that cost-effectiveness ratios were more sensitive to variations in effectiveness than cost and that for bupropion and NRT, cost-effectiveness generally remained, even when input parameters are varied greatly, suggesting that this will be apparent in routine clinical practice. Varenicline also generally demonstrated cost-effectiveness at a 'willingness-to-pay' threshold of £20,000 per QALY, but exceeded this when inputted values for potential effectiveness were at the lower end of the range explored. With available data, only indirect comparisons between RPIs are possible and, therefore, assessments of their relative cost-effectiveness should only be made with caution.
4. There were no data available from smokers attending NHS SSS which could be used to draw relapse curves to reflect their experiences of relapse to smoking; curves derived were, therefore, based entirely on data from cessation trials in which smokers received interventions similar to those delivered by NHS SSS. Systematic searching and consideration of retrieved articles identified 16 RCTs meeting all review inclusion criteria, investigating NRT, bupropion and varenicline combined with intensive behavioural support. For all drugs, there was substantial relapse to smoking after treatment courses had finished (i.e. between 3 and 12 months into quit attempts). Eliminating such relapse would improve cessation rates at 12 months by 13%, 14% and 19% for NRT, bupropion and varenicline, respectively (though these figures are derived using some pooled abstinence estimates which have substantial heterogeneity). Quit attempts involving NRT appeared to have the highest early relapse rates, when trial participants would be expected to still be on treatment, but for those involving bupropion and varenicline little relapse was apparent during this time. However, this observation could have arisen because bupropion and varenicline trials assessed smoking cessation by repeatedly assessing short periods of abstinence from smoking, rather than asking about continuous cessation between participants' quit dates and all follow-up points.

Conclusions

Study findings suggest that extending pharmacotherapy treatment (such as NRT, bupropion or varenicline) after smokers have stopped smoking using these drugs, is both effective and cost-effective for preventing relapse to smoking. UK managers of the NHS SSS indicated that they were favourably inclined towards providing RPIs, but currently used ones for which there is no evidence of effectiveness. We identified apparently different trajectories of relapse across the three main treatments used in the NHS SSS (NRT, bupropion and varenicline), but similar declines in abstinence after 3 months when most treatment would have ended, illustrating the potential impact of extending the treatment period for preventing relapse.

Recommendations for research (in priority order)

1. Further research investigating the use of NRT, bupropion and varenicline (the three pharmacotherapies used in the NHS SSS) for relapse prevention is required, including the following:
   i. Placebo RCTs to investigate the (cost) effectiveness of these RPIs as an extension to current NHS SSS cessation support – most review trials were conducted in countries without organised cessation services and, hence relapse prevention interventions may have different outcomes in the UK.
   ii. Studies of the acceptability of extended use of pharmacotherapies for relapse prevention in NHS SSS users, and particularly of bupropion, which is the least frequently used cessation therapy in England, the acceptability of these pharmacotherapies for relapse prevention will influence their uptake.

   iii. Whether or not the addition of behavioural RPIs, delivered in the early stages of quit attempts using NRT can have an adjunctive, positive impact on cessation rates.
   iv. Confirmation of whether the different trajectories of relapse that we observed for NRT, bupropion and varenicline are valid (i.e. a more rapid relapse rate for users of NRT in the first month compared with the other two drug treatments) and occur when these treatments are used in routine NHS SSS clinical practice.
2. The following research into behavioural relapse prevention interventions is required:
   i. RCTs to confirm or refute the finding that self-help interventions, delivered to smokers who have achieved abstinence unsupported, have long-term effectiveness for preventing relapse to smoking.
   ii. RCTs to investigate whether or not self-help interventions delivered to smokers who have achieved abstinence with NHS SSS support are effective.
   iii. Further research on interventions that showed potential effectiveness, such as individual counselling for pregnant women and the use of telephone support after cessation treatment, and test whether or not these might have long-term effectiveness.
3. Methodological standardisation: among relapse prevention trials identified for this report, there was huge variation in the definition of RPIs, the characteristics of smokers these were delivered to, follow-up periodicity and outcome measurement after randomisation. Also among cessation trials used to derive relapse curves, reporting of outcomes seriously restricted the data available. In order to permit coherent synthesis of future research findings in this important field, we recommend that practitioners and researchers investigating this field agree common standards for:
   i. The definition of RPIs: in particular, consensus is needed as to whether behavioural RPIs, delivered alongside smoking cessation interventions to smokers either prior to or soon after quit attempts have started *can* or *should* be categorised as different to smoking cessation interventions. If there is consensus about such interventions being different, clear definitions for both are required.
   ii. Methodological standards for the conduct and reporting of behavioural and pharmacological relapse prevention trials.
   iii. Cessation trials should report the percentage of participants who make no attempt to stop smoking on target quit dates and should report continuous and point prevalence smoking cessation measures simultaneously at all follow-ups.

Implications for health care

Some NHS SSS are providing RPIs, but where this occurs, those with the weakest evidence base are generally used, illustrating a requirement for the emerging evidence base and guidance to be made available as soon as possible. Should the NHS decide to encourage and fund the use of RPIs for smokers who have become abstinent with NHS SSS support, new incentives are likely to be required before NHS SSS will substantially adopt their use. Currently, NHS SSS are performance-managed on their ability to achieve targets set for short-term (i.e. 4-week) periods of cessation; managers perceived these targets were a clear disincentive to spending on interventions such as RPIs, which might enhance longer term abstinence but not their clients' initial, monitored cessation rates. Any integration of RPIs into the NHS SSS should include sufficient monitoring such that an assessment of their cost-effectiveness in routine use can be made.

Chapter 1
Introduction

Introduction

Smoking remains a major, international cause of morbidity and mortality, and killed approximately 80,000 people in England in 2007.[1] Reducing smoking is therefore a major priority for governments and health systems like the UK National Health Service (NHS). Following the publication of the Government's White Paper, *Smoking Kills*,[2] in 1998, a comprehensive tobacco control strategy has been implemented, aimed at reducing uptake of smoking and increasing quitting among existing smokers. The strategy has involved a combination of population tobacco control interventions (such as price rises, an advertising ban and smoke-free legislation) combined with treatment for dependent smokers through the NHS. Treatment is provided principally through a national network of NHS Stop Smoking Services (NHS SSS), first implemented in 2000 after piloting in a number of deprived areas.[3] Similar services have been set up in the other UK countries. The NHS SSS provide evidence-based smoking cessation treatment, which is highly cost-effective,[4] and over 4 million people have set a quit date through the services since their inception, with over 2 million stopping smoking at 4 weeks[5] and a substantial proportion remaining permanently abstinent. Nevertheless, it is estimated that approximately 75% of these 4-week quitters subsequently relapse back to smoking ('relapsers') within 6 months of their quit date.[6] This project aimed to investigate whether and how the NHS SSS could reduce this proportion of relapsers.

Background

Smoking as a drug dependence

There is strong evidence of pharmacological, as well as psychological, dependence on cigarettes.[1] Nicotine obtained from cigarettes meets all the standard criteria used to define a drug of addiction or dependence and most smokers continue to smoke because they are addicted to nicotine. Smoking is therefore a difficult behaviour to change, often taking several attempts over a period of years before permanent cessation is successfully achieved and as such, can be seen as a chronically relapsing behaviour. This is similar to other drug taking behaviour that persists in the face of serious negative health consequences.[7] Hence, although the majority of smokers report wanting to stop, each year only around a third make a quit attempt and only 2% succeed.[1]

The process of relapse

Attempts to stop smoking are characterised by a period of initial abstinence followed by an extended period when the abstainer is at a high risk of relapse, but this risk reduces over time.[8] The risk of relapse is greatest in the first few weeks after quitting when withdrawal effects peak, hence relapse to smoking occurs quickly, with many smokers not even managing to stay abstinent for 1 day.[9] Lapses (defined as isolated events or slips followed by a renewal of abstinence) predict subsequent relapse (defined as fully going back to smoking), and those who maintain abstinence for the first 2 weeks are more likely to be abstinent 6 months later.[10] After the first few weeks of abstinence, withdrawal symptoms reduce and confidence in remaining abstinent increases.[9] However, abstainers continue to relapse for months, even years, after the quit attempt, although a recent study of natural relapse patterns in different populations indicated that relapse dropped to around 5% after more than 2 years.[11]

The process of relapse is not yet fully understood, and theoretical models focus on specific mechanisms of drug motivational processes (e.g. Herd),[12] which increasingly recognise relapse to smoking as a dynamic process difficult to predict and prevent, and likely to involve a complex interaction of factors.[13] Individual factors, such as more dependent smoking, craving, self-efficacy, perceived benefits of smoking, and cues, such as the presence of smokers, situations or behaviours associated with previous smoking, as well as negative effects (e.g. stress), have been shown to trigger lapses and relapse.[14–16]

Little is known about how to prevent relapse. Early theorists[12] believed that abstainers should try to recognise the high-risk situations in

which they are likely to relapse and then learn to use cognitive and behavioural strategies to cope with these situations. Over time, the use of effective medications has also been added to these strategies. Shiffman[13] recently summarised current thinking suggesting that treatment needed to 'imbue the person with the ability to respond more effectively to a wide range of situational challenges'. However, very few interventions have been shown to be effective for relapse prevention, an issue we discuss further below.[17]

The need for support with quitting and the NHS SSS

In contrast to the evidence base for relapse prevention treatments, evidence for the use of acute cessation treatments has grown rapidly over recent decades and a variety of effective treatments now exist which can increase the success of stopping smoking up to fourfold[18] compared with no support. In the UK, NHS SSS were set up to offer evidence-based treatment to smokers wanting to stop, in recognition of the fact that many smokers needed such support and although these services are cost-effective, relapse is still the most common outcome for those using them.[6]

The English Department of Health (DoH) publishes guidance for the NHS SSS to ensure they target their efforts at those most in need, in particular routine and manual smokers, and deliver the most effective treatment,[19] referring to guidance on efficacy.[20] The NHS SSS aim to reach as many smokers as possible through health professionals' brief interventions, their onward referral to the NHS SSS of those who need more support and also with smokers' self-referrals.[19] In general, the NHS SSS offer flexible treatment, which usually involves the most effective combination of individual or group behavioural therapy, backed-up by the offer of smoking cessation medications, such as nicotine replacement therapy (NRT), bupropion and, more recently, varenicline.[19]

Historically, the success of NHS SSS has been measured by monitoring the numbers of smokers who access services and set dates for quitting smoking, and, of these, the numbers who are not smoking 4 weeks after their quit dates; challenging primary care trust (PCT) targets have been set for delivery against these measures.[21] Recent guidance indicates an aspiration that, in time, at least 5% of smokers from areas served by NHS SSS should set quit dates with services' help annually but, currently, monitoring of '4-week quitters' is still required. Although services are encouraged to offer, for at least 4 weeks after smokers' quit dates, the most effective cessation treatments (including behavioural support), there is little contemporary information on the treatments actually offered. Also concerns have been expressed that the focus on 4-week quit rates militates against the provision of support beyond this initial period, despite the possibility that treatments like relapse prevention interventions might sustain successful quit attempts in the longer term.[3] In addition, although the services are encouraged to monitor longer-term success at 1 year,[19] their funding is not dependant on this and many services find such monitoring difficult in practice. For these reasons the focus on NHS SSS delivering short-term quitters is likely to deter services from offering relapse prevention treatments.

Given the addictive nature of smoking, this focus on short-term therapy is at odds with the extended duration of therapy and follow-up recognised for other drugs of dependence.[22] Understanding relapse, methods to reduce relapse and the feasibility and effectiveness of introducing these in NHS SSS are therefore important issues to explore.

Rationale for current research

At the time this project was commissioned, a Cochrane review[23] (and summary journal article with searching until August 2004)[24] had found no evidence for the effectiveness of any specific type of relapse prevention intervention (RPI) but also noted that there was only a small evidence base from which this conclusion was drawn. The review included trials delivered to smokers with varied characteristics both before and after their quit attempts had started. However, subgroup analysis of smokers who had completed smoking cessation programmes, which provided data most relevant to the UK context, found some evidence for the effectiveness of NRT and bupropion in relapse prevention. It was possible that the methods used to combine outcome data, interventions and population groups in the Cochrane review, may have obscured real effects and, therefore, there was a need to update this using refined methodology to ensure any effective RPIs, particularly those of relevance to the NHS SSS, were identified.

Clearly, if an updated review demonstrated one or more RPIs to be effective for preventing relapse

to smoking, determining whether or not the use of such therapies could represent good value to the NHS would be important. Although we were aware of no trials conducted in the UK, using a modelling-based approach and incorporating all available efficacy evidence could determine the likely cost-effectiveness of any effective interventions that might be introduced into the UK context. This would provide useful information to inform policy decisions about the need for further research into RPIs; the utility of their introduction of into routine NHS SSS clinical care or even whether or not it would be in the best interests of the NHS not to pursue further use or evaluations of RPIs at this time. For this modelled, health economic evaluation, estimates for the effectiveness of RPIs derived from an updated efficacy review would be appropriate.

Another important issue was the need to clarify the 'natural history' of relapse among smokers attempting cessation with help from effective, evidence-based cessation treatments, such as those delivered by the NHS SSS. Previously, an attempt to derive relapse curves describing the experiences of smokers who try to stop smoking unsupported found that most are smoking again within 8 days and only 3–5% are still abstinent at 6–12 months.[8] However, as supported quit attempts are more successful than unsupported ones, relapse curves for smokers who attempt to stop smoking while using evidence-based support are likely to be very different. Although relapse curves for smokers trying to quit with the use of NRT had been produced, these incorporated insufficient data to predict confidently relapse in the very early stages of smokers' quit attempts when the highest rate of relapse might be expected.[25] Consequently, we undertook a systematic review to derive 'relapse curves' reflecting the experiences of smokers, such as those treated by NHS SSS, who use evidence-based cessation therapies to help them stop smoking. We aimed to determine the proportions of treated smokers still abstinent at set times after starting quit attempts to help inform future decisions about when, in relation to the initiation of quit attempts, future experimental relapse prevention treatments might be tested or, indeed, when effective ones might be introduced into clinical practice.

Finally, we wanted to determine that, should any RPIs be found to be effective or promising for further evaluation, how feasible it could be to either test or introduce these into routine NHS SSS clinical practice. To achieve this aim we undertook qualitative work and a survey of NHS SSS managers to ascertain current practice and any barriers to introducing effective RPIs.

Objectives

1. To survey NHS SSS managers in order to:
   i. Describe and categorise RPIs that are currently used in UK NHS SSS.
   ii. Describe the current treatment provided by UK NHS SSS for smokers who are trying to stop.
   iii. Ascertain barriers to the trialling or introduction of RPIs within current clinical practice.
2. To update estimates of effectiveness in the Cochrane review on interventions for preventing relapse to smoking, altering analysis methods, as appropriate, to enhance interpretation of findings.
3. To assess which studies, included in 1 above, provide findings that are generalisable to NHS SSS and which test interventions that might be acceptable to introduce within the UK.
4. To determine the cost-effectiveness of those RPIs, identified in 3 above, which could potentially be delivered by the NHS SSS.
5. To derive 'relapse to smoking' curves for smoking cessation attempts made with the support of evidence-based cessation treatments, such as those delivered by NHS SSS, using (1) prolonged and (2) point abstinence from smoking as outcome measures.
6. To identify deficiencies in the evidence base concerning the use of RPIs for smoking cessation and to identify priorities for future research.

Research methods

The project was divided into four distinct phases with very different methodologies: qualitative research with a convenience sample of NHS SSS managers to inform the development of a subsequent survey of all UK NHS SSS managers; a systematic review investigating the efficacy of RPIs; a cost-effectiveness analysis; and a further systematic review to derive the relapse curves for smokers receiving evidence-based treatment of the type delivered by the NHS SSS. These four phases of the research are described in detail in the following four chapters and the methods used in each phase of the project are described

at the outset of each. Perhaps because so little is known about the relapse process, researchers testing out interventions aimed at preventing relapse, have tended to develop their own criteria as to what RPIs should encompass. There is no internationally accepted definition for RPIs, the components parts of RPIs, how these are used and who they are targeted at are generally defined by the investigators themselves such that in some studies it can be difficult to tell the difference between smoking cessation and RPIs.

Consequently, for our survey of NHS SSS managers we derived a definition for RPIs which was informed by our qualitative research and so, relevant to their context; for our 'efficacy' systematic review, we used investigators' (i.e. trialists') definitions for RPIs and in our 'relapse curve' review we defined relapse as any return to smoking after a quit date set within trials.

Chapter 2

Provision of relapse prevention interventions in NHS SSS

Background

As stated in Chapter 1, the effectiveness and cost-effectiveness of NHS SSS are well established, with more than half of English services' clients achieving self-reported abstinence from smoking for at least 4 weeks.[6] However, rates of relapse to smoking are high, with around 75% of those abstinent 4 weeks after their quit date restarting smoking by 1 year.[6] The use of effective RPIs could therefore greatly improve long-term cessation rates for the NHS SSS, but little is known about the current provision of RPIs in the services and the feasibility of adding these to existing treatment provision, should effective RPIs be identified.

We therefore carried out two complementary studies to explore these factors. The first was a qualitative study with a convenience sample of 16 health professionals working in the UK NHS SSS that aimed to explore managers' understanding of the term RPIs, their attitudes towards, and experiences of, providing RPIs in clinical practice and factors that they thought could hinder or encourage the efficient provision of RPIs in the services. Building on the findings of this study, we then carried out a UK-wide survey of NHS SSS managers to describe and quantify the current provision of RPIs in services in the UK and ascertain barriers to the trialling, or introduction, of RPIs within clinical practice.

Methods

Qualitative research

Design

Health professionals attending a UK-wide smoking cessation conference in 2007 were asked to indicate their willingness to be interviewed at a later date on relapse prevention provision with NHS SSS and 23 professionals provided contact details. All 23 professionals were e-mailed 7 months after the conference, invited to reconfirm their willingness to take part and agree a convenient time to be interviewed. Non-respondents to the e-mail were contacted via telephone 2 weeks later. We identified issues of potential importance to RPIs from the literature and, using these, a semi-structured interview schedule, with prompts was developed (see Appendix 1). Throughout interviews, open-ended questions were used to encourage participants to give their views and these were conducted by one author (SA) via telephone in January and February 2008. Interviews covered the following subjects: knowledge and understanding of relapse prevention, types and duration of RPI provided, and barriers and challenges encountered. Each interview lasted 20–25 minutes and all were audio-taped and transcribed verbatim.

Analysis

Box 1 summarises the process of data analysis, which involved using the Framework Method.[26] The first stage of analysis involved one author identifying initial themes or concepts which were derived from the data, rather than being imposed by the researchers.[27] The definition of emergent themes and categories were checked against the data, and subsequently refined in an iterative process.[28] Themes and subthemes were given unique codes and a manageable index was constructed. The index was subsequently applied to the raw data, and the references were noted in the margins of the transcripts. The next stage involved constructing charts with rows and columns for each of the main themes and subthemes that emerged. This process of 'charting' allows allocation of the main themes to each column on the chart, and each interview transcript is assigned to a particular row; it ensures that enough data and context are included in the charts such that the analyst is not required to go back to the transcribed data to understand the point being made.[26] After charting all the interviews, interview text relating to the research aims and objectives was collated from the themes and subthemes. Finally, two additional authors read a sample of 10 randomly selected transcripts and confirmed that the transcripts were coded consistently and they contained data that supported the key findings of the study, with any disagreements being resolved by discussion.

BOX 1 *Process of data analysis*

SA reads all transcripts in an iterative process to identify themes and subthemes

SA designs a framework (index) with themes and subthemes and their working definitions

TC and AMcN agree working definitions for the emerging themes and subthemes

SA codes the transcripts for the themes. Data relating to each theme is assembled. TC and AMcN independently read 10 randomly selected transcripts to see if they are being coded consistently

Working definitions for themes and subthemes are refined. The framework (index) is restructured to reflect the changes

SA recodes the transcripts using the refined definitions

TC and AMcN check reliability of the data and interpretation of the findings at each stage of the process

Survey

Using emergent findings from our systematic review (see Chapter 3, Results) and the qualitative research detailed below, issues of potential importance to the provision of RPIs in the NHS SSS were identified and, from these, a structured questionnaire was developed (see Appendix 2) which was made available online at a temporary website address (www.smokingcessationmanagers.org). The questionnaire was designed to obtain information pertaining to current provision of treatment for smoking cessation as well as current and future RPI provision and then the feasibility of providing the most promising RPIs in routine clinical practice. A clear definition of RPIs was provided at the outset of the questionnaire, (building on that discussed in the introductory chapter), namely 'Relapse Prevention Interventions (or Relapse Prevention Treatments) are behavioural or drug therapies delivered after acute smoking cessation treatment has ended and resulted in abstinence from smoking. Relapse Prevention Interventions therefore seek to reduce relapse to smoking among abstinent smokers'. We also distinguished RPIs from interventions delivered to smokers within quit attempts who had recently lapsed and were smoking again and which aimed to prevent brief lapses from becoming full relapses. Our qualitative work suggested that such interventions were frequently deployed (see below) and so respondents were, asked to indicate provision of such treatments.

The Smoking Cessation Service Co-ordinator (SCSC) database of England, Scotland, Wales and Northern Ireland (a database held by organisers of a national conference held annually for health professionals working in the NHS SSS across the UK and for whom membership was updated annually) was used in December 2008 to identify 185 managers of the UK NHS SSS. Managers were e-mailed a flyer advertising the survey with a link to the survey homepage and asked to complete the questionnaire hosted there. Non-respondents were followed up via a reminder e-mail and telephone call inviting them to visit the survey homepage and complete the survey. Responses were anonymous and data were summarised descriptively using SPSS, version 16.0, for Microsoft Windows®. No hypotheses generating statistical analyses were originally planned, but some comparisons are presented for descriptive purposes.

Results

Qualitative research

Of the 23 individuals who had indicated their willingness to participate in the study, four could not be contacted and three potential participants indicated that they no longer wished to participate, leaving a total of 16 individuals with whom interviews were conducted (12 with females). Fifteen interviewees were smoking cessation professionals who were also responsible for overseeing the day-to-day activities of their respective services or actively involved in managing one aspect of the service in which they worked and one was a regional tobacco control lead.

Three broad themes emerged from interview data: beliefs, knowledge and understanding of relapse prevention; RPIs for abstinent/lapsed and relapsed smokers, and barriers and challenges (*Box 2*).

BOX 2 *Index of themes and subthemes*

Knowledge and understanding
Prevention of lapses
Treatment of lapses
Treatment of relapsed smokers

Relapse prevention support for abstinent/lapsed and relapsed smokers
Support for abstinent/lapsed smokers
Content:
Behavioural counselling and pharmacotherapy
Telephone follow-up
Social activities
Uptake
Support for relapsed smokers
Content:
Rolling groups
Recycling – fresh quit attempt
Uptake

Barriers and challenges
Funding
Government targets
Paucity of information about effective relapse prevention interventions

The following sections describe these themes in more detail. Quotes are reported in *Boxes 3–6* and are attributable to individual interviewees by code numbers.

Knowledge and understanding of relapse prevention

Interviewees had diverse perceptions of relapse prevention as a concept and shared no common definition of what this should entail (*Box 3*). Their definitions of relapse prevention mostly appeared to be informed by the ways in which the cessation services for which they worked currently attempted to help abstinent smokers to remain stopped and achieve long-term abstinence. Interviewees believed that relapse prevention should be mainly provided for abstinent smokers to help them remain smoke-free and prevent lapses by extending their acute treatment. Some health professionals also believed that RPIs could be used for the treatment of lapsed (i.e. people who had smoked one or two cigarettes) or relapsed smokers (i.e. people who were now smoking regularly again).

Prevention of lapses

Most participants understood/thought that relapse prevention involved preventing lapses by providing treatment for longer than a 'usual' 7- to 8-week period, believing that, irrespective of the type of intervention used, offering acute cessation treatment for longer periods would ensure that more smokers remained abstinent. Almost all participants stated that relapse to smoking was most frequent when smokers ran out of medication, which perhaps explains the strong belief that extending treatment would prevent lapses. Treatments described were often group or individual behavioural support, extended beyond the usual time frame for which acute cessation treatment was provided.

Treatment of lapses

A small number of interviewees described relapse prevention as providing support for smokers who have already had a minor 'lapse' (i.e. smoked a few cigarettes during an otherwise abstinent period) to prevent subsequent complete relapse. Interviewees believed that a single lapse could be sufficient to precipitate a later, complete relapse and that managing these would substantially reduce the risk of smokers returning to regular smoking. Interviewees, again, provided a content-centred definition for relapse prevention as being the treatment of lapses citing the provision of behavioural support and pharmacotherapy as potentially effective for those who had smoked a few cigarettes during an otherwise abstinent period.

Treatment of relapsed smokers

Interviewees also described relapse prevention as providing treatment for smokers who have fully relapsed to smoking. They defined this, again, in terms of the content of the relapse prevention intervention and revealed that this usually involved encouraging the client to begin a fresh quit attempt and begin acute cessation treatment again, or attend 'rolling groups' (defined below).

Relapse prevention interventions for abstinent/lapsed and relapsed smokers

Interviewees described RPIs for abstinent/lapsed and relapsed smokers in terms of the types of support which could be provided and this differed for the two groups. Behavioural treatments, telephone follow-up calls and social activities represented the bulk of interventions provided for

BOX 3 *Knowledge and understanding of relapse prevention*

Prevention of lapses

'Relapse prevention is making sure that, to try and stop people lapsing back to smoking, that's what I understand relapse prevention would mean'. Interviewee no 8

'It is some action, some clinical action that the practitioner takes in order to prevent the patient from in the first place lapsing that automatically implies that it would help prevent relapse'. Interviewee no 12

'Relapse prevention to me is, we have an open clinic, we see them initially for at least 7 weeks, but it doesn't finish at either at 6 or 7 weeks, they can come for as long as they like'. Interviewee no 13

Treatment of lapses

'Well it's for people who have tried to stop smoking and have lapsed, and they don't want to go back through the whole system again, they just need something to get them back on track again'. Interviewee no 10

'I've always felt that it's enabling clients to remain quit in the long-term...so that at the point where they've had one lapse, they actually get support to prevent them from turning into one great big relapse'. Interviewee no 2

Treatment of relapsed smokers

'It's really about people who have relapsed to smoking, regularly, and have gone into full-blown relapse, where they are now smoking regularly, and they need help to actually stop'. Interviewee no 1

abstinent smokers and those who had experienced brief lapses, whereas rolling groups and recycling (in which relapsed smokers are treated as fresh quit attempts) were treatment modalities that interviewees described as being accessed by relapsed smokers. Interviewees also reflected on the uptake of such support when offered within their services (*Boxes 4* and *5*).

Support for abstinent/lapsed smokers: content

Behavioural counselling and pharmacotherapy

Interviewees revealed that behavioural counselling was one of the most favoured forms of treatment for smokers who remained abstinent or who despite one or two brief lapses remained smoke-free. This was described as being provided either individually or to groups in which clients are helped to identify situations and triggers that might lead to smoking lapses or relapse and taught strategies to help overcome cigarette urges and prevent lapses or full-blown relapse to smoking. Clients are also helped to understand that relapse is a spontaneous, unplanned thought process or phenomenon which is often triggered by external factors such as holidays, bereavement, and unexpected personal or financial difficulties, and are equipped with strategies to deal with these. Few individuals spontaneously mentioned the use of pharmacotherapy to prevent relapse, but all were asked to comment on the feasibility of using pharmacotherapies for relapse prevention (given emerging evidence on its effectiveness, see Chapter 3, Pharmacotherapy interventions) and most interviewees were positive about this.

Telephone follow-up

Some interviewees reported that their services provide telephone follow-up calls or text messaging to support abstinent clients who had completed acute cessation treatment. Advisors kept in touch with abstinent smokers via telephone to provide motivation and support, when needed, and to help them remain smoke-free with relatively short calls (< 10 minutes) made at convenient times for clients. During the call, the advisor reiterated the advantages of remaining smoke-free and reminded clients to contact the service once he/she experiences the urge to smoke a cigarette. Interviewees were quick, however, to point out that this proactive telephone counselling was logistically difficult and, as many clients found the calls intrusive, not a favoured intervention. They believed calls could be an unwelcome reminder for smokers that abstinence could be difficult to maintain.

Social activities

Interviewees talked about using 'diversion therapy' as a RPI for abstinent smokers. This was often reported to involve engaging clients in activities designed to take their minds off smoking, and provide them with feelings of well-being and importance, Activities were specially organised and could be conducted by the smoking cessation service or in community or leisure centres. Regular group activities could be led by an abstinent smoker and those described included baking/cooking, community services and visiting hospices or nursing homes to lend support to residents.

BOX 4 *Relapse prevention interventions for abstinent/lapsed smokers*

Content

Behavioural counselling and pharmacotherapy

'We run a group, so they can come in for a series of sessions which cover general healthy lifestyle, like healthy eating, getting advice, and stress reduction'. Interviewee no 6

'Well everything that is involved in behavioural support, going through every situation they may encounter, preparing themselves for that, looking at tactics to cope with situations...if they've got anything in particular they're worried about, we will approach it in a practical but relaxed manner'. Interviewee no 2

'We work with people, whatever their issues/triggers are, we would deal with, it doesn't matter what it is, if its debt management, crisis resolution, if in quitting smoking they've got problems that need dealing with, we would deal with it'. Interviewee no 5

'I would strongly recommend that (pharmacotherapy) because as I said, a lot of patients reported that they actually relapsed right after they are not provided with medications'. Interviewee no 3

'I think it (pharmacotherapy) would be fantastic'. Interviewee no 5

Telephone follow-up

'We do telephone follow-ups, say between 6 and 12 months, just to ask them how they are getting on, and to let them know they can access the service again and again, at any point they need'. Interviewee no 18

'The problem you have there is if you are going to phone everybody, you have to have the manpower, the resources to do that, from a resource point of view, I wouldn't have time to phone everybody at the moment'. Interviewee no 13

'It would be very hard for us to that, to phone everyone up would be ideal but impossible at the moment'. Interviewee no 15

Social activities

'We do use interventions such as diversion therapy, by getting people into community groups and community support...we don't send them home to continue sorting out themselves, we get them out in the community, get them busy and get them involved in things, they need to be busy and out there and feeling useful…we get them to go to care homes and just you know, do peoples' hair and make them cups of tea, its just engaging them with whatever involves them'. Interviewee no 5

Uptake

'I think the picture is actually, people poorly attend relapse prevention. Because they feel once they've actually reached the quit, they don't need any help...a lot of smokers don't want you chasing them up, a lot of them are fed up if you do contact them'. Interviewee no 6

'We used to, a couple of times a year, we'd put on like an open session, and invite everybody who'd been to the group in the last year, we'd put on a bit of food and make it a social event, and do some stuff about staying quit, but very few people attended, so it tended to be a waste of our time, so we didn't continue it'. Interviewee no 16

Uptake

Interviewees revealed that where RPIs had been offered, most clients did not access them, making it difficult to sustain their provision; clients generally used services for help with cessation and interviewees' perceived that their services might not be viewed as providers of support to prevent relapse.

Support for relapsed smokers: content

Rolling groups

In some services, smokers who had already been treated but had relapsed to smoking were able to access 'rolling groups'. Health professionals described this as an 'open door' policy, with relapsed clients always free to return to the service and rejoin cessation-orientated support groups. 'Rolling groups' would not have fixed start or completion dates, so clients wishing to re-enter the service for help would be able to do so. Groups were perceived as able to provide clients the opportunity to mix with individuals who had received acute cessation treatment, relapsed, but had been able to become abstinent again. The groups are often led by a trained advisor, focusing on helping smokers deal with circumstances that might lead to relapse.

Recycling – fresh quit attempt

In other services smokers who have suffered a full-blown relapse were encouraged to re-enter complete cessation treatment programmes. Interviewees reporting this believed that, after complete relapse to smoking, support aimed at relapse prevention is no longer appropriate and the individuals need to restart the quitting process.

Uptake

It was perceived that this process of 're-cycling' was often hampered by smokers' unwillingness to admit relapses and re-engage with smoking cessation advisors due to profound feelings of failure and embarrassment. Health professionals believed an important focus in the management of smoking relapse should be to help the smoker overcome such emotions and suggested that making clients aware of the possibility of relapse, early in their quit attempts, might prepare smokers for relapse to diminish such negative emotions arising.

Barriers and challenges to using relapse prevention interventions

Funding and pressure to meet Government targets (which are focused on short-term cessation) and paucity of information on the effectiveness of RPIs were repeatedly identified as challenges to their provision (*Box 6*).

Funding

Nearly all health professionals stated that drug budgets and funding constituted major obstacles to the introduction of RPIs. A number of interviewees revealed that they had stopped providing RPIs due to a lack of funds for additional support beyond that provided during cessation treatment. Interviewees were positive about providing these interventions for motivated smokers, if health authorities allocated adequate funding.

Government targets focused on short-term cessation

Interviewees' accounts suggested that the need to meet Government targets for NHS SSS exerts considerable pressure on them. Even for health professionals who were interested in and willing to provide RPIs, the pressure to achieve short-term cessation for smokers (i.e. 4-week quits) often reduced the amount of time and resources that could be devoted to RPIs. Interviewees recognised this conflict and repeatedly identified this as a substantial barrier to the provision of RPIs within their services.

Paucity of information about effective relapse prevention interventions

A lack of available evidence on the effectiveness of RPIs was also perceived as a barrier to their use by some participants. It was believed that it would be easier to provide these interventions for motivated smokers if there was a readily available and accessible evidence base detailing the relative effectiveness of different RPIs. Many indicated that they would be able to integrate RPIs into their mainstream service, but only if there was sufficient evidence regarding the effectiveness of these interventions.

Survey

A total of 96 managers completed the survey (52% response rate): 54 responded to the first e-mail and completed the questionnaire, with a further 42 respondents completing the survey after e-mail and telephone reminders.

BOX 5 *Relapse prevention interventions for relapsed smokers*

Content

Rolling groups

'We don't have any formal relapse groups, but there are no barriers to re-entry of the service, for example in my 12-week group, drop-in group, people can come along who have relapsed and rejoin the group again'. Interviewee no 12

'We have a rolling group that is open for anybody who wants to come back in at any time'. Interviewee no 14

Recycling

'Yes, it's a new quit attempt isn't it? (For relapsed smokers). You would go over the reasons for relapse and then you need to go through the whole process of another quit attempt'. Interviewee no16

Uptake

'A lot of people would rather, even though you've built up a rapport, struggle than bother you, so they think, oh no, I've failed now, they may have had one, two cigarettes, they don't contact you, so that tends to be a problem'. Interviewee no 8

'I think, when you, from my experience as an ex-smoker, if you're trying to give up, and you've slipped up, and then somebody is ringing you, you think Oh God no, it's that woman again, and feel really bad'. Interviewee no 13

'The trouble is when people do relapse there's sort of, they're embarrassed to come back'. Interviewee no 15

BOX 6 *Barriers and challenges relating to provision of RPIs in the NHS SSS*

Funding

'We used to have a relapse prevention session, wherein we invite everyone that came to our service to attend these clinics, but we don't do that anymore because of financial pressures'. Interviewee no 3

'I think most primary care trusts would be prepared to pay for a course of treatment, but not an extended course of treatment, that's why they cut down to stop methods unlikely to be funded locally'. Interviewee no 4

Government targets

'If you've got very busy clinics and you have Department of Health Targets to meet, you know, there's always a bit of a squeeze, in terms of how much time you've got for people to see you beyond their successful 4 week quit'. Interviewee no 7

'I think you know, the fact that we are so target driven, and the fact that reporting successes is at a month rather than if it was 3 months or something like that, you know the whole drive would be to see patients longer … although I think targets are probably a good thing overall, because it does focus you on hitting the three pots and all the rest of it, but I think it can be a bit counter productive'. Interviewee no 14

Paucity of Information

'I don't think we've got anything in black and white, to be honest'. Interviewee no 1

Current provision of smoking cessation treatments

Table 1 shows the provision of cessation treatments reported by managers as being used in services they ran; reported treatments for relapse prevention are also shown. Nearly all, 99%, reported that their services provided individual behavioural interventions, with NRT the next most popular treatment provided, by 98% (*Table 1*). A high proportion of managers (92.7%, $n = 85$) also reported that their services recommended NRT combinations (this question was not asked in relation to relapse prevention provision).

Current provision of RPIs

More than half of respondents, 58.3% ($n = 56$) reported that their services currently provided RPIs and *Table 1* shows managers' reported provision of the different types. The most popular form of RPI was telephone follow-up counselling, reported to be provided by just over three-quarters of the managers providing RPIs, followed by individual counselling (54%). Pharmacotherapy support was reported to be provided by under half of those providing RPIs, with NRT being the most frequently used.

Of those services reporting provision of RPIs, 60.7% ($n = 34$) stated that these were offered to abstinent smokers for as long as these clients perceived they required them, 25.0% ($n = 14$) for 3–6 months and one service (1.8%) did so for ≤3 months. Of the 40 services reporting that they did not currently provide RPIs, 42.5% ($n = 17$) had provided such interventions in the past and cited the following reasons for no longer offering this kind of support: pressure to meet government targets (64.7%, $n = 11$) services; poor client attendance (70.6%, $n = 12$); inadequate funding (29.4%, $n = 5$); and a belief that RPIs are ineffective (17.6%, $n = 3$).

Managers that responded to the first survey e-mail were compared to those that completed the survey after a reminder. There was no association between timing of responses and reported provision of RPI [odds ratio (OR) 0.77, 95% confidence interval (CI) 0.34 to 1.75].

Current provision of treatment for brief lapses

A large percentage of managers of NHS SSS, 77.1% ($n = 74$), also reported providing treatment for clients who had suffered a brief lapse to smoking. Of these, 72.9% of services ($n = 70$) indicated the types of support provided: one-to-one sessions (32.8%, $n = 23$); rolling groups and drop-in sessions (7.1%, $n = 5$); telephone support of services (8.5%; $n = 6$); combinations of pharmacotherapy, telephone support, and one-to-one behavioural counselling (15.7%, $n = 11$); while 35.7% ($n = 25$) services continued acute cessation treatment. Although managers who provided RPIs were more likely to provide treatment for brief lapses than those not providing RPIs, this was not statistically significant (OR 1.55, 95% CI 0. 59 to 4.04, $p = 0.37$).

There was no association between timing of responses to the survey and reported provision of treatment of brief lapses (OR 1.92, 95% CI 0.70 to 5.26).

TABLE 1 *Provision of cessation and relapse prevention in NHS*

	Type of treatment % of those providing cessation or RPI (*n*)					
	Individual behavioural counselling	**Group behavioural counselling**	**Telephone counselling**	**NRT**	**Bupropion**	**Varenicline**
Cessation (*n* = 96)	99% (95)	87.5% (84)	81.2% (78)	97.9% (94)	86.5% (83)	92.7% (89)
Relapse prevention (*n* = 56)	73.2% (41)	53.6% (30)	76.8% (43)	48.2% (27)	21.4% (12)	19.6% (11)

Feasibility of relapse prevention interventions

Respondents were asked to indicate the likelihood of future RPI provision within their NHS SSS. Managers who had indicated that RPIs were not currently provided were asked to indicate the likelihood of providing RPIs in the future and those already providing RPIs were asked about the likelihood of continuing this provision. Nearly two-thirds, 65.6% ($n = 63$) managers, thought it very likely or likely that they would continue to provide, or start to provide, RPIs in their services, with the remainder not sure or thinking it unlikely that they would provide RPIs in the future. Among the latter group, the reasons cited for this were: cessation orientated targets focused on 4-week quit rates (66.7%, $n = 22$); inadequate funding (42.9%, $n = 14$); and the fact that clients had usually relapsed before they recontacted the cessation service (24%, $n = 8$).

The 33 respondents who indicated that they were not sure or thought it unlikely that their services would provide RPIs in the future, were then asked to assume that barriers to provision of RPIs were removed, and to hypothesise, in this instance, which RPIs they might encourage their NHS SSS to offer to abstinent quitters after smoking cessation treatment. Of these, around three-quarters thought it very likely or likely that they would provide individual or group behavioural counselling without the hindrance of barriers [(78.8%, $n = 26$) and (72.7%, $n = 24$) respectively], followed by NRT (57.6%, $n = 19$), NRT combinations (54.5%, $n = 18$), varenicline (24.2%, $n = 8$) and bupropion (21.2%, $n = 7$).

There was no association between timing of responses to the survey and the reported likelihood of future relapse prevention provision (OR 1.05, 95% CI 0.45 to 2.46).

Discussion

Summary of findings

Qualitative research

The sample of health professionals interviewed did not have a shared definition or understanding of RPIs. Instead, interviewees used their experiences to conceptualise relapse prevention, often basing this on the kinds of RPIs that the services in which they worked offered to clients. Interviewees believed that introducing RPIs into NHS SSS would be hindered by lack of funding, current performance targets focused on achieving short-term abstinence from smoking and the lack of an evidence base. They reported low uptake of RPIs in services providing them and interviewees were negative about introducing additional, proactive telephone support counselling as an RPI, but were much more positive about the possibility of using pharmacotherapy for this purpose.

Survey

Just over half of the managers responding to the survey reported providing RPIs based on the definition we provided and used throughout this report, despite at the time the survey was carried out, a weak evidence base (for pharmacological RPIs)[23] and an absence of guidance on the provision of RPIs within NHS SSS. The most frequently provided RPIs were telephone and individual behavioural counselling, RPIs for which there was no evidence of effectiveness; which has not changed as a consequence of reviews conducted within this report. Around three-quarters of the managers also reported treating lapses among smokers trying to stop, but as this is not the main focus of this report and there is only a very small evidence base to support this kind of intervention, such provision is not discussed further. Most managers of NHS SSS were favourably inclined towards continuing or introducing RPIs but were

most positively orientated towards providing those for which there was very little evidence of effectiveness. Similar to the findings from the qualitative research, the most commonly cited reasons for not providing RPIs were the NHS SSS short-term abstinence targets and inadequate funding for RPI delivery.

Strengths and limitations

To our knowledge, these are the first studies to explore smoking cessation professionals' experiences of, beliefs about, and current provision of RPIs within the NHS SSS or indeed in any other health system and the findings have highlighted relevant issues that could hinder or facilitate the introduction of RPIs into the NHS. Our qualitative research sample was small and it is possible that by interviewing a larger, more diverse group, we would have found other important factors relating to the use of RPIs, however, similarities inherent in the accounts we obtained, suggest that we have identified most of the major issues. Also, as our sample comprised volunteers from those attending a smoking cessation conference, one might expect their views on RPIs to be better informed than those of others working in the field. Our survey results are based on smoking cessation managers' self reports and may have overestimated the rates of RPI provision; for example, managers may have been unwilling to reveal that they do not provide some form of RPI in their services. However, we believe that biases in the reporting among this sample are an unlikely explanation for our findings, given the lack of current evidence on the effectiveness of RPIs at the time the survey was carried out. The survey is also limited by the response rate as just over half of managers completed the online questionnaire. A greater response rate may have produced more varied results; non-responders to the survey may have different experiences of providing RPIs in their services, although a comparison of the two waves of responses to the survey showed that there were no differences in variables relevant to the focus of this report.

Important emergent issues

The varied descriptions of RPIs in the qualitative research indicated that health professionals working in the NHS SSS did not share a common definition of what these interventions should involve. While some believed relapse prevention should be aimed at lapsed smokers, more commonly it was perceived appropriate for preventing relapse among smokers who were still abstinent and attempting to quit, in concordance with the definition we use in this report. However, often no distinction was made between RPIs and routine cessation treatment. It is, perhaps, unsurprising to find differences of opinion about RPIs among health professionals, because the scientific literature on the subject at the time the research was carried out described studies which conceptualised relapse prevention in different ways too[23] (as discussed in the next chapter).

When provided with a definition of RPIs, over half the managers in the survey reporting providing them, despite the then weak evidence base,[23] and two-thirds reported being likely to provide them in the future. This enthusiasm may have reflected a desire to improve support provided to smokers, who have a high relapse rate from acute cessation treatment, or their anecdotal experience of the effectiveness of RPI, or a perception that smokers appreciate being provided with RPIs. While this wasn't explored in our research, there was little support for the latter explanation as participants in the qualitative research expressed concern about the low uptake of RPIs, which had often led to these being withdrawn, and was perceived as a major potential barrier to their successful introduction. They also thought that relapsed smokers were embarrassed about their 'failure' and hence did not return for treatment. This view is consistent with the literature; lapsed smokers often feel guilty[12] and experience negative affect and decreased confidence in their ability to quit.[29]

Managers favoured behavioural intervention over drug treatments and, at the time of the survey, there was insufficient evidence to say whether either was, indeed, effective. However, our subsequent systematic review (see Chapter 3), found drug treatments and not behavioural ones effective for smokers who achieve abstinence after receiving support, as those using NHS SSS do. This suggests that overall findings from this report could help the NHS SSS clinical practice to become more evidence based. Survey respondents preferred telephone follow-up of clients for behavioural RPIs, though there is no evidence that this is effective and, conversely, the qualitative interviewees found little or no enthusiasm for this, citing that few abstinent smokers welcomed this type of contact that was also logistically challenging to undertake.

We examined whether the preference for the provision of behavioural treatments reflected

provision of acute cessation treatment. While this could explain the use of telephone support (81% of services provided telephone support as acute cessation treatment), this explanation does not clarify the disparity between the high percentage of services offering bupropion and varenicline for acute cessation treatment and the low percentage offering these pharmacotherapies for relapse prevention, despite at the time some, albeit weak, evidence for their effectiveness.[23] In the absence of any barriers, individual and group counselling were also favoured for relapse prevention, while the pharmacotherapies were the least favoured. However, when provision of RPIs was explored in the qualitative research, interviewees believed that pharmacotherapy used as extended treatment for relapse prevention could be easily integrated into current routine practice, as long as costs were addressed.

In addition to cost, the other substantive perceived barrier to any form of RPI provision were the current performance management targets for the NHS SSS. For example in October 2002, the English DoH stated an aim that 800,000 smokers would successfully quit following help from smoking cessation services by 2006[21] and this was subsequently translated into an aspiration that services should treat at least 5% of their local population of smokers in the course of a year, with an expected validated success range of 35% to 70% at 4 weeks.[1] For these targets, success involves smokers achieving a 4-week period of abstinence, so there is considerable pressure on services to achieve a high throughput of smokers who manage to stop smoking for at least 1 month. Interviewees' comments reflected this perceived pressure and indicated that the provision of RPIs, which, if effective, could be expected to improve longer term but not short-term quit rates, could not be a priority for services without a change in the targets against which they are measured.

The survey data indicated that current provision of acute cessation treatment largely reflects UK guidance,[30,31] and our survey suggests that similar evidence-based guidance is needed to support managers wishing to provide RPIs in order to ensure that, in the future, the most promising and effective RPIs can be introduced into routine care, assuming that any perceived barriers are removed.

Chapter 3

Systematic review investigating effectiveness of relapse prevention interventions

Background

A 2005 Cochrane review found no convincing evidence for the effectiveness of either behavioural or pharmacological RPIs.[23] However, trials investigating drug treatments provided relatively weak evidence that extended courses of NRT might reduce relapse among abstinent quitters.[23] An update of the 2005 review again found behavioural RPIs ineffective, but findings for drug interventions were less straightforward; bupropion was not found to work for relapse prevention, whereas the one trial of varenicline found this effective and the length of smokers' abstinence periods prior to starting RPIs appeared to influence their effectiveness.[17] Two large trials, in which participants were abstinent for only 24 and 48 hours before commencing NRT as a relapse prevention treatment found NRT effective for this, but two smaller ones with much longer abstinence periods did not.[17] Methods of combining outcomes in Cochrane reviews may have obscured real effects of RPIs; both pooled smoking status at final follow-up,[17,23] resulting in data collected at different times after randomisation and hence at varying periods into participants' quit attempts, being aggregated. For example, abstinence rates at 5 and 12 months after participants started RPI treatments could be combined, potentially yielding clinically heterogeneous comparisons.

The research question

In this chapter, we address the research question, 'Are smoking relapse prevention interventions effective in reducing rates of relapse to smoking?' by conducting a systematic review with an identical search strategy to that used in the Cochrane reviews, but in which only data collected at similar follow-up time points are synthesised. We investigate the impact of RPIs delivered to both recently-abstinent and non-abstinent smokers, but our primary analyses determine the effects of RPIs delivered to smokers who are recently-abstinent (referred to as abstinent smokers or abstainers), because this is the way relapse prevention treatments would probably be used in routine clinical practice in the UK. We also assess the impact of using RPIs alongside traditional smoking cessation treatments by analysing trials which randomise (non-abstinent) smokers and which deliver RPIs and cessation therapies simultaneously. In summary this review investigates whether or not pharmacological or behavioural RPIs increase long-term abstinence from smoking when delivered to smokers or to smokers who have managed to stop and remain abstinent for a period.

Methods

Search strategy

The search strategies undertaken were identical to those used in the 2005 Cochrane review[23] and intended to update this and so were conducted between 2004 (when searches for this review concluded) and July 2008. In addition to searching the Cochrane Tobacco Addiction Group register of trials, we also searched MEDLINE, the Cochrane Central Register of Controlled Trials (CENTRAL), EMBASE, PsycINFO, the Science Citation Index and Social Science Citation Index. To identify grey literature we also searched the abstracts of the annual meeting of the Society for Research on Nicotine and Tobacco, contacting authors for further information about their research, where relevant. The bibliographies of retrieved references were also scanned for further relevant publications and studies in all languages/from all countries were considered. Full details of search strategies used are documented in Appendix 3.

The titles and abstracts identified from searches were assessed independently by two authors (TC and AMcN). Studies were excluded if it was clear that the study did not refer to a randomised controlled trial (RCT) of an intervention used for relapse prevention. Two authors then independently assessed each study to determine whether it met the pre-specified selection criteria, with any difference being resolved through discussion with remaining authors.

Inclusion and exclusion criteria

Type of studies

Randomised control trials with a minimum of 6 months' follow-up after randomisation, including studies that randomised smokers and also people who had recently smoked and were now abstinent. Trials of behavioural interventions that randomised smokers were included only if study titles and abstracts explicitly mentioned a focus on relapse prevention or maintenance or if the study tested the effect of extended telephone contact after an initial intervention had been delivered, irrespective of whether or not a specific focus on relapse prevention or maintenance was mentioned.

Types of participants

Individuals who had quit smoking on their own, individuals undergoing enforced abstinence and smokers participating in treatment programmes.

Types of interventions

Interventions which investigators in individual studies state are intended to prevent relapse to smoking compared to either:

- No intervention.
- A shorter or less intensive intervention.
- An intervention not oriented towards relapse prevention.

These were either behavioural interventions:

- Group meetings.
- Face-to-face sessions.
- Written or other materials.
- Proactive or reactive telephone support.

Or:

- Pharmacological interventions.

Main outcome measure

The primary outcome for this review was abstinence from smoking, ascertained preferably as continuous abstinence, with point prevalence abstinence used if this was not recorded.

Data extraction strategy

All authors participated in data extraction with two authors working independently on each paper, using a specially designed data extraction form and differences being resolved through discussion. The data extracted included:

- Description of study (design, duration of trial, unit of randomisation, unit of analysis).
- Description of treatments (type, dose, duration).
- Participants (inclusion and exclusion criteria, demographic data, number lost to follow-up).
- Outcome measure (primary and secondary).
- Results (abstinence at 1–3 months, 6–9 months and 12–18 months).

Attempts to obtain missing data from the authors of the manuscripts were made, where possible. Data were checked and entered into REVIEW MANAGER, version 5, by one author (SA).

Quality assessment

The methodological quality of the included studies was assessed using the Cochrane Collaboration's recommended tool for assessing the risk of bias which evaluated aspects of trial design: methods of randomisation sequence generation and allocation concealment; blinding; adequate assessment of incomplete data; comparability of groups at baseline; and whether treatments were adequately described.

Data analysis

For studies with similar types of intervention, a meta-analysis was performed to calculate a weighted intervention effect across trials using a random effect (DerSimonian and Laird) model and results are expressed as pooled ORs with 95% CIs. Numbers needed to treat (NNT) for additional beneficial outcomes were calculated using pooled baseline event rates, where significant comparisons were seen. Statistical heterogeneity was assessed using I^2 and where heterogeneity levels were detected ($I^2 > 80\%$), studies were summarised individually.[32] Follow-up time points were defined as follows: (1) short term, 1 month (permitted range 1–3 months), (2) medium term, 6 months (range 6–9 months) and (3) long term, 12 months (range 12–18 months), with the long-term follow-up point considered as the primary end point time. In trials of pregnant/postpartum women, abstinence was also reported at delivery or the last follow-up prior to this. Where there were multiple intervention groups within a trial, pair-wise comparisons were made for each active intervention versus control, with the results in the non-control being divided by the number of pair-wise comparisons, so participants in the control group were not double counted. Funnel plots were used to assess publication bias.

Results

Number of studies identified

The search strategy generated 1598 potentially relevant references and after title/abstract assessment 144 papers were retrieved and examined; results of this process are summarised in *Figure 1*.

Included studies

Fifteen studies met our inclusion criteria, and these were added to the 39 studies from the earlier Cochrane review,[23] giving 54 studies in total that are summarised in *Tables 4–10*; 18 randomised smokers and 36 abstinent smokers.

Studies randomising abstinent smokers

Of the 36 studies[33–39,40,41,63–89] randomising abstinent smokers, 28[40,41,63–88] investigated the effectiveness of behavioural interventions for relapse prevention (14 in pregnant or postpartum women) and eight investigated pharmacotherapies.[33–39,89] Of these 36 studies, 13[36,63,64,66,69,73,76,78–80,86,88,89] measured continuous abstinence, 28[33–39,40,41,64,65,67,68,70–77,79,81–85,87] point prevalence abstinence (defined as not smoking within either the previous 7 or 30 days) and five[36,64,73,76,79] used both. Twenty-seven[33–40,63,65,67–72,75–81,83,84,86–89] trials verified self-reported smoking status using either expired air carbon monoxide (20 trials),[31,34–39,63,67,69,72,78–80,84,86–89] urinary or saliva cotinine (six trials),[65,68,70,71,75,81] or saliva thiocyanate (one trial)[40] and nine trials[41,64,66,73,74,76,77,82,85] presented self-reported abstinence only. All studies used a parallel group design except one which was cluster randomised;[41] however, any dependency in the data due to clustering was found to be negligible and, therefore, this study was analysed with the others.

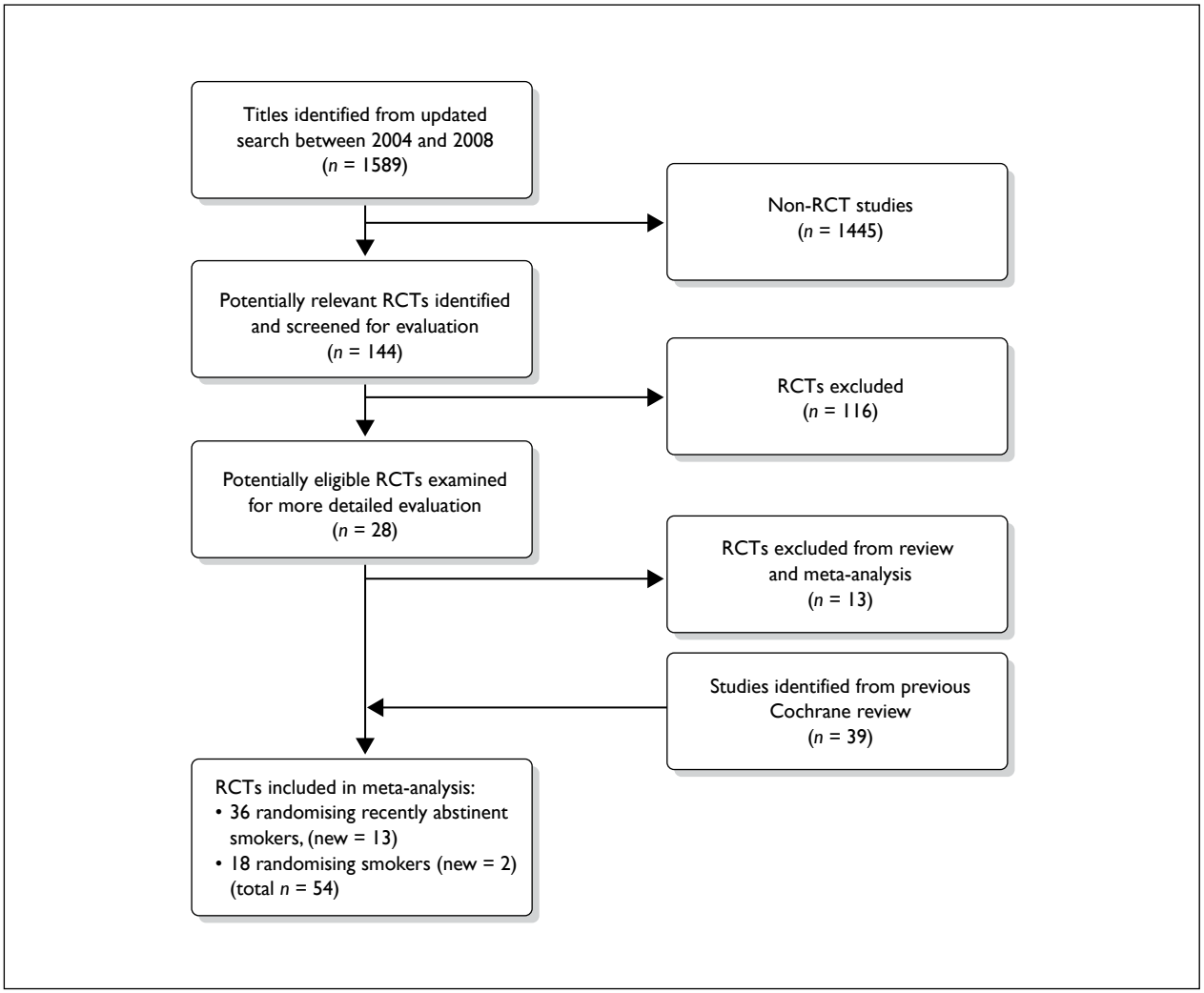

FIGURE 1 *Flow chart of study retrieval process.*

The methodological quality of all included studies is summarised in *Table 2*.

Studies randomising smokers

Of the 18 studies[42–46,48–60] that randomised smokers, nine investigated the effectiveness of interventions matched for programme length,[42–46,48–51] six compared interventions of varying programme lengths[52–57] and two trials examined the effectiveness of RPI adjuncts to cessation programmes.[58,59] Thirteen of these trials verified self-reported smoking abstinence with carbon monoxide measurements,[42,45,46,48–50,52–55,57,58,60] one used saliva thiocyanate,[44] another saliva cotinine,[59] two verified abstinence with urine cotinine[43,56] and one used self-reported abstinence only.[51] We categorised one study which randomised 362 cigarette smokers prior to their receiving open-label treatment with bupropion and NRT[60] with the 'randomising smokers' group, but the 2009 Cochrane review[17] judged this to have randomised abstinent smokers.

Excluded studies

Details of excluded studies are summarised in *Table 3*; these were retrieved and examined, but failed to meet one or more of the inclusion criteria in terms of study participants, type of interventions and type of outcome measures. The 2009 Cochrane review[17] excluded one study which we have included;[39] this randomised abstinent smokers to receive 5-mg or 20-mg rimonabant or placebo for 42 weeks after 10 weeks of open-label treatment with rimonabant. We excluded two studies which are included in the Cochrane review:[17] one randomised abstinent smokers who had lapsed, rather than smokers or abstinent smokers[61] and the other included many participants who were not smokers and analysed their outcomes with smokers.[62]

Comparison categories

To enable interpretation of findings and avoid heterogenic comparisons, we have divided trials into nine categories according to their participants (i.e. smokers or abstinent smokers) and the types of intervention delivered (i.e. pharmacological or behavioural and subcategories within each). Within each category, details of included studies, characteristics of interventions and outcome assessments are provided and the effectiveness of interventions is investigated, where appropriate, by meta-analysis. The 10 comparison categories are as follows:

Studies randomising abstinent smokers

1. Behavioural interventions in pregnant and postpartum women.
2. Behavioural interventions in other population groups (including aided, unaided and enforced abstinent smokers).

Pharmacotherapy interventions:

3. Bupropion.
4. NRT.
5. Varenicline.
6. Rimonabant.

Studies randomising smokers

7. Behavioural programmes with interventions and control groups matched for contact time and duration.
8. Behavioural programmes with interventions of different intensity.
9. Relapse prevention adjuncts to cessation programmes.
10. Pharmacotherapy interventions – bupropion.

Studies randomising abstinent smokers

Behavioural interventions in pregnant and postpartum women

Details of included studies

Table 4 gives details of studies in this category. Of the 14 studies,[40,63–75] 13 were carried out within hospitals, clinics or health centres[40,63–74] and one study was conducted within paediatric practices.[73] All provided information on age of participants, smoking history, educational and employment status and eight studies information on race or ethnicity of participants.[40,65–68,70,74,75] Two studies were conducted in low-income women[67,70] and four studies randomised postpartum women only.[64,69,73,74] All 14 studies[40,63–75] provided details of smoking status at different follow-up points in pregnant women who had stopped smoking prior to randomisation or in postpartum women who were still abstinent after delivery.

Characteristics of interventions

Two trials used three interventions of varying intensities,[65,66] one investigated two interventions of different intensities[73] and the remaining 11 trials compared one intervention with usual care control groups. In two studies, interventions were delivered in women's homes,[64,70] two mailed

TABLE 2 *Methodological quality of included studies using the Cochrane Collaboration's recommended tool for assessing methodological quality and risk of bias*

Study	Method of sequence generation described	Allocation concealment	Blinding	Incomplete outcome data adequately addressed	Groups comparable at baseline	Treatments adequately described
Becona and Vazquez (1997)[42]	No	Unclear	No information	Not reported	Yes	Yes
Borland *et al.* (2004)[76]	Yes	Not used	Participants blinded	Yes	Yes	Yes
Brandon *et al.* (1987)[52]	No	Unclear	No information	Not reported	Yes	Yes
Brandon *et al.* (2000)[77]	No	Not used	No information	Yes	Yes	Yes
Brandon *et al.* (2004)[78]	No	Not used	No information	Yes	Yes	Yes
Buchkremer *et al.* (1991)[43]	No	Unclear	No information	Yes	Not reported	Yes
Conway *et al.* (2004)[41]	Yes	Unclear	No information	Not reported	Not reported	Yes
Copeland *et al.* (2006)[79]	Yes	Unclear	Therapists blinded	Yes	Yes	Yes
Covey *et al.* (2007)[33]	Yes	Adequate	Participants and clinicians	Yes	Yes	Yes
Croghan *et al.* (2007)[34]	Yes	Adequate	Participants and clinicians	Yes	Yes	Yes
Curry *et al.* (1988)[44]	Yes	Unclear	No information	Yes	Yes	Yes
Davis and Glaros (1986)[45]	No	Unclear	No information	Not reported	Yes	Yes
Emmons *et al.* (1988)[46]	No	Unclear	Therapists blinded	Yes	Yes	Yes
Ershoff *et al.* (1995)[75]	No	Unclear	Clinicians blinded	Yes	Yes	Yes
Fortmann and Killen (1995)[35]	Yes	Unclear	No information	Yes	Yes	Yes
Hall *et al.* (1984)[48]	No	Unclear	No information	Yes	Yes	Yes
Hall and Killen (1985)[53]	No	Unclear	No information	Not reported	Yes	Yes
Hall *et al.* (1987)[54]	No	Unclear	Therapists blinded	Yes	Yes	Yes
Hajek *et al.* (2001)[63]	No	Adequate	No information	Yes	Yes	Yes
Hajek *et al.* (2002)[80]	Yes	Adequate	No information	Yes	Yes	Yes
Hannover *et al.* (2009)[64]	Yes	Unclear	No blinding	Yes	Yes	Yes
Hasuo *et al.* (2004)[81]	Yes	Not used	No blinding	Yes	Yes	Yes
Hays *et al.* (2001)[36]	Yes	Adequate	Investigators and participant blinded	Yes	Yes	Yes

continued

TABLE 2 *Methodological quality of included studies using the Cochrane Collaboration's recommended tool for assessing methodological quality and risk of bias (continued)*

Study	Method of sequence generation described	Allocation concealment	Blinding	Incomplete outcome data adequately addressed	Groups comparable at baseline	Treatments adequately described
Hurt *et al.* (2003)[37]	No	Unclear	Investigators and participant blinded	Yes	Yes	Yes
Japuntich *et al.* (2006)[58]	No	Unclear	No information	Yes	Yes	Yes
Killen *et al.* (1984)[55]	Yes	Unclear	No information	Yes	Yes	Yes
Killen *et al.* (1990)[38]	Yes	Adequate	Participants and therapists blinded	Yes	Yes	Yes
Lando *et al.* (1996)[59]	No	Unclear	No information	Yes	Yes	Yes
Killen *et al.* (2006)[60]	Yes	Unclear	No information	Yes	Yes	Yes
Klesges *et al.* (1999)[82]	No	Unclear	No information	Yes	Yes	Yes
Lifrak *et al.* (1996)[56]	Yes	Unclear	No information	Yes	Yes	Yes
Lowe *et al.* (1997)[40]	No	Unclear	No information	Yes	Not reported	Yes
Mayer *et al.* (2006)[83]	No	Unclear	Investigators blinded	Yes	Yes	Yes
McBride *et al.* (1999)[65]	Yes	Unclear	No information	Yes	Yes	Yes
McBride *et al.* (2004)[66]	No	Unclear	No information	Not reported	Not reported	Yes
Mermelstein *et al.* (2003)[84]	No	Unclear	Investigators blinded	Yes	Yes	Yes
Morasco *et al.* (2006)[67]	No	Unclear	No information	Yes	Yes	Yes
Niaura *et al.* (1999)[49]	No	Unclear	Counselors blinded	Yes	Yes	Yes
Niaura (2005)[39]	No	Unclear	Participants blinding	Not reported	Yes	Yes
Pbert *et al.* (2004)[68]	No	Unclear	No information	Yes	Yes	Yes
Powell and McCann (1981)[85]	No	Unclear	No information	Yes	Yes	Yes
Ratner *et al.* (2000)[69]	No	Unclear	Data collectors blinded	Not reported	Not reported	Yes
Razavi *et al.* (1999)[86]	Yes	Adequate	No blinding	Yes	Yes	Yes
Ruger *et al.* (2008)[70]	No	Unclear	No information	Not reported	Yes	Yes
Schmitz *et al.* (1999)[50]	No	Unclear	Raters blinded	Yes	Yes	Yes
Schroter *et al.* (2006)[51]	No	Unclear	No information	Yes	Yes	Yes

TABLE 2 *Methodological quality of included studies using the Cochrane Collaboration's recommended tool for assessing methodological quality and risk of bias (continued)*

Study	Method of sequence generation described	Allocation concealment	Blinding	Incomplete outcome data adequately addressed	Groups comparable at baseline	Treatments adequately described
Secker-Walker *et al.* (1995)[71]	No	Unclear	No information	Yes	Yes	Yes
Secker-Walker *et al.* (1998)[72]	No	Unclear	No information	Yes	Yes	Yes
Severson *et al.* (1997)[73]	Yes	Unclear	No information	Yes	Yes	Yes
Shoptaw *et al.* (2002)[57]	Yes	Unclear	No information	Yes	Yes	Yes
Smith *et al.* (2001)[87]	Yes	Unclear	No blinding	Yes	Yes	Yes
Stevens and Hollis (1989)[88]	Yes	Unclear	No information	Yes	Yes	Yes
Tonstad *et al.* (2006)[89]	Yes	Unclear	Participants and investigators blinded	Yes	Yes	Yes
Van't Hof *et al.* (2000)[74]	No	Unclear	No information	Not reported	Yes	Yes

TABLE 3 *List of excluded studies. Includes only studies identified from new search*

Study	Reason for exclusion
Boyle *et al.* (2007)[90]	The study did not test the effect of extended telephone contact after an initial intervention was delivered. It randomised participants into a no contact control group and a telephone counselling group
Chirikos *et al.* (2004)[91]	A cost-effectiveness analysis of secondary data
Cox *et al.* (2004)[92]	Examined the efficacy of bupropion in smokers with a past history of depressive disorder
Fang *et al.* (2004)[93]	A literature review of postpartum relapse prevention strategies
George *et al.* (2000)[94]	Mainly a smoking cessation study that compared the American Lung Association's behavioural programme to a manualised smoking cessation treatment programme designed for patients with schizophrenia
Hoving *et al.* (2006)[95]	Examined predictors of smoking relapse, did not compare two or more interventions
Japuntich *et al.* (2006)[58]	Examined the efficacy of internet interventions for smoking cessation only
Juliano *et al.* (2006)[61]	The study investigated the effect of rapid smoking on lapses, not relapse
Ma *et al.* (2005)[96]	Examined predictors of smoking cessation and maintenance in pregnancy. It did not compare two or more interventions
Partin *et al.* (2006)[97]	Examined the effectiveness of an intervention for increasing repeat treatment for tobacco dependence
Rigotti *et al.* (2006)[98]	Telephone counselling was not delivered after an initial intervention
Suplee (2005)[99]	Randomised individuals from a non-probability convenience sample
Sutton and Gilbert (2007)[100]	Telephone counselling was not delivered after an initial intervention, not focused on relapse prevention

interventions to women,[65,75] two used telephone interventions[64,69] and two involved interventions delivered in paediatricians offices and well-baby clinics.[73,74] Six studies delivered interventions *during pregnancy* only,[40,63,68,70,72,75] examining the effect of individual behavioural counselling on abstinence at various follow-up points. Four

TABLE 4 *Behavioural interventions in pregnant and postpartum women*

Study	Setting/ randomisation	Participants	Interventions	Outcome measure/ follow-up points	Verification
Ershoff *et al.* (1995)[75]	USA, randomisation occurred prior to patient contact	171 pregnant recent quitters, average length of prior abstinence 31 days	Two groups: Four booklets given at baseline visit, four relapse prevention booklets mailed weekly A 1-page tip sheet on behavioural techniques for avoiding relapse	Point prevalence abstinence at the end of pregnancy	Urinary cotinine verified abstinence
Hajek *et al.* (2001)[63]	UK, cluster randomisation	249 pregnant recent quitters	Advice from midwife Usual care	Continuous abstinence at the end of pregnancy and in the medium term	Carbon monoxide verified abstinence
Hannover *et al.* (2009)[64]	Germany, simple randomisation based on alternation	304 women who were abstinent at baseline	Telephone booster sessions 4 and 12 weeks after counselling and motivational interviewing Usual care	Continuous abstinence at medium and long term	Self-reported abstinence only
Lowe *et al.* (1997)[40]	USA, method of randomisation not stated	78 pregnant women who had quit within the past 3 months	Relapse prevention materials, counselling, reinforcement at routine visits by clinic staff Usual care	Point prevalence abstinence at the end of pregnancy	Saliva thiocyanate verified abstinence
McBride *et al.* (1999)[65]	USA, randomisation method not stated	897 pregnant smokers and recent quitters	Three groups: Pre/postpartum group: self-help booklet, personalised letter, relapse prevention kit, prepartum telephone counselling, postpartum telephone counselling and three postpartum newsletters at 2, 6 and 12 weeks postpartum Prepartum group: all of the above except postpartum telephone counselling and postpartum newsletters Booklet only group	Point prevalence abstinence at short, medium and long term	Salivary cotinine verified
McBride *et al.* (2004)[66]	USA, randomisation method not stated	625 pregnant women, 54% already quit	Usual care: provider advice to quit smoking at first prenatal visit and mailed self-help guide Woman-only: usual care components, late pregnancy relapse prevention kit, six counselling calls (three in pregnancy and three postpartum) by health advisor Partner assisted: woman-only intervention and partner assistance	Continuous abstinence at the end of pregnancy and at short, medium and long term	Self-reported abstinence
Morasco *et al.* (2006)[67]	USA, randomisation method not stated	33 women who had spontaneously quit smoking	A 90-minute psychotherapy session, followed by bimonthly prenatal telephone calls during pregnancy, and monthly calls after delivery, in addition to usual care Usual care: smoking cessation booklet	Point prevalence abstinence at the end of pregnancy and at medium term	Carbon monoxide verified

TABLE 4 *Behavioural interventions in pregnant and postpartum women (continued)*

Study	Setting/ randomisation	Participants	Interventions	Outcome measure/ follow-up points	Verification
Pbert *et al.* (2004)[68]	USA, randomisation by centre	158 pregnant women who had quit spontaneously at baseline	Special intervention, included provider training, office practice management system to screen for smoking status and programme boards to co-ordinate transfer of documentation among clinics Usual care: interventions were brief and delivered during prenatal and postnatal clinic visits	Point prevalence abstinence at the end of pregnancy, short and medium term	Saliva cotinine verified abstinence
Ratner *et al.* (2000)[69]	Canada, computer-generated randomisation	251 pregnant women, abstinent for 6 weeks prior to delivery	Brief hospital intervention after birth, written materials and eight telephone follow-up calls postpartum Usual care without any tobacco reduction counselling	Continuous abstinence at medium and long term	Carbon monoxide verified abstinence
Ruger *et al.* (2008)[70]	USA, randomisation method not stated	49 abstinent smokers at baseline	Motivational intervention at three home visits Usual care	Point prevalence abstinence at medium and long term	Salivary cotinine verified abstinence
Secker-Walker *et al.* (1995)[71]	USA, randomisation method not stated	165 women who had quit smoking during pregnancy	Individual counselling at first, second and third prenatal visits and at 36 weeks' gestation and 6 weeks post partum Usual care	Point prevalence abstinence at the end of pregnancy and at long term	Urine cotinine/ creatinine ratio verified
Secker-Walker *et al.* (1998)[72]	USA, method of randomisation not stated	125 women who had quit smoking during pregnancy	Structured intervention from physician and individual counselling by nurse at the first, second, third, fifth and the 36-week prenatal visits Usual care	Point prevalence abstinence at the end of pregnancy	Carbon monoxide verified abstinence
Severson *et al.* (1997)[73]	USA, cluster randomisation by practice	1026 abstinent new mothers	Extended condition: written materials provided at the first paediatrician's visit and a letter to the mother signed by the paediatrician, counselling at the first four well-baby visits and a specially developed video shown at one of the visits Minimal condition: written materials at first visit only	Continuous abstinence at long term	Self-reported abstinence only
Van't Hof *et al.* (2000)[74]	USA, randomisation method not stated	277 women who had quit during pregnancy	A 5- to 30-minute relapse prevention intervention from a Visiting Nurse Association nurse at baseline and reinforcements at 2-week, 2-month and 4-month well-baby visits Standard care from paediatric provider	Point prevalence abstinence at medium term	Self-reported abstinence only

trials delivered smoking RPIs *postpartum*;[64,69,73,74] two investigated the effectiveness of individual behavioural counselling[73,74] and the remainder assessed the combined effect of individual behavioural counselling and telephone booster sessions.[64,69] Four trials[65–67,71] initiated smoking relapse prevention interventions *during pregnancy and continued postpartum*; one of these delivered a combination of self-help interventions and telephone counselling,[65] another investigated individual behavioural counselling[71] and two trials compared individual and telephone counselling with control groups.[66,67]

Outcome assessment

Self-reported smoking status was validated in 10 studies.[40,63,65,67–72,75] Five studies reported smoking status at delivery,[40,63,67,72,75] nine studies presented abstinence at 6 months' follow-up[63–70,74] and four studies reported abstinence at both 6 and 12 months' follow-up.[63,65,69,70] Nine studies presented point prevalence abstinence,[40,65,67,68,70–72,74,75] while five presented continuous or sustained abstinence.[63,64,66,69,73]

Effectiveness of interventions

One study reported that the intervention administered appeared effective at 6 months, an effect which diminished over time and disappeared at 12 months' follow-up.[73] The other 13 studies reported that interventions designed to reduce relapse in pregnant and/postpartum women did not appear effective.[40,63–72,74,75]

Analyses

Interventions delivered during pregnancy

Pooled analyses of behavioural interventions delivered during pregnancy at delivery/the longest follow-up prior to delivery failed to detect a significant effect (pooled OR 1.18, 95% CI 0.85 to 1.62, $I^2 = 0\%$, five studies; *Figure 2*). Three of these studies[40,63,75] do not provide details of the exact follow-up point, and abstinence was measured at delivery. One study reported abstinence during the 34th week of pregnancy,[75] while the last study in this category measured abstinence at 36 weeks.[72] Only one study in this category assessed abstinence at short-term follow-up[68] and the intervention did not appear to have an effect on abstinence (OR 0.83, 95% CI 0.43 to 1.58). Pooled analysis of three studies at the medium-term follow-up was not performed due to significant levels of heterogeneity between the studies ($I^2 = 81\%$). In all three studies individual behavioural counselling did not significantly appear effective at reducing relapse (OR 0.88, 95% CI 0.49 to 1.58),[63] (OR 0.35, 95% CI 0.18 to 0.70)[68] and (OR 3.45, 95% CI 0.95 to 12.62)[70] respectively. Only one study reported data at long-term follow-up[72] that found no significant effect with individual counselling (OR 0.76, 95% CI 0.36 to 1.57).

Interventions delivered postpartum

Individual counselling

Individual behavioural counselling did not appear effective at the medium-term follow-up in one study (OR 0.83, 95% CI 0.51 to 1.34)[74] but appeared effective in the long term in one large trial (OR 1.38, 95% CI 1.05 to 1.82).[73] No data were available for short-term follow-up in either study.

Individual and telephone counselling combinations

Two trials[64,69] randomised participants to receive individual counselling plus telephone booster sessions. Pooled analysis of both trials failed to detect a significant effect at medium-term follow-up (pooled OR 1.33, 95% CI 0.94 to 1.90, $I^2 = 4\%$), and at long-term follow-up (pooled OR 0.91, 95% CI 0.63 to 1.32, $I^2 = 0\%$, *Figure 2*). No data were available for short-term follow-up.

Interventions delivered during pregnancy and continued postpartum

Self-help interventions and telephone counselling

A combination of self-help booklets (written materials intended to prevent relapse) and pre- and postpartum telephone counselling exerted a moderately significant effect on abstinence rates at short-term follow-up in one study (OR 1.60, 95% CI 1.15 to 2.23) and in the medium term (OR 1.60, 95% CI 1.16 to 2.21).[65] This effect was not present at long-term follow-up (OR 1.04, 95% CI 0.76 to 1.44).

Individual counselling

One study[71] delivered individual behavioural counselling to participants during pregnancy and postpartum, but failed to detect evidence for an effect at the longest follow-up prior to delivery (OR 0.91, 95% CI 0.46 to 1.79) and at long-term follow-up (OR 1.02, 95% CI 0.53 to 1.96). No data were available for short- and medium-term follow-ups.

Individual and telephone counselling combined

Two trials[66,67] examined the effectiveness of individual counselling followed by pre- and postpartum telephone counselling calls. The interventions did not appear effective at delivery (pooled OR 1.07, 95% CI 0.53 to 2.14, $I^2 = 12\%$) or at medium-term follow-up (pooled OR 1.23, 95% CI 0.80 to 1.88, $I^2 = 0\%$; *Figure 2*). Only one study reported data at short- and long-term follow-ups[66] that found no significant effect at either follow-up.

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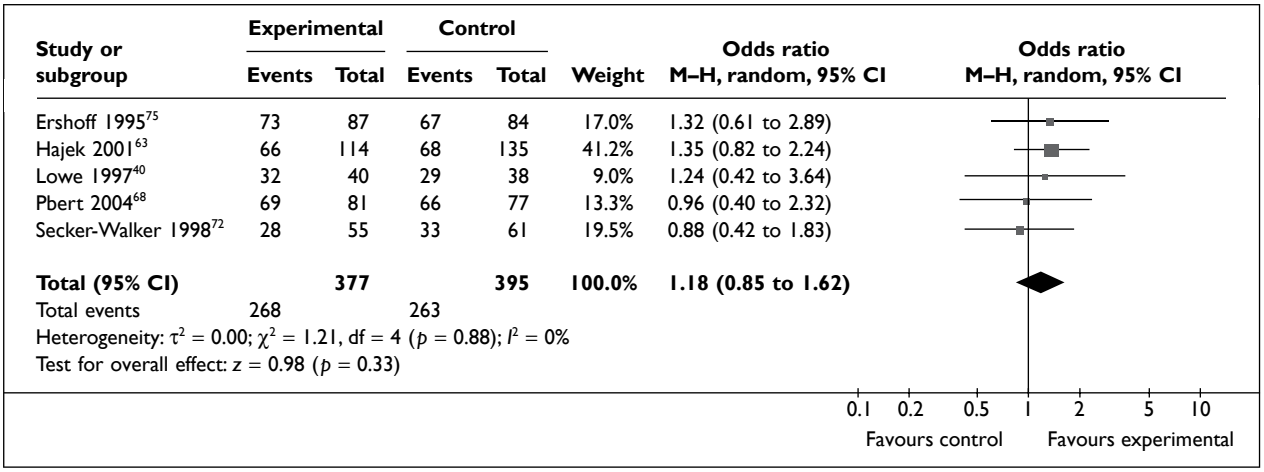

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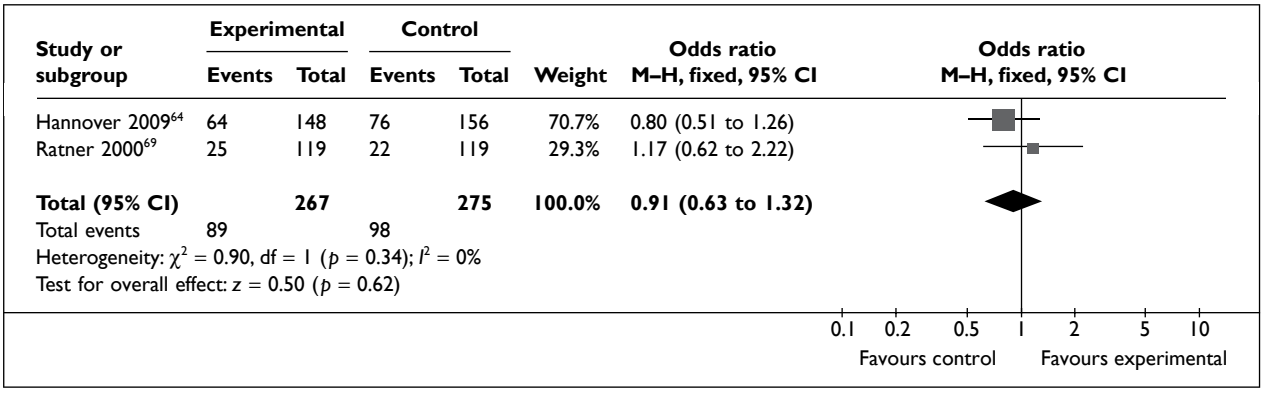

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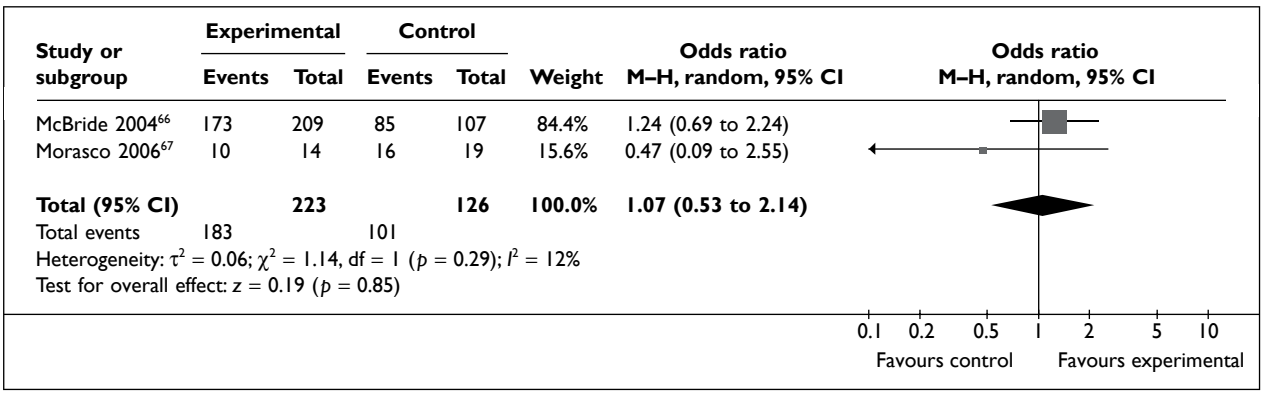

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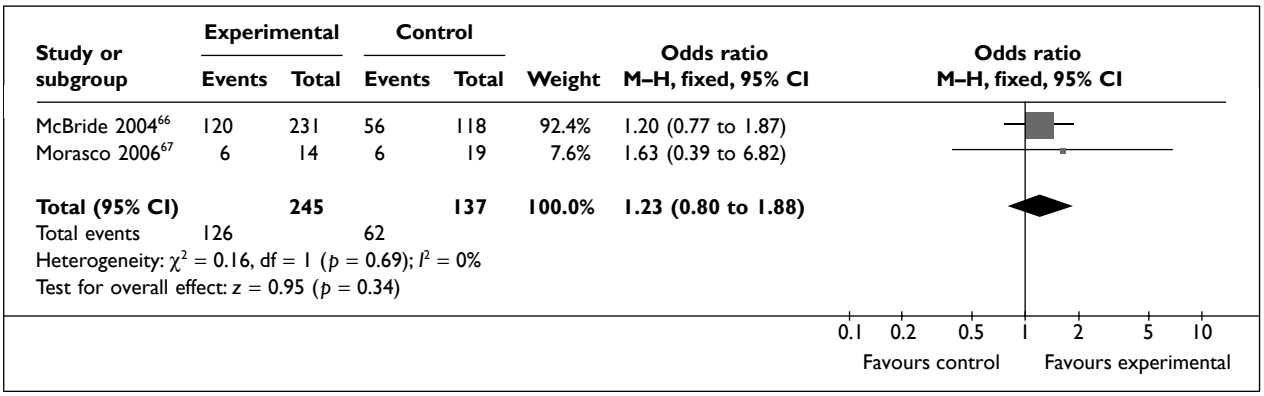


FIGURE 2 *Behavioural relapse prevention interventions in pregnant and postpartum women. (a) Individual counselling delivered during pregnancy at longest follow-up prior to delivery; (b) individual and telephone counselling delivered postpartum at long-term follow-up; (c) individual and telephone counselling delivered during pregnancy and postpartum at longest follow-up prior to delivery; and (d) individual and telephone counselling delivered during pregnancy and postpartum at medium-term follow-up.*

Behavioural interventions in other population groups

There were 14 studies in this category[41,76–88] and *Table 5* summarises these.

Details of included studies

Two studies involved military recruits[41,82] and eight studies community volunteers,[76–79,84,85,87,88] two trials were conducted in hospital in-patients[80,81] and two were conducted in the workplace;[83,86] two studies were conducted in women only.[41,79] We have divided studies in this section according to three types of participant: unaided abstinent smokers (five studies);[76–78,80,81] aided abstinent smokers (seven studies in which participants had achieved abstinence with support from a formal smoking cessation programme);[79,83–88] and individuals undergoing enforced abstinence (two studies).[41,82] The length of abstinence prior to randomisation in trials of unaided abstinent smokers ranged from 1 week to 1 month.

Unaided abstinent smokers

Characteristics of interventions

These five studies examined the effectiveness of self-help booklets and letters, telephone counselling and individual counselling.[76–78,80,81]

Self-help booklets and letters

Three trials assessed the effectiveness of repeated mailings of relapse prevention-orientated booklets and letters:[76–78] one investigated the impact of booklets' content and mailing frequency in a 2×2 factorial design;[78] a second compared mailing of booklets with a 'non-mailing' control group;[77] and a third compared computer-generated (tailored) letters and standard self-help materials.[76] In the former two studies above, participants had achieved at least 1 weeks' abstinence prior to enrolment and in the latter study participants required at least 24 hours' abstinence to participate.

Telephone counselling

One study examined the effectiveness of postdischarge telephone counselling in hospital in-patients who had stopped smoking within 31 days of admission into hospital.[81]

Individual counselling

One study examined the effect of a combination of individual behavioural interventions in individuals admitted to hospital after myocardial infarction (MI) or for cardiac bypass surgery, and who had not smoked since admission. Interventions included verbal advice, a self-help booklet, a written quiz on the contents of the booklet, carbon monoxide readings, signed declaration of commitment, contact with other people giving up and a sticker in hospital notes.[80]

Outcome assessment

Two studies present point prevalence abstinence only;[77,81] three validated smoking status biochemically;[77,80,81] and two reported abstinence at one follow-up point only.[77,78]

Effectiveness of interventions

Two trials detected no effect[79,80] and three studies reported that the interventions appeared effective at preventing relapse to smoking.[76–78]

Analyses

Pooled analysis of data from the three studies of self-help booklets and letters at long-term follow-up indicated a significant effect on abstinence rates[76–78] (pooled OR 1.52, 95% CI 1.15 to 2.01, $I^2 = 0\%$, NNT = 14; *Figure 3*); and one study found

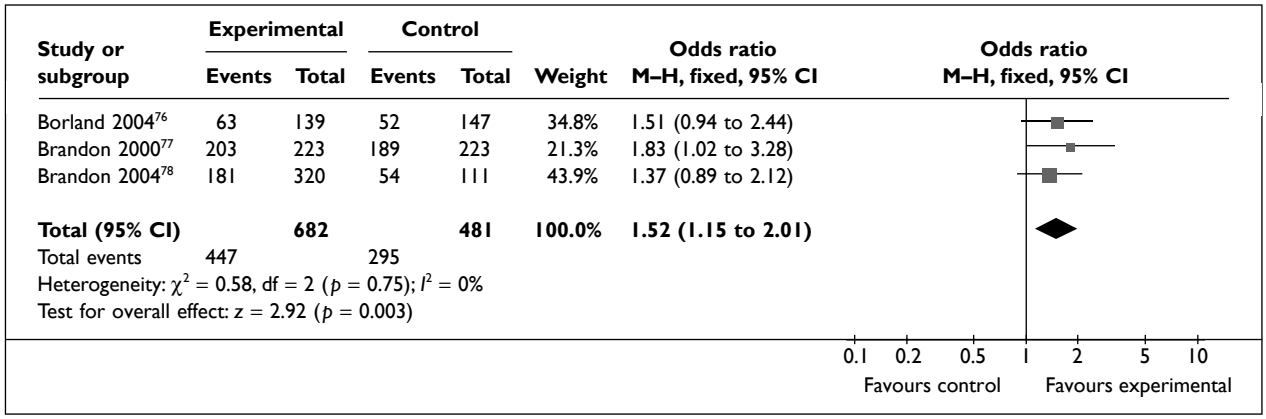


FIGURE 3 *Behavioural relapse prevention interventions in unaided abstinent smokers. Self-help booklets and letters at long-term follow-up.*

TABLE 5 *Behavioural interventions in other population groups*

Study	Setting/ randomisation	Participants	Interventions	Outcome measure/ follow-up points	Verification
Borland *et al.* (2004)[76]	Australia, randomisation by computer-generated numbers	286 smokers who were quit at baseline	Tailored advice letters based on standardised telephone assessment, control group received No extra treatment, sent printed self-help materials for 12 months	Continuous abstinence at medium and long term	None, self-report only
Brandon *et al.* (2000)[77]	USA, randomisation method not stated	446 ex-smokers, abstinent at least 7 days at baseline	Four groups: Single booklet at the time of enrolment Single booklet and hotline number Eight booklets mailed at enrolment, 1, 2, 3, 5, 7, 9 and 12 months Eight booklets and hotline number	Point prevalence abstinence at long term	None, self-report only
Brandon *et al.* (2004)[78]	USA, randomisation method not stated	Community volunteers, 431 abstinent at time of baseline assessment	Four groups: Single booklet at time of enrolment Repeated mailings at enrolment, 1, 2, 3, 5, 7, 9 and 12 months Massed mailing of all eight booklets at once Repeated letters at same intervals as repeated mailings and single booklet at enrolment	Continuous abstinence at long term only	Carbon monoxide verified self-reported abstinence
Conway *et al.* (2004)[41]	USA, naval training, cluster randomisation by division	1682 female navy recruits, abstinent for 2 months during training	Three groups: Standard treatment (control): the recruit training ban and small amount of health education Mail Intervention group: regular mailings with incentive items and standard treatment Telephone helpline group: access to helpline and standard treatment Smoking was banned for 8 weeks	Point prevalence abstinence at short, medium and long term	Self-report only
Copeland *et al.* (2006)[79]	USA, random assignment sequence generated by statisticians	76 abstinent participants at the end of initial smoking cessation treatment	A 2-week smoking cessation treatment. At the end of 2 weeks, participants were randomised to: Individually tailored cessation maintenance and dietary and weight-control intervention Group cessation therapy and dietary and weight-control intervention Interventions were delivered in six sessions spread over 38 weeks	Continuous abstinence at short and medium terms	Carbon monoxide verified self-reported abstinence

continued

TABLE 5 *Behavioural interventions in other population groups (continued)*

Study	Setting/ randomisation	Participants	Interventions	Outcome measure/ follow-up points	Verification
Hajek *et al.* (2002)[80]	UK, randomisation via serially numbered opaque, sealed envelopes	540 smokers or recent quitters who had not smoked since hospital admission	Single session intervention lasting 20–30 minutes including carbon monoxide reading, booklet on smoking and cardiac recovery, commitment, reminders Verbal advice, smoking cessation booklet	Continuous abstinence at short and long term	Carbon monoxide verified abstinence
Hasuo *et al.* (2004)[81]	Japan, computer-generated randomisation	106 hospital in-patient volunteers who had quit smoking 31 days prior to recruitment	Telephone counselling at 7, 21 and 42 days postdischarge Control: no additional contact. All received nurse-mediated behaviourally oriented in-patient counselling focused on relapse prevention	Point prevalence abstinence at short, medium and long term	Urine cotinine verified
Klesges *et al.* (1999)[82]	USA, cluster randomisation	18,010 air force recruits, underwent enforced abstinence during training	Single, adjunctive 50-minute intervention geared to convince recruits to stay quit after smoking ban Smoking ban	Point prevalence abstinence at long term	Self-reported only
Mayer *et al.* (2006)[83]	Belgium, randomisation by company	275 workers at 42 companies who had undergone cessation treatment with 3-month smoking cessation programme	Workplace group counselling: 10 sessions bimonthly during the first month, and monthly in the remaining 8 months; each session lasted 1 hour 30 minutes Proactive telephone counselling: 10 sessions, bimonthly during the first month, and monthly afterwards; each telephone call lasted a minimum of 10 minutes	Point prevalence abstinence at medium term	Carbon monoxide verified abstinence
Mermelstein *et al.* (2003)[84]	USA, cluster randomisation by group	341 abstinent participants at the end of 7-week group cessation programme	Weekly proactive, intensive telephone calls for 3 weeks, followed by three telephone calls on alternate weeks, 15 minutes per call Non-specific guidance, words of encouragement at same times as above	Point prevalence abstinence at long term	Carbon monoxide verified
Powell and McCann (1981)[85]	USA, randomisation method not stated	51 abstinent community volunteers	Three groups: 4-week support group Telephone contact system which allowed subjects to telephone one another No contact control group	Point prevalence abstinence at short, medium and long terms	Self-reported abstinence only
Razavi *et al.* (1999)[86]	Belgium, randomisation by company, using random numbers	344 participants abstinent at the end of 3-month cessation programme	10 monthly sessions led by trained counsellor 10 monthly group sessions led by former group smokers No relapse prevention treatment	Continuous abstinence at medium term	Carbon monoxide verified abstinence

TABLE 5 *Behavioural interventions in other population groups (continued)*

Study	Setting/ randomisation	Participants	Interventions	Outcome measure/ follow-up points	Verification
Smith *et al.* (2001)[87]	USA, randomisation method not stated	677 community volunteers, abstinent at the end of 1-week group orientation meetings and two individual counselling sessions	Three groups: CBT – six 90-minute sessions in 4 weeks MI – six 90-minute sessions in 4 weeks No additional treatment	Point prevalence abstinence at medium and long term	Carbon monoxide verified abstinence
Stevens and Hollis (1989)[88]	USA, randomisation by predetermined number list	587 abstinent smokers after 4-day cessation programme	Skills training programme, three sessions, subjects developed coping strategies for likely relapse situations Discussion control condition, three sessions, subjects discussed maintenance, and not relapse prevention No treatment control	Continuous abstinence at short, medium and long term	Carbon monoxide verified abstinence

CBT, cognitive behaviour therapy; MI, motivational interviewing.

significant increases in abstinence rates at medium-term follow-up (OR 1.72; 95% CI 1.01 to 2.92).[76] No data were available for short-term follow-up.

Telephone counselling did not have an effect on abstinence rates at any of the three follow-ups respectively (short term, OR 1.52, 95% CI 0.59 to 3.92; medium term, OR 1.06, 95% CI 0.47 to 2.38; long term, OR 1.23, 95% CI 0.57 to 2.64).

Individual counselling did not appear to have an effect on abstinence rates in the short and long terms respectively (OR 1.04, 95% CI 0.73 to 1.47; OR 0.86, 95% CI 0.60 to 1.23). No data were available for medium-term follow-up.

Aided abstinent smokers

Characteristics of interventions

Of these seven studies,[79,83–88] four investigated behavioural counselling delivered to groups,[85–88] one[84] studied the effect of telephone call content, one[83] compared proactive telephone counselling to workplace group counselling and another[79] examined the effect of individual behavioural counselling.

Group counselling

These four trials compared group behavioural counselling to usual care or no intervention.[85–88] One study randomised participants who had achieved 1 weeks' abstinence with counselling and NRT,[87] two after 1 week[88] and 5 days[85] of group counselling and, in one trial, 3 months' abstinence, achieved with group behavioural support and NRT,[86] were required before randomisation.

Telephone counselling (content)

One study assessed the effect of the content of telephone calls, randomising participants into a 'basic' content group or 'enhanced' content group;[84] they received group counselling and pharmacotherapy in a 7-week abstinence period prior to randomisation.

Telephone counselling (proactive)

One study[83] compared workplace group counselling to proactive telephone counselling; participants were abstinent for 3 months, using a smoking cessation programme prior to randomisation.

Individual counselling

One study[50] randomised abstinent smokers who had achieved abstinence with 2 weeks of group counselling to receive either group-based or individually-tailored relapse prevention treatment; the authors hypothesised that smoking abstinence rates would be higher in individuals assigned to the individually-tailored intervention.

Outcome assessment

One study reported point prevalence and continuous abstinence rates,[79] four trials reported point prevalence only[83–85,87] and two studies presented continuous abstinence only;[86,88] all trials biochemically validated outcomes.

Effectiveness of interventions

Interventions in four trials were reportedly effective at reducing relapse rates,[79,84,85,88] but the remaining trials had negative outcomes.[83,86,87]

Analyses

Pooled analysis of data from two studies of group behavioural counselling at short-term follow-up appeared to have a significant effect (pooled OR 2.55, 95% CI 1.58 to 4.11, $I^2 = 0\%$),[85,88] but a pooled analysis of data from four studies at the medium-term follow-up did not detect a significant effect (pooled OR 1.20; 95% CI 0.72 to 2.00, $I^2 = 68\%$),[85–88] and a pooled analysis of data from three of the studies at the long-term follow-up point also did not detect a significant effect (pooled OR 0.98, 95% CI 0.55 to 1.76, $I^2 = 63\%$; *Figure 4*).[85,87,88]

Enforced abstinent smokers

Characteristics of interventions

Two studies[41,82] assessed the effect of behavioural interventions in individuals that were undergoing enforced abstinence.

Group counselling

One study[82] randomised military personnel after 6 weeks of a smoking ban and presented abstinence at long-term follow-up only.

Telephone counselling

One study[41] randomised military personnel into either a telephone counselling group, a self-help group and a control group after 8 weeks of a smoking ban respectively.

Outcome assessment

Both trials presented point prevalence abstinence, and neither validated outcomes.

Effectiveness of interventions/analyses

The group counselling intervention did not appear effective at long-term follow-up (OR 0.93, 95% CI 0.85 to 1.02). Telephone counselling was effective in the short term (OR 1.26, 95% CI 1.06 to 1.49); however, the effect was lost in the medium term (OR 0.89, 95% CI 0.76 to 1.05) and in the long term (OR 0.96, 95% CI 0.82 to 1.13).

Pharmacotherapy interventions

Table 6 gives details of all trials involving pharmacotherapy interventions.

Pharmacotherapy interventions – bupropion

Details of included studies

Of the eight pharmacotherapy trials,[33–39,89] four assessed the effectiveness of bupropion for relapse prevention;[33,34,36,37] two of these also examined the effects of bupropion and NRT combined, and NRT alone.[33,34] Participants in all trials were community volunteers and participants were treated in the following ways prior to randomisation: bupropion and NRT for 8 weeks,[33] NRT patch for 8 weeks[37] or bupropion treatment for 7 weeks[36] or 3 months.[34] In two studies, participants still smoking at the end of open-label treatment were treated for an additional 3 months,[34] and 8 weeks[37] respectively until they became abstinent.

Characteristics of interventions

Abstinent participants at the end of open-label treatment received bupropion for 16 weeks,[33] 6 months,[37] 9 months[34] and 45 weeks.[36] Identical placebos and additional behavioural counselling were used in all four studies.

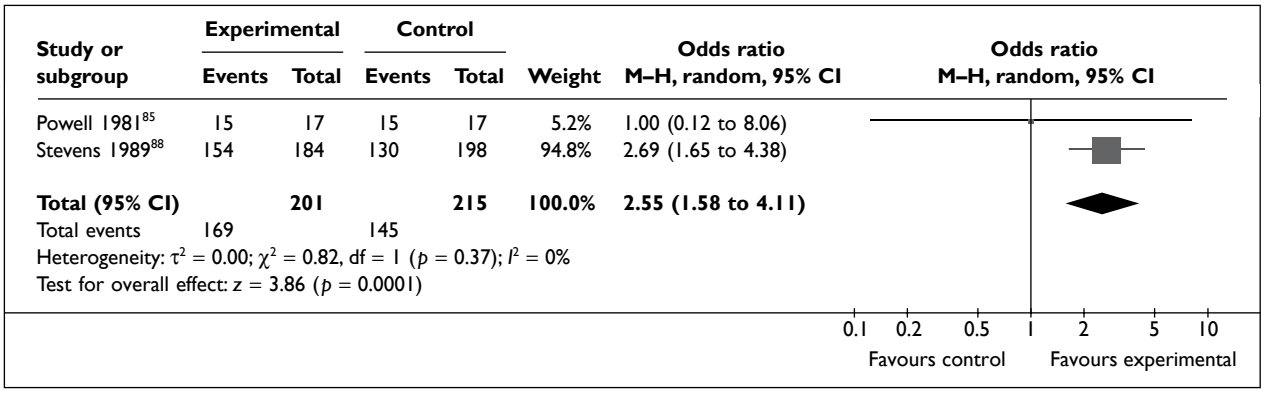
Outcome assessment

All trials validated self-reported smoking status biochemically. One reported both point prevalence and continuous abstinence as primary outcomes,[36] two presented point prevalence abstinence[34,37] and one reported time to relapse as a primary outcome.[33] Two studies reported abstinence data at seven follow-up points after randomisation,[36,37] one at 12 follow-up points after randomisation[34] and another at 14 follow-up points after randomisation.[37]

Effectiveness of interventions

In three studies[33,34,36] maintenance treatment with bupropion appeared to exert a modest benefit for preventing relapse. In two studies,[33,36] bupropion's advantage diminished when the treatment period ended. In the two trials that also combined NRT and bupropion, one found that the combination did not reduce relapse rates,[33] while the other study reported that NRT and bupropion combination reduced relapse rates.[34]

a)



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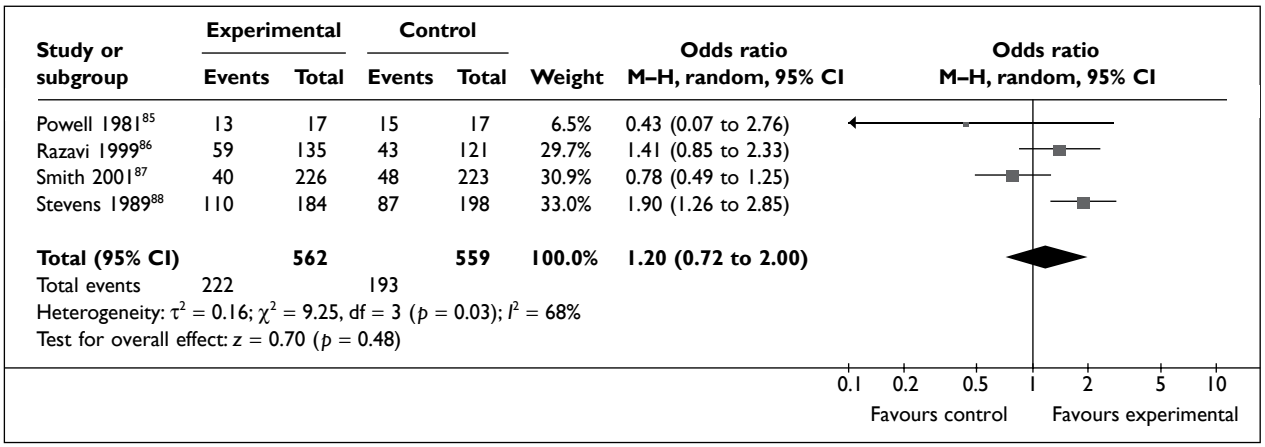

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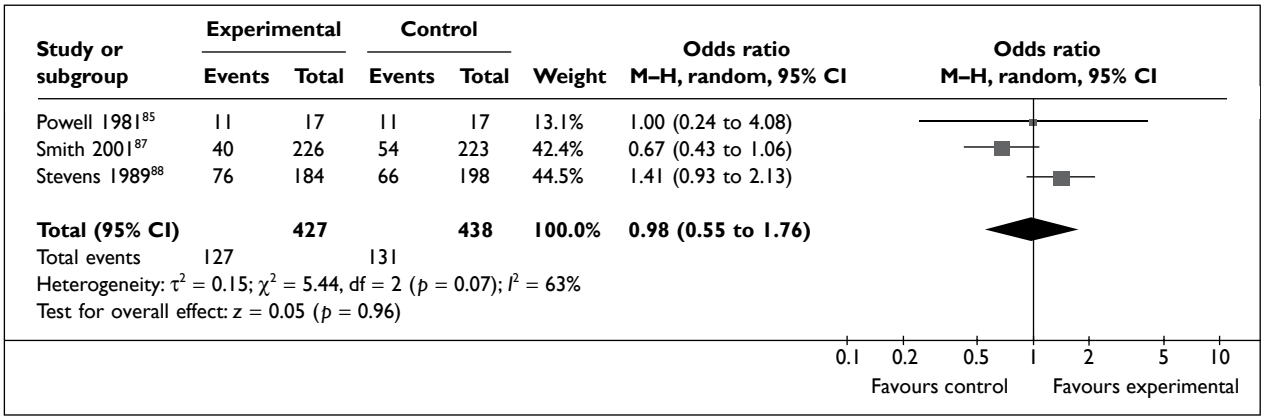

FIGURE 4 *Behavioural relapse prevention interventions in aided abstinent smokers. (a) Group counselling at short-term follow-up; (b) group counselling at medium-term follow-up; and (c) group counselling at long-term follow-up.*

Analyses

Pooled analysis of two heterogeneous trials of bupropion did not detect any effect in the short term (pooled OR 1.38, 95% CI 0.64 to 2.96; $I^2 = 76\%$; *Figure 5*),[36,37] or with the inclusion of other studies, in the medium term (pooled OR 1.56, 95% CI 0.95 to 2.56, $I^2 = 56\%$). However, the estimated effect for relapse prevention treatment with bupropion reached statistical significance when assessed at long-term follow-up (pooled OR 1.49, 95% CI 1.10 to 2.01, $I^2 = 0\%$; NNT = 11, four studies). Pooled analysis of two trials that combined bupropion and NRT did not show any effect in either the medium term (pooled OR 1.94, 95% CI 0.50 to 7.51, $I^2 = 64\%$; *Figure 6*) or long term (pooled OR 1.31, 95% CI 0.46 to 3.79, $I^2 = 30\%$; *Figure 6*). No data were available for short-term follow-up analysis.

Pharmacotherapy interventions – nicotine replacement therapy

Details of included studies

Four trials assessed the impact of NRT on relapse rates;[33–35,38] two used factorial designs,[33,34] one was a 2 × 2 factorial design[35] and the other a 4 × 3 crossed factorial design.[38] All randomised community volunteers; two included participants who had achieved unaided abstinence for 24 hours[35] and 48 hours[38] respectively. In the remaining two trials, participants received open-label treatment with bupropion and NRT patch for

TABLE 6 *Pharmacotherapy interventions*

Study	Setting/ randomisation	Participants	Interventions	Outcome measure/follow-up points	Verification
Covey *et al.* (2007)[33]	USA, computer-generated randomisation	294 abstinent smokers at the end of 8-week open-label bupropion and nicotine patch	All abstinent at the end of 8 weeks randomised to 16 weeks of: Bupropion and nicotine gum Bupropion and placebo gum Nicotine gum and placebo pill Placebo pill and placebo gum	Point prevalence abstinence at medium and long term	Carbon monoxide verified self-reported abstinence
Croghan *et al.* (2007)[34]	USA, Pocock–Simon randomisation, stratified	405 smokers who were quit after 3 months of open-label treatment with either bupropion (300-mg SR); or nicotine inhaler (16 cartridges/ day) or both	Nicotine inhaler or placebo Bupropion or placebo Nicotine inhaler combined with placebo bupropion Placebo inhaler combined with bupropion Nicotine inhaler combined with bupropion Placebo inhaler combined with placebo bupropion. Additional counselling was provided, all participants received smoking cessation booklet. All treatments were administered for 36 weeks	Point prevalence abstinence at medium and long term	Carbon monoxide verified self-reported abstinence
Fortmann and Killen (1995)[35]	USA, randomisation method not stated	1044 smokers quit for 24 hours	Participants randomised into: Nicotine gum only Self-help materials Nicotine gum and self-help materials Monetary incentive only Interventions administered for 6 months	Point prevalence abstinence at short, medium and long term	Carbon monoxide verified self-reported abstinence
Hays *et al.* (2001)[36]	USA, computer-generated randomisation	429 smokers who were quit after 7 weeks open-label bupropion	Bupropion, 300 mg/day for 45 weeks Placebo All received physician advice, self-help booklets and brief individual counselling at follow-ups	Continuous abstinence at short, medium and long term	Carbon monoxide verified abstinence
Hurt *et al.* (2003)[37]	USA, randomisation by dynamic allocation, stratified	176 smokers who were abstinent after 8 weeks of nicotine patch therapy	Bupropion 300 mg/day for 6 months Placebo	Point prevalence abstinence at short, medium and long term	Carbon monoxide verified abstinence

TABLE 6 *Pharmacotherapy interventions (continued)*

Study	Setting/ randomisation	Participants	Interventions	Outcome measure/follow-up points	Verification
Killen *et al.* (1990)[38]	USA, method of randomisation not stated	1218 smokers who had quit for 48 hours	Nicotine gum ad lib (whenever there's urge to smoke) Nicotine gum fixed (one piece for at least 12 hour/ day) Placebo gum No gum Interventions administered for 6 months	Point prevalence abstinence at short, medium and long term	Carbon monoxide verified abstinence
Niaura (2005)[39]	Multiple country study	1661 successful quitters after 10 weeks of 5-mg or 20-mg rimonabant	Rimonabant 20 mg/day Rimonabant 5 mg/day Placebo Treatment was for 1 year	Point prevalence abstinence at short and medium term	Carbon monoxide verified
Tonstad *et al.* (2006)[89]	Multiple country, computer-generated randomisation sequence, stratified by centre	1210 abstinent participants at the end of 12 weeks of open-label treatment with varenicline	All participants received 10-minute counselling sessions at each clinic visit Varenicline, 1 mg twice daily for additional 12 weeks Placebo, 1 mg twice daily for additional 12 weeks	Continuous abstinence at short and medium term	Carbon monoxide verified abstinence

8 weeks[33] or NRT inhaler for 3 months[34] to achieve abstinence. NRT gum was the relapse prevention treatment in two trials,[35,38] one used NRT inhaler[34] and the final trial used NRT patch;[33] and one trial provided a monetary incentive for participants.[35]

Characteristics of interventions

One trial was not a placebo RCT and compared different doses of NRT gum and different intensities of behavioural self-help interventions with each other;[35] the behavioural interventions compared comprised self-help relapse prevention materials and no intervention. One study randomised participants into four different NRT gum-dosing regimens and three levels of self-guided behavioural intervention;[38] participants received NRT gum for 16 weeks after randomisation,[33] and NRT inhaler for 9 months after randomisation[34] in two studies respectively.

Outcome assessment

Three studies reported point prevalence abstinence[34,35,38] and all validated self-reported outcomes biochemically. One study reported abstinence data at 12 follow-up points after randomisation,[34] another at 14 follow-up points[33] and remaining trials reported abstinence at three follow-up points.[35,38]

Effectiveness of interventions

In one trial,[33] gum use was reported as low, but this appeared effective at reducing relapse rates and in another, NRT had no statistically significant effect[34] and in two studies NRT appeared effective in reducing relapse to smoking in the long term.[35,38]

Analyses

Pooled analysis of the two trials of NRT which assessed effectiveness at short-term follow-up was not performed due to high levels of heterogeneity ($I^2 = 85\%$), but results from these individual studies both showed statistically significant increases in the odds of abstinence (*Figure* 7).[35,38] More conclusive evidence of an effect for NRT was seen in a pooled analysis of these studies and two more smaller trials with low levels of heterogeneity, at the medium- (pooled OR 1.56, 95% CI 1.16 to 2.11, $I^2 = 37\%$, NNT = 14, four trials) and long-term follow-ups (pooled OR 1.33, 95% CI 1.08 to 1.63, $I^2 = 0\%$, NNT = 20, four trials).

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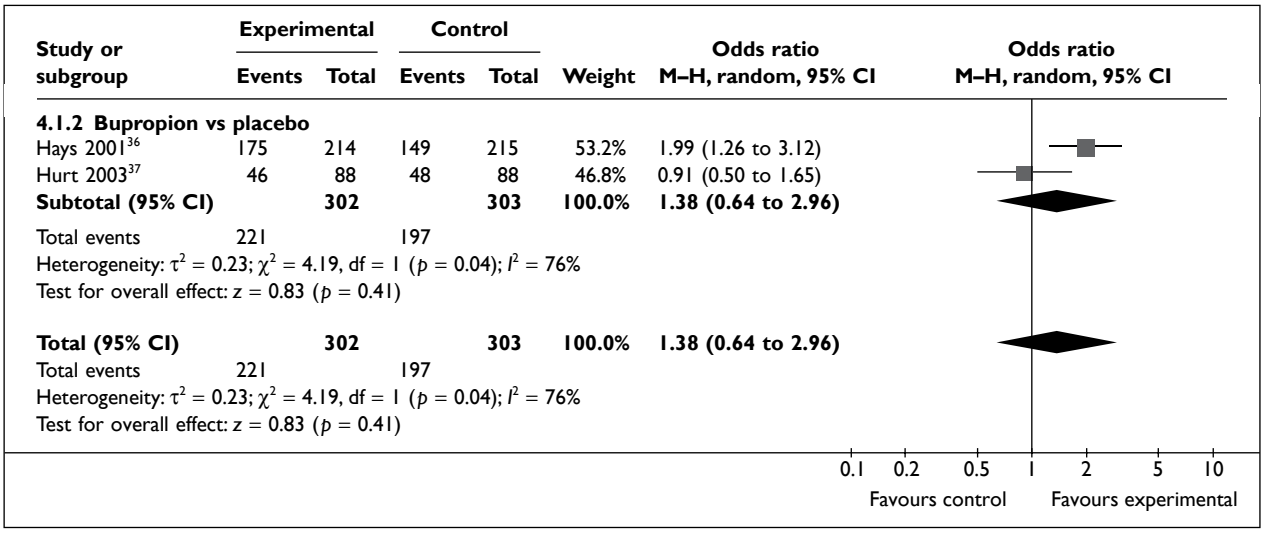

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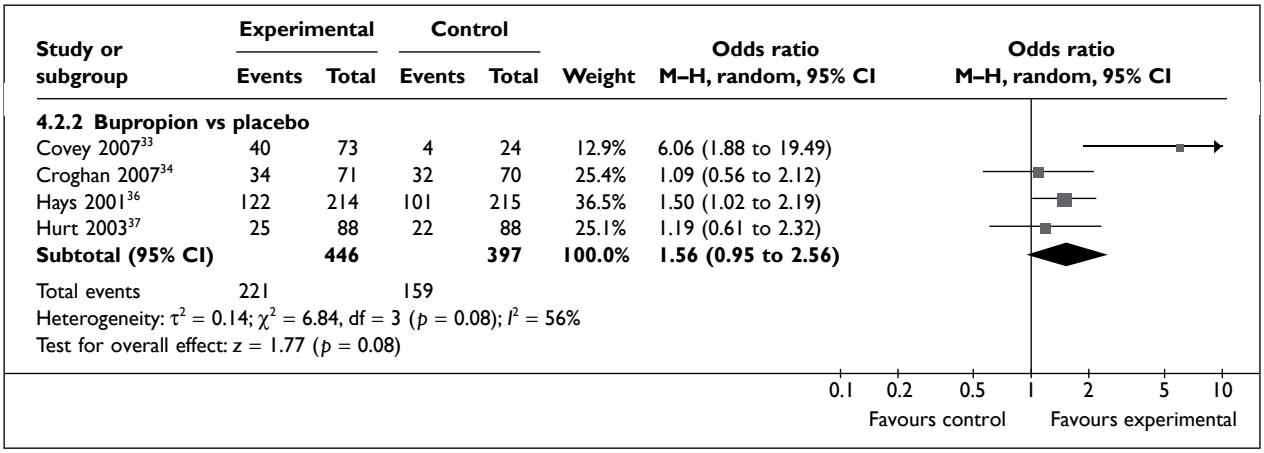

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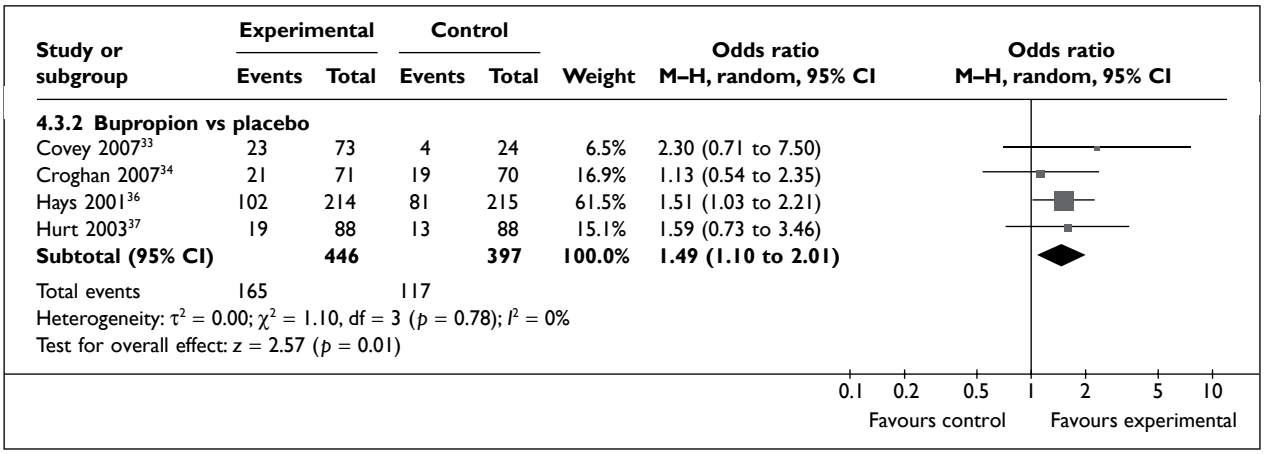

FIGURE 5 *Bupropion for relapse prevention. Participants were randomised after variable treatment periods with either open-label bupropion and/or nicotine replacement patch. (a) Short-term follow-up; (b) medium-term follow-up; and (c) long-term follow-up.*

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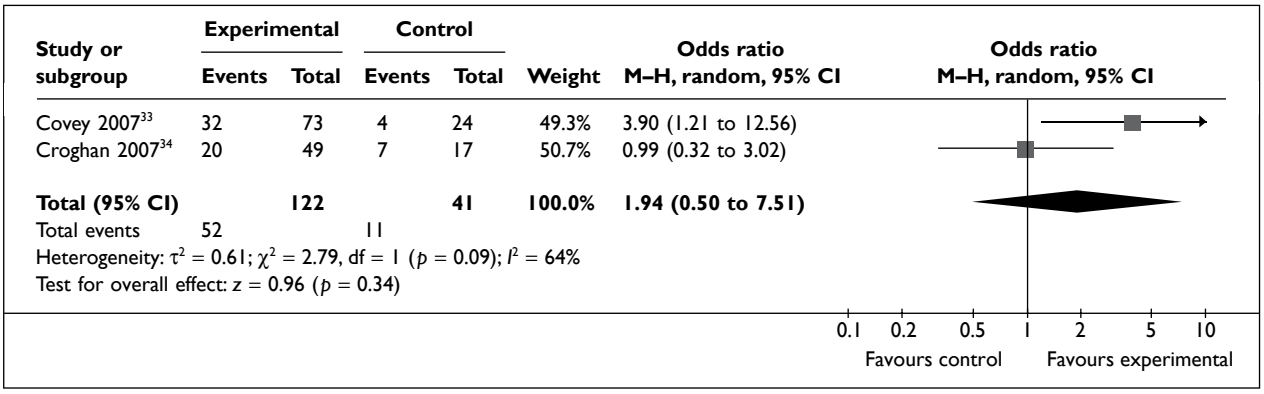

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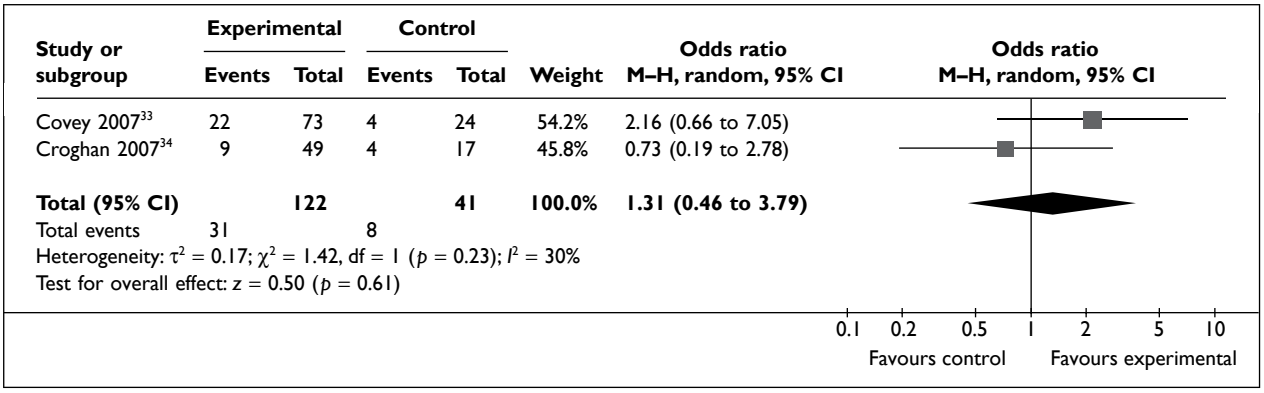


FIGURE 6 *Bupropion and NRT for relapse prevention. Participants were randomised after variable treatment periods with bupropion and NRT. (a) Medium-term follow-up; and (b) long-term follow-up.*

Pharmacotherapy interventions – varenicline

Details of included study

One trial of varenicline[89] was included; community volunteers treated at multiple medical clinics in seven countries were enrolled.

Characteristics of intervention

Participants received smoking cessation counselling at each clinic visit and either varenicline 1 mg or identical placebo twice daily for 12 weeks after an initial 12 weeks of open-label treatment (0.5 mg varenicline for the first 3 days, 0.5 mg twice daily for the next 4 days, and 1 mg twice daily for 11 weeks).

Outcome assessment

Point prevalence and continuous abstinence were reported at 10 follow-up points and biochemically validated.

Effectiveness of intervention

A significant effect for varenicline was detected in the short-term (OR 2.54, 95% CI 1.93 to 3.36, NNT = 6) and medium-term (OR 1.40, 95% CI 1.12 to 1.76, NNT = 12) follow-ups. No data were available for longer-term follow-up.

Pharmacotherapy interventions – rimonabant

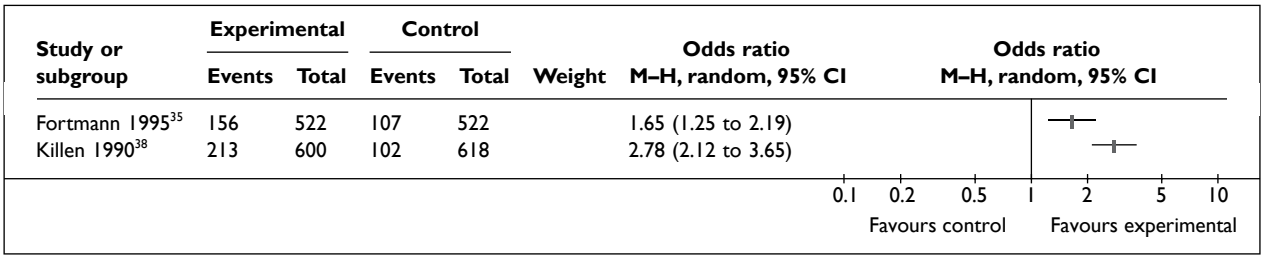
Details of included study

One study of rimonabant, conducted in three countries, was included.[39]

Characteristics of intervention

Smokers were initially randomised to receive either 5-mg rimonabant or 20-mg rimonabant for 10 weeks and those who achieved abstinence were rerandomised to either 5-mg or 20-mg rimonabant daily or identical placebos for 42 weeks, followed by a 50-week non-treatment follow-up period.

a)



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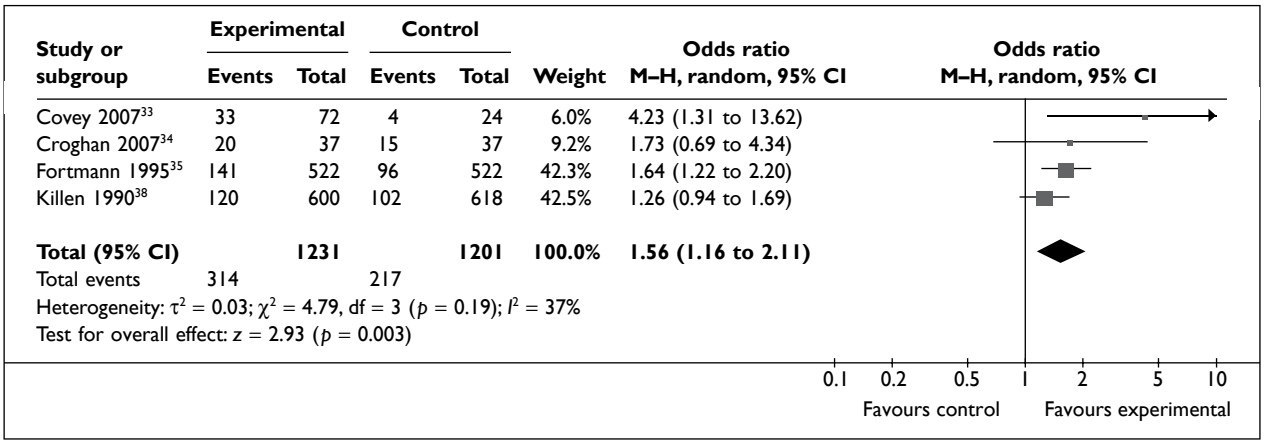

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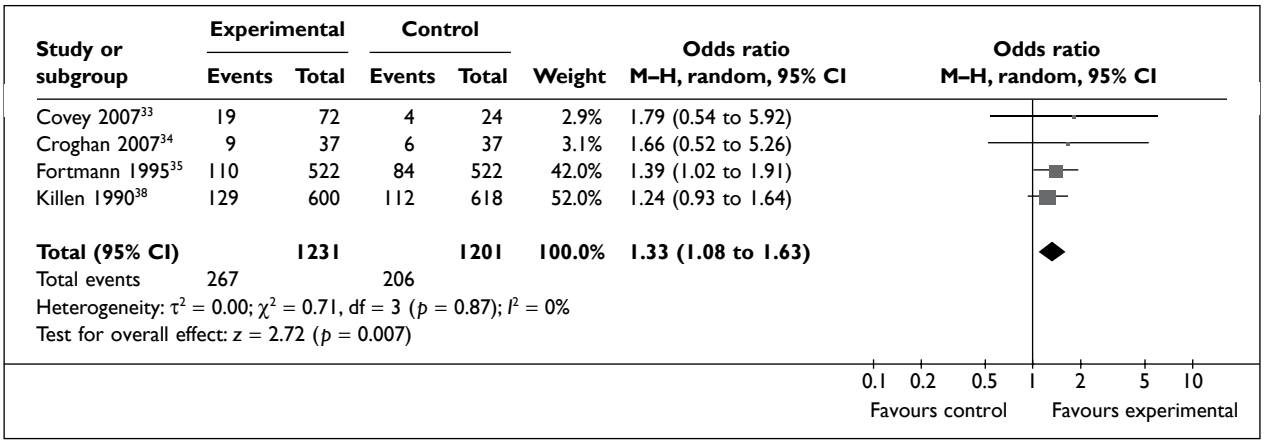

FIGURE 7 *Nicotine replacement therapy for relapse prevention. Participants randomised after unassisted abstinence or variable treatment periods with nicotine inhaler or bupropion plus nicotine replacement patch. (a) Short-term follow-up; (b) medium-term follow-up; and (c) long-term follow-up.*

Outcome assessment

Self-reported abstinence from smoking was verified biochemically, with abstinence data reported at 18 follow-up points.

Effectiveness of intervention

Treatment with rimonabant appeared to reduce rates of relapse to smoking, with OR 1.67 (95% CI 1.14 to 2.46) in the short term and OR 1.48 (95% CI 1.14 to 1.93) in the medium term.

Studies randomising smokers

Behavioural interventions matched for programme length

Details of included studies

Nine of the 18 trials that randomised smokers tested relapse prevention-orientated interventions in behavioural programmes, investigating the impact of RPI programme content by matching

programme length but varying contents in intervention and control groups;[42–46,48–51] details are given in *Table 7*. One study included only women with either confirmed coronary artery disease or risk factors for this,[50] another enrolled workplace volunteers in four local businesses.[51] The seven remaining studies recruited community volunteers.[42–46,48,49] All studies in this category reported demographic characteristics of participants except one.[43] One trial used a 2 × 2 factorial design.[48]

Characteristics of interventions

Seven studies randomised participants into either a treatment or control group;[42–44,46,48,50,51] one trial had four treatment groups,[49] and one, three.[45] Participants in three trials received NRT in addition to behavioural treatment.[43,49,51] In one trial,[48] eight of the 14 treatment sessions also involved 6 and 30 second aversive smoking. Subjects were instructed to inhale on three consecutive cigarettes of their usual brand either every 6 or 30 seconds. The subjects were encouraged while smoking, to focus on the negative aspects of smoking, and subjects were videotaped, and replayed to the subject after the session. The remaining six sessions comprised either a skills training treatment or a discussion control.

One trial compared a behavioural programme that placed emphasis on absolute abstinence to a RPI and evaluated each programme in group and self-help formats.[44] One study randomised participants into a control group that received standard treatment, an enhanced control group that received standard treatment in addition to discussions of 11 problem situations and an

TABLE 7 *Behavioural interventions matched for programme length*

Study	Setting/ randomisation	Participants	Interventions	Outcome measure/ follow-up points	Verification
Becona and Vazquez (1997)[42]	Spain, randomisation method not stated	76 community volunteers, all smokers at baseline	Standard behavioural intervention (control group) Relapse prevention group Interventions administered for 8 weeks	Point prevalence abstinence at short, medium and long term	Carbon monoxide verified self-report
Buchkremer *et al.* (1991)[43]	Germany, randomisation method not stated	74 community volunteers	Self management with training in relapse coping strategies Self management without training in relapse coping strategies Interventions administered for 9 weeks	Point prevalence abstinence at short, medium and long term	Self-report only
Curry *et al.* (1988)[44]	USA, randomisation method described	139 community volunteers, 48 randomised to two types of group treatment	Relapse prevention group Absolute abstinence group	Point prevalence abstinence at medium and long term	Saliva thiocyanate verified abstinence
Davis and Glaros (1986)[45]	Canada, randomisation method described	45 community volunteers	Experimental Enhanced control Control Interventions administered for 8 weeks in all three groups	Point prevalence abstinence at short, medium and long term	Carbon monoxide verified self-report
Emmons *et al.* (1988)[46]	USA, randomisation method described	49 community volunteers	Broad spectrum group Relapse prevention group Interventions administered for 8 weeks in both groups	Point prevalence abstinence at medium and long term	Saliva thiocyanate verified self-reported abstinence

continued

TABLE 7 *Behavioural interventions matched for programme length (continued)*

Study	Setting/ randomisation	Participants	Interventions	Outcome measure/ follow-up points	Verification
Hall *et al.* (1984)[48]	USA, randomisation method not stated	135 community volunteers	Skills training Discussion control Interventions administered for 6 weeks in both groups	Point prevalence abstinence at medium and long term	Carbon monoxide verified self-reported smoking status
Niaura *et al.* (1999)[49]	USA, randomisation method not stated	129 community volunteers	Brief cognitive behavioural group Cognitive behavioural with nicorette gum Cognitive behavioural and cue exposure Cognitive behavioural, cue exposure and nicorette gum Interventions administered in six sessions over 3 weeks in all four groups	Point prevalence abstinence at short, medium and long term	Carbon monoxide verified self-reported smoking status
Schmitz *et al.* (1999)[50]	USA, randomisation method not stated	160 women with either coronary artery disease or risk factors for coronary artery disease	Coping skills relapse prevention Health belief model Interventions administered over 6 weeks	Point prevalence abstinence at short and medium terms	Carbon monoxide verified self-report
Schroter *et al.* (2006)[51]	Germany, randomisation method described	79 workplace volunteers at four businesses	Relapse prevention Standard behavioural treatment Interventions administered over 8 weeks. Participants also received NRT	Continuous abstinence at short and long term	Self-report only

experimental group that received cognitive behavioural skills training aimed specifically at preventing relapse.[45] Another study in this category randomised smokers to receive, for 8 weeks, either in the relapse prevention group, 12 hours of treatment and self-help booklets containing homework exercises, and a 'broad spectrum' group in which participants were provided with group support during times when the most difficulty with cessation was anticipated.[46] In one study, participants in the workplace received either a standard behavioural treatment over 8 weeks which focused on monitoring smoking behaviour and setting a quit date, or a RPI which focused on analysis of, and development of, coping strategies for prototypical high-risk situations.[51]

Outcome assessment

Five trials validated abstinence with exhaled carbon monoxide,[42,45,48–50] two used saliva thiocyanate,[44,46] and two used no validation.[43,51] One study reported both point prevalence and continuous abstinence[51] and remaining studies reported point prevalence abstinence only.

Effectiveness of interventions

One trial reported that the interventions were effective in reducing relapse to smoking[48] and the remaining trials had negative results.

Analyses

Pooled analysis of nine trials[42–46,48–51] in the short term did not detect evidence for the effectiveness of behavioural interventions among smokers; OR 0.67 (CI 0.44 to 1.01, $I^2 = 14\%$). No evidence for the effectiveness of these interventions was detected in the medium- and long-term analyses; OR 0.99 (CI 0.71 to 1.39, $I^2 = 0\%$, seven trials) and OR 1.09 (CI 0.72 to 1.67, $I^2 = 14\%$, seven trials) respectively (*Figure 8*).

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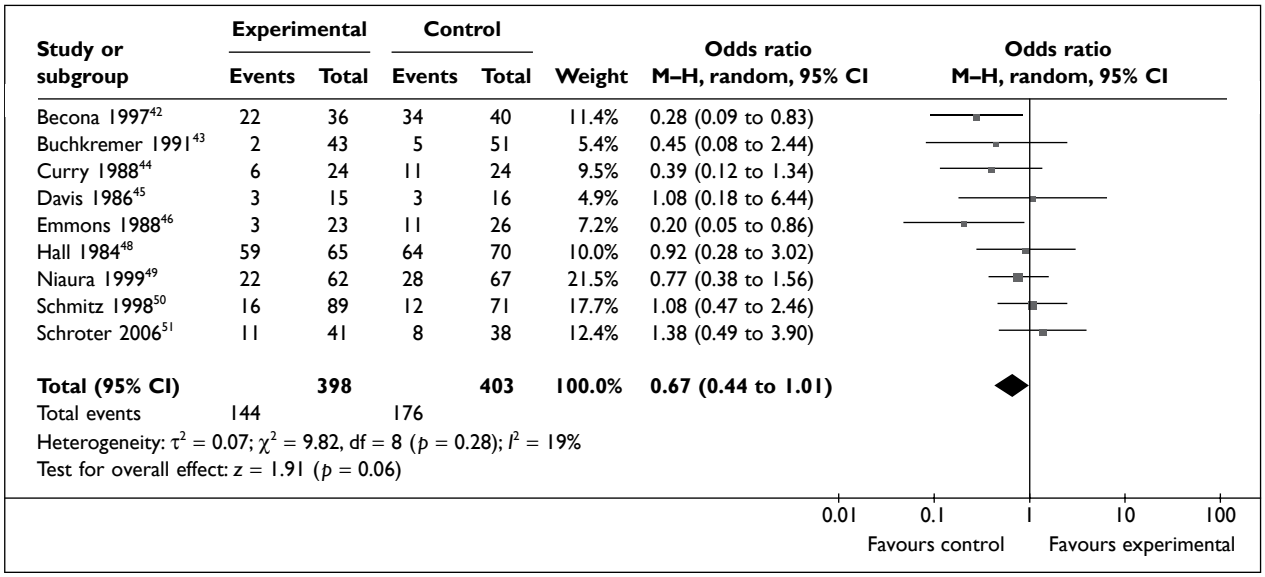

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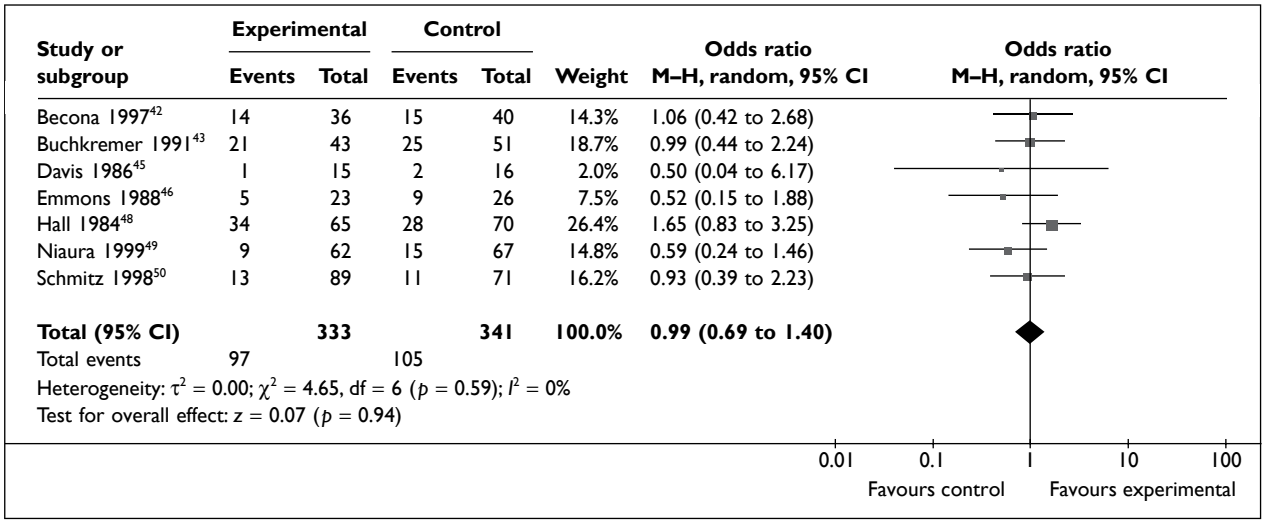

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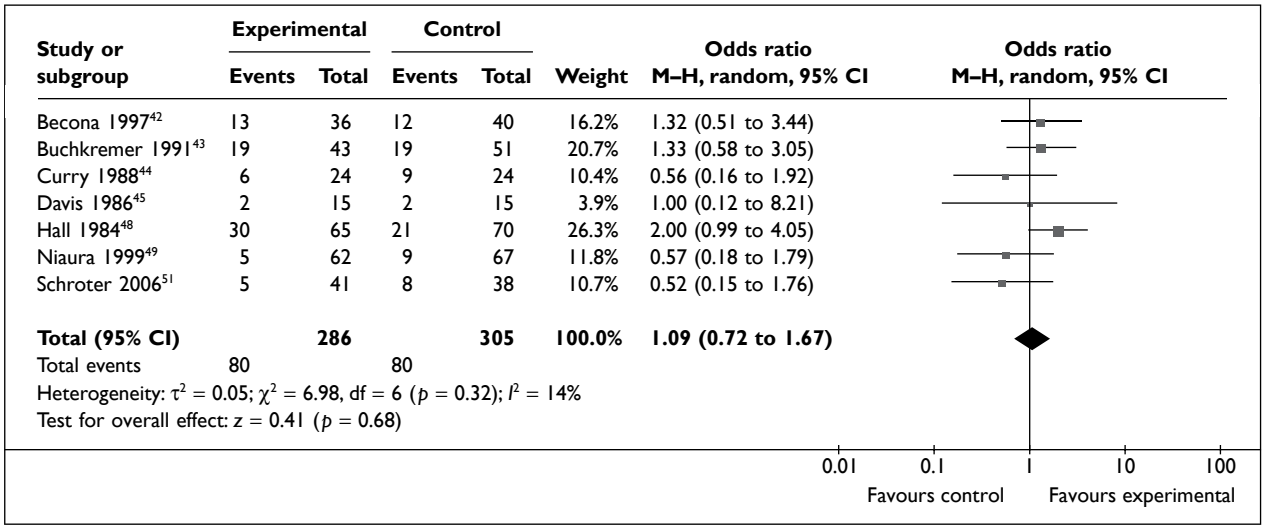

FIGURE 8 *Studies randomising smokers with interventions matched for programme length. Interventions were administered for equal durations in both control and intervention groups. (a) Short-term follow-up; (b) medium-term follow-up; and (c) long-term follow-up.*

Studies investigating behavioural interventions of differing intensities

Six studies (*Table 8*) randomised participants into intervention and control groups of varying intensities.[52–71] These studies investigated the impact of behavioural RPIs delivered to smokers as additional components of cessation programmes which resulted in longer treatment programmes; trials in this category do not have intervention and control groups matched for length, rather intervention group programmes are administered for longer periods because of additional relapse prevention content, or deliver content with additional components not included in control group treatments.

Details of included studies

One study only enrolled heavy smokers, five trials recruited community volunteers and one recruited clinic volunteers.[57] Two trials used a 2 × 2 factorial design.[54,57]

TABLE 8 *Studies investigating behavioural interventions of different intensities*

Study	Setting/ Randomisation	Participants	Interventions	Outcome measure/ follow-up points	Verification
Brandon *et al.* (1987)[52]	USA, randomisation method not stated	57 community volunteers, heavy smokers only	Maintenance treatment plus rapid puffing Maintenance treatment alone Counselling only Interventions administered over 2 weeks. Subjects in maintenance groups had four meetings each lasting an hour. Subjects in control group had one meeting only	Point prevalence abstinence at short, medium and long term	Carbon monoxide verified self-report
Hall and Killen (1985)[53]	USA, randomisation method not stated	84 community volunteers in relevant arms	Intensive behavioural treatment Same as 1. With NRT gum Low contact with nicotine gum (control) Interventions were administered over 8 weeks	Point prevalence abstinence at short, medium and long term	Plasma thiocyanate verified self-report
Hall *et al.* (1987)[54]	USA, randomisation method not stated	139 community volunteers	2 × 2 factorial design Low contact group: five sessions Intensive behavioural group: 14 sessions	Point prevalence abstinence at short, medium and long term	Serum thiocyanate and carbon monoxide verified abstinence
Killen *et al.* (1984)[55]	USA, randomisation method not stated	44 community volunteers in relevant arms	Nicotine gum in addition to 20 minute weekly clinic attendance for 7 weeks Skills training only plus once a week therapist led meetings for 7 weeks Combined (1 and 2)	Continuous abstinence at short and medium term	Saliva thiocyanate and carbon monoxide verified abstinence
Lifrak *et al.* (1996)[56]	USA, randomisation method not stated	69 community volunteers	High-intensity group, interventions administered weekly for 16 weeks Moderate-intensity group, interventions administered weekly for 4 weeks	Point prevalence abstinence at short, medium and long term	Urine cotinine verified abstinence
Shoptaw *et al.* (2002)[57]	USA, randomisation method stated	175 clinic volunteers at three narcotic treatment centres	Group counselling weekly for 12 weeks NRT only	Point prevalence abstinence at medium and long term	Carbon monoxide verified abstinence

Characteristics of interventions

In four studies, participants received nicotine patch therapy or nicotine gum in addition to behavioural treatment.[52–55] The intervention condition in one trial[54] included 6 second aversive smoking of three cigarettes, relapse prevention training and written exercises. Treatment was provided in 14 75-minute sessions. Participants in the control condition completed exercises, read educational materials and participated in group discussions. Treatment was provided in five sessions and meetings lasted 60 minutes. In another study,[53] participants in the intervention group completed eight 30-second aversive smoking sessions, and received videotaped feedback of the sessions in addition to behavioural relapse prevention treatment. Participants in the control group received nicotine gum and four treatment sessions which involved discussion of reading materials only. One trial[52] randomised participants into one of two treatment conditions or a control condition. All participants received six treatment sessions which included 30 minutes rapid smoking at each session. Thereafter, subjects in one treatment condition received counselling and three rapid-puffing trials with three cigarettes and met at 2, 4, 8 and 12 weeks' post-treatment follow-up. Subjects assigned to the second treatment condition met at the same intervals post-treatment and received behavioural counselling only. Subjects in the control group met once, at the 12-week post-treatment follow-up.

All subjects in another trial[55] received behavioural counselling for 1 week and an aversive smoke-holding procedure designed to create aversion to smoking. One treatment condition in this trial consisted of nicotine gum and attendance at a drop-in clinic weekly for 6 weeks. Individuals in the second treatment condition attended two therapist-led weekly meetings for 6 weeks and did not receive nicotine gum. Participants in the third treatment condition received a combination of both treatments.

A further study[56] randomised participants to receive either moderate intensity behavioural intervention in addition to nicotine patch treatment. The behavioural intervention was administered in four sessions. Individuals in the intervention group received 16 sessions of high intensity cognitive behavioural relapse prevention treatment.

Participants in one trial[57] were assigned to one of four treatment conditions – patch only, relapse prevention and patch, patch plus contingency management, and patch plus the combination of relapse prevention and contingency management. Relapse prevention treatment used psychosocial techniques to enhance coping skills, while contingency management allowed participants to earn money for every breath sample provided at or below 8 parts per million (p.p.m.).

Outcome assessment

Two studies validated abstinence with exhaled carbon monoxide and serum thiocyanate,[54,55] plasma thiocyanate was used in one[53] exhaled carbon monoxide was used alone in two,[52,57] and urinary cotinine in one trial.[56]

Effectiveness of interventions

In the two trials which simultaneously used NRT as a cessation treatment, behavioural RPIs appeared to be effective at preventing relapse.[53,54] Two studies reported that participants in intervention groups had lower relapse rates than their control counterparts,[55,57] but evidence for efficacy was not maintained in the long term in one study.[57] Two studies reported that interventions were not effective in reducing relapse to smoking.[52,56]

Analyses

Pooled analysis revealed that the interventions were not effective in the short, medium and long term respectively with pooled OR 1.11 (95% CI 0.49 to 2.49, $I^2 = 69\%$, six studies, short term), 1.01 (95% CI 0.57 to 1.80, $I^2 = 47\%$, six studies, medium term) and 0.86 (95% CI 0.56 to 1.31, $I^2 = 0\%$, five studies, long term; *Figure 9*).

Relapse prevention adjuncts to cessation programmes

Two studies (*Table 9*) provided adjunctive interventions, aimed at preventing relapse to smoking, in addition to smoking cessation treatments. One provided telephone support at specific intervals after a multisession smoking cessation clinic and the other provided access to a specially designed computer program in addition to the control condition components.

Additional proactive telephone contact

Details of included study and characteristics of intervention

One study[59] is included in this category. It randomised community volunteers into either a telephone support group or a no-contact comparison that they received after an initial 8-week smoking cessation programme. Participants attended 15 smoking cessation sessions with

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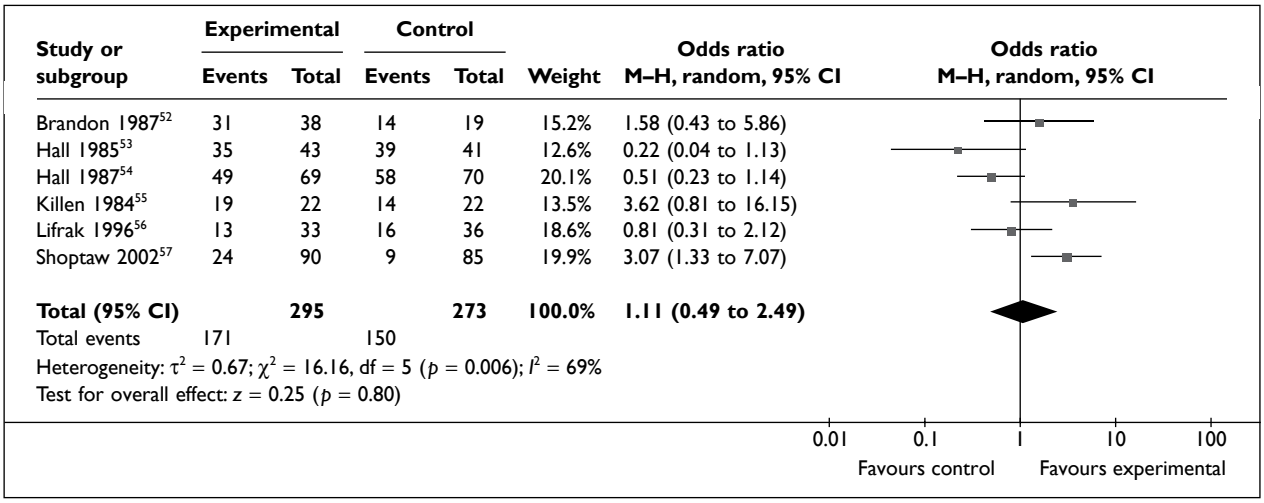

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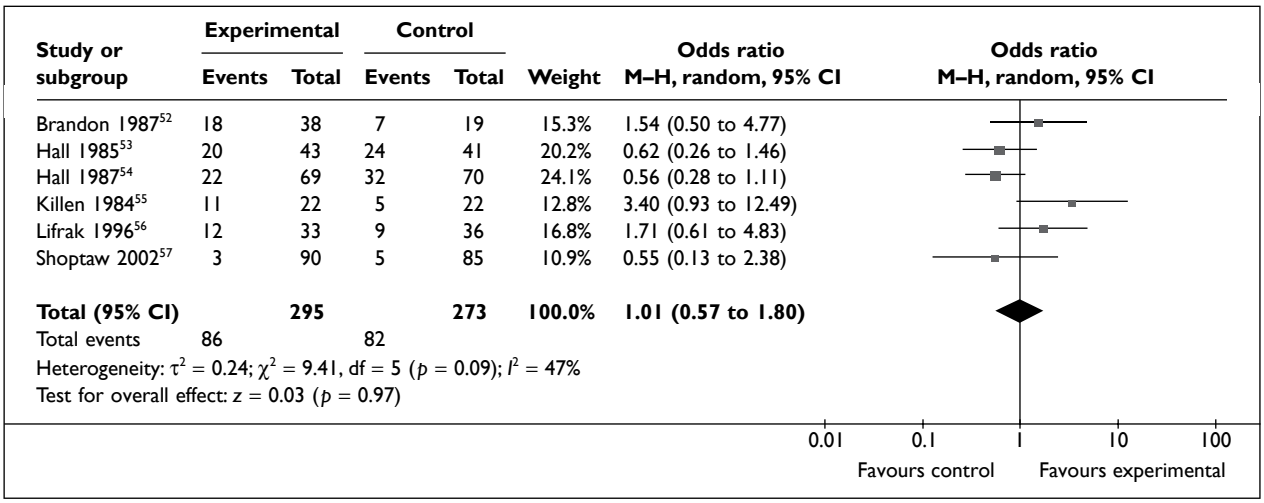

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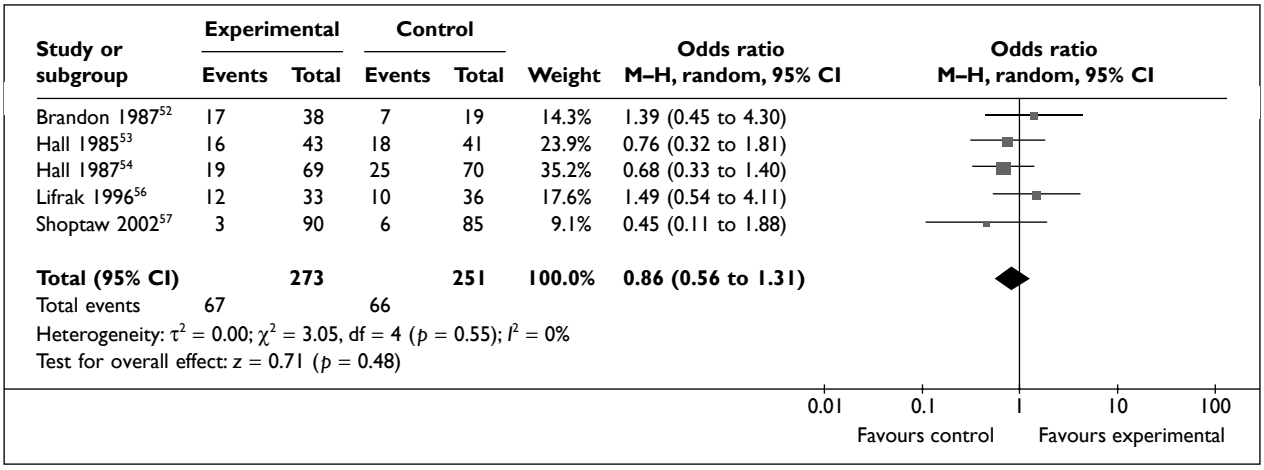

FIGURE 9 *Studies randomising smokers with different intensity programmes. Interventions varied in intensity and timing. (a) Short-term follow-up; (b) medium-term follow-up; and (c) long-term follow-up.*

TABLE 9 *Relapse prevention adjuncts to cessation programmes*

Study	Setting/ randomisation	Participants	Interventions	Outcome measure/ follow-up points	Verification
Japuntich *et al.* (2006)[58]	USA, randomisation method not stated	284 community volunteers	Bupropion, behavioural counselling and internet intervention Bupropion and counselling only	Point prevalence abstinence at short and medium term	Carbon monoxide verified abstinence
Lando *et al.* (1996)[59]	USA, community volunteers, randomisation method not stated	1083 heavy smokers, community volunteers	Telephone support with calls at 3, 9 and 21 months after target quit date Comparison group All subjects attended cessation clinic for 8 weeks. Interventions began in third week	Point prevalence abstinence at medium and long term	Saliva cotinine verified self-reported smoking abstinence

a 3-week preparation phase and a 5-week maintenance phase. Subjects in intervention group received telephone calls at 3, 9 and 21 months after targeted quit date.

Outcome assessment
Abstinence was recorded at 6, 12, 24 and 34 months after target quit date and was verified by saliva cotinine.

Effectiveness of intervention
Telephone intervention appeared effective at 6 and 24 months but this effect was lost at 34 months' follow-up.

Additional internet intervention

Details of included study and characteristics of intervention
One study[58] examined the effectiveness of an internet-based smoking cessation intervention in addition to bupropion and behavioural counselling compared to a bupropion and behavioural counselling only control group. The study tested the efficacy of an internet intervention, the Comprehensive Health Enhancement Support System for Smoking Cessation and Relapse Prevention, as an adjuvant to standard care. Participants in the intervention condition received 9 weeks of twice-daily bupropion, three brief behavioural counselling sessions, five follow-up visits and access to the internet intervention for 90 days, and were instructed to log into the program daily.

Outcome assessment
Point prevalence abstinence was reported at 3 and 6 months from the start of the study. Abstinence was verified using carbon monoxide measurements.

Effectiveness of intervention
The intervention did not appear effective at either 3 or 6-month follow-up points.

Pharmacotherapy interventions – bupropion

Table 10 gives details of the single study that randomised smokers and then tested a pharamacotherapy (bupropion) intervention plus 30 minutes of behavioural counselling at clinic visits after open-label bupropion treatment.[60]

Outcome assessment

Point prevalence and continuous abstinence rates were reported. Abstinence was verified using carbon monoxide measurements.

Effectiveness of interventions

The intervention appeared effective at reducing relapse to smoking.

Discussion

In this review, data from multiple trials suggest that bupropion prevent relapse to smoking when used by smokers who have already achieved abstinence using drug cessation treatments; four trials suggest NRT prevents relapse to smoking, although two of these trials involved smokers who were unsupported quitters after only a very short period of abstinence; based on data from one trial, varenicline also appears effective.

TABLE 10 *Pharmacotherapy interventions – bupropion*

Study	Setting/ randomisation	Participants	Interventions	Outcome measure/ follow-up points	Verification
Killen *et al.* (2006)[60]	USA, community volunteers, permuted block randomisation	362 adult smokers, community volunteers	Bupropion 150 mg/day for 14 weeks Matching placebo	Point prevalence abstinence at medium and long term	Carbon monoxide verified abstinence

Observed effects are long term; for every 11 abstinent smokers who use bupropion to prevent relapse, one extra non-smoker can be expected at 12 months and the corresponding NNT for NRT is 20 abstinent smokers. When used by smokers who have managed to stop smoking without accessing any support, self-help, behavioural interventions also appear effective in preventing relapse at 12 months.

By categorising trials according to their participants' characteristics and the nature of interventions delivered and combining outcome data collected only at similar time points, we have produced findings that would not have been obvious had we merely replicated previous Cochrane review methods. These combined smoking outcome data obtained between 6 and 24 months that, we believe, may have contributed to a less statistically powerful meta-analysis than ours. Statistical power refers to the likelihood of detecting within a sample an effect or relationship that exists within a population. Meta-analysis of individual studies can increase statistical power by reducing the standard error of the weighted average effect size. Combining different outcome time points compromises the validity and precision of the weighted average effect size and ultimately produces a less powerful meta-analysis, as is the case with the Cochrane review.

In contrast we have minimised methodological heterogeneity that might otherwise have obscured the real effects of interventions and this has probably given rise to our different findings. Additionally, the Cochrane reviews analysed trials that investigated NRT and bupropion, delivered as a combined intervention, together with those of bupropion alone. We could think of no theoretical reason for combining data in this way and conducted separate analyses for these different interventions; this may also account for differences between our findings and those of Cochrane reviews. In addition, the Cochrane reviews combined trials testing a variety of different behavioural interventions; however, we examined behavioural interventions according to their delivery modality and by population group separately. This separating out of interventions resulted in a key difference between our analyses and the Cochrane review, namely that self-help booklets and letters were effective for preventing relapse when used by abstainers who have managed to stop smoking without using any smoking cessation support.

Trials included in this review evaluated the effectiveness of the interventions both while treatment was ongoing and after this had ended and our short- and medium-term follow-up abstinence rates may, therefore, reflect the fact that some participants were still receiving treatment at these times. For bupropion, a significant effect was not detected in the short and medium term, but only in the long term after treatment had ended whereas NRT appeared to exert an effect both during treatment and in the long term when treatment had concluded. These findings highlight a need for drug relapse prevention trials that measure specifically, abstinence at follow-up points during the non-treatment follow-up phase.

Evidence for the use of pharmacotherapies, and particularly of bupropion, to prevent relapse seems most relevant to the UK NHS. In relapse prevention trials, bupropion was introduced only after smokers had used pharmacological cessation therapies to achieve relatively sustained abstinence periods; similarly any relapse prevention treatment introduced in the UK, would be likely to follow cessation support delivered by NHS SSS which usually includes drug treatments. Although effective for relapse prevention, the way NRT was used in relapse prevention trials would not, perhaps, translate so readily to the UK context; in two NRT trials, NRT was used by smokers after only very short abstinence periods (maximum length 48 hours), without the use of evidence based support or treatments. These two trials, therefore, enrolled 'unsupported quitters' and although these trials contributed substantially to the observed efficacy of NRT, smokers who

are motivated enough to access evidence-based cessation support, like routinely-delivered NHS SSS support, might respond differently to NRT used for relapse prevention. However, NRT is the most frequently used pharmacotherapy among smokers who access NHS SSS support and this popularity indicates that further evaluation of its potential role for relapse prevention is warranted. Varenicline shows promise as a relapse prevention treatment; one trial demonstrated medium-term efficacy when this was used as NHS SSS might do so, but further studies are required to confirm or refute this. Finally, it is noteworthy that self-help RPIs are effective for smokers who have achieved abstinence without the use of any cessation support (called 'unsupported quitters'). Such interventions might also have an adjunctive effect when used by smokers who have achieved abstinence after using evidence based cessation interventions, like those delivered by NHS SSS, and research is needed to investigate this issue and also further investigate the potential of self-help to reduce relapse among 'unsupported quitters'.

Data are presented as ORs abstinence of smoking at end of pregnancy/longest follow-up before delivery, short- (1–3 months), medium- (6–9 months), and long- (12–18 months) term follow-up for behavioural relapse prevention intervention as compared to control. Data are presented for continuous abstinence where available. Squares represent ORs and horizontal lines denote 95% CIs. The size of the square corresponds to the weight of the study in the meta-analysis.

Chapter 4

Cost-effectiveness of interventions to reduce relapse following smoking cessation

Introduction

Meta-analyses presented in Chapter 3 suggest that extending treatment with bupropion, NRT and varenicline may be effective at preventing smokers who have recently achieved abstinence from relapsing back to smoking. Smoking cessation interventions are among the most cost-effective that any health care system can employ and, as RPIs enhance cessation rates, these are also potentially very cost-effective. However, as drug treatments for relapse prevention are issued for much longer than standard periods, the costs of delivering RPIs will be far higher than those attributed to smoking cessation interventions, reducing cost-effectiveness ratios. Consequently, in this chapter, we present a formal cost-effectiveness analysis of those RPIs identified as potentially effective by our systematic review and which could also be incorporated into current NHS clinical care.

Aims and objectives

The aim of this chapter was to determine the cost-effectiveness of interventions for preventing smokers, who have recently become abstinent, from relapsing back to smoking. Specifically, the model will assess the costs and outcomes associated with the following interventions, compared to no intervention:

- bupropion
- NRT
- varenicline.

These interventions were selected because our systematic review (see Chapter 3) demonstrated evidence that each could be effective when used by smokers who had stopped smoking after using evidence-based cessation support (i.e. smokers who are similar to those who access and use NHS SSS cessation support in quit attempts). The analysis aims to estimate the lifetime costs (including the intervention costs and those associated with smoking-related comorbidities) and the lifetime health outcomes [measured using quality-adjusted life-years (QALYs)] of a cohort of patients who have recently quit smoking; incremental cost-effectiveness ratios (ICERs) are provided to help inform decisions about the best 'value-for-money' options for using RPIs within the UK NHS.

Methods

Overview of methods

A cohort simulation model was designed to estimate the costs and QALYs associated with interventions to reduce relapse following initial smoking cessation and to determine and compare different interventions' relative cost-effectiveness. A hypothetical cohort of 1000 smokers who had recently initiated quit attempts ('recent quitters') was assembled; this was intended for use in a simulated 'population cohort' approach with modelling in 6-monthly cycles over cohort smokers' lifetimes. In each cycle, 'recent quitters' could:

- relapse (i.e. become a 'smoker')
- remain a non-smoker (i.e. a 'former smoker')
- die.

Figure 10 demonstrates the relationships between smoking status and smokers' comorbidities permitted by the model which are explained further below.

In each cycle, smokers and former smokers have a chance of experiencing one or more of five potential comorbidities:

- lung cancer (LC)
- coronary heart disease (CHD)
- chronic obstructive pulmonary disease (COPD)
- MI
- stroke.

First, estimates for the prevalences of each comorbidity within regular and former smokers of different ages and genders were calculated; below, further details of methods used are given. To calculate the number of people with comorbidities,

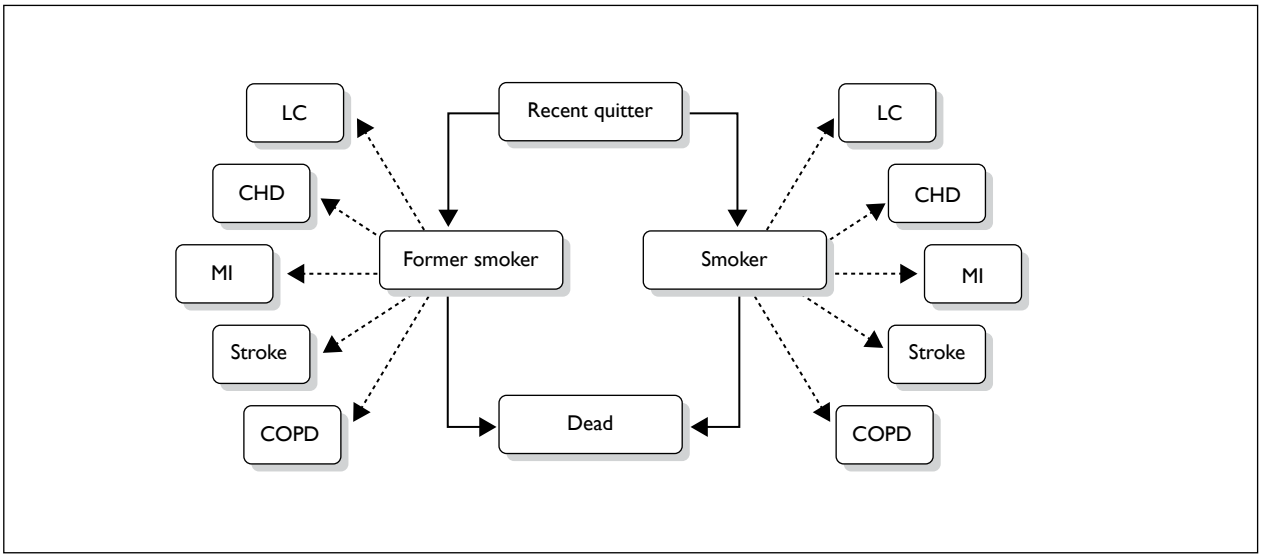

FIGURE 10 *Movement between health states (note that a smoker can have more than one comorbidity).*

in each cycle, the numbers of smokers and former smokers were multiplied by the estimated prevalences (e.g. to calculate the number of smokers with LC, the number of smokers in each cycle was multiplied by the prevalence of LC among smokers). One qualification is that, as there were insufficient available data on the relative risks (RRs) of former smokers experiencing comorbidities, the model could not take into account the impact of the length of abstinence from smoking amongst former smokers; therefore, the same smoking-related costs are attributed to recent or long-term ex-smokers.

The likelihood of a cohort individual being a smoker or former smoker and also of developing one or more comorbidities in each cycle varies with their age. Each comorbidity has an associated cost and utility [quality of life (QoL)]; to enable the total costs and utilities of the interventions to be compared with 'no intervention', the number of people with each comorbidity was, within each cycle, multiplied by the associated cost/utility of that comorbidity, giving an estimated cost/utility for each comorbidity, and these were summed together to calculate an overall estimate for total cost/utility. The cost-effectiveness of individual relapse prevention treatments were determined by inputting the costs of these treatments into the simulation cohort and modelling their impact on cohort utilities, using estimates for effectiveness derived from Chapter 3.

Study population

The cohort is flexible and the cost and QALY outcomes for each combination of age and gender were estimated (e.g. for a 16-year-old man, 16-year-old woman, 17-year-old man, 17-year-old woman, etc.). Population weights derived from population estimates provided by the Office for National Statistics[101] (see Appendix 4) were then applied to each cohort group, to ensure that the cohort was representative of the England and Wales population. The costs and QALY outcomes for each age–gender group were also multiplied by these weights to ensure overall QALY outcomes were similarly representative. We did not weight cohort simulations to reflect the sociodemographic characteristics; theoretically this would only have been possible using data on variations in model parameters (e.g. rates of complications, comorbidities, smoking status, etc.) with these characteristics, but such data were unavailable.

Data

This section describes the data sources from which estimates for parameters used in the cohort simulation were derived.

Literature search

Electronic databases (MEDLINE and PubMed), the Worldwide Web and references listed in identified articles were searched for relevant studies (see Appendix 5). Where there were any gaps, the Centre for Reviews and Dissemination (CRD, University of York, York, UK) carried out further

searches. Data were required for the following areas:

- mortality, by age, gender and smoking status
- prevalence of each comorbidity, by age, gender and smoking status
- utilities for each comorbidity
- costs for each comorbidity.

Mortality

We estimated mortality by age, gender and smoking status, reflecting general population mortality rates for the cohort (see Appendix 6),[102] using a number of data sources. Firstly, mortality rates per 1000 men and smoking exposure data from Doll *et al.*,[103] a study of doctors' mortality, were used to derive ORs for mortality among former (A) and non-smokers (B), compared with current smokers (*Table 11*). The Actuary Life Tables[102] provide the 'real' mortality for each age (C) and the prevalence of smoking for each age and gender (D) was taken from the *Health Survey for England*[105] (*Table 12*). These data were used to calculate the actual mortality rates for smokers (E), former smokers (F) and non-smokers (G), by ensuring that the following equation was satisfied:

$$(E \times D1) + (F \times D2) + (G \times D3) = C$$

Where E : F = the OR, A; E : G = B

This calculation is best illustrated by example; taking a 44 year old and substituting the prevalence of smoking and the actual mortality rate into the equation gives:

$$(E \times 0.26) + (F \times 0.21) + (G \times 0.53) = 0.002144$$

Further substituting the ORs reduces the equation to:

$$(E \times 0.26) + (E \times 0.21 \times 0.7143) + (E \times 0.53 \times 0.571) = 0.002144$$

This allows the equation to be solved as follows, to give an accurate estimate of the mortality for a 44-year-old smoker, former smoker and non-smoker:

$$(E) = \frac{0.002144}{(0.26 + (0.21 \times 0.71423) + (0.53 \times 0.571))}$$

$$(E) = 0.0030$$

$$(F) = 0.0021$$

$$(G) = 0.0017$$

This process was repeated for all ages.

Calculation of the prevalence by smoking status of each comorbidity

We searched for information concerning: (1) the prevalence, by age, of each comorbidity in the general population, regardless of smoking status (A), (2) the RR of each comorbidity by smoking status [i.e. smokers vs former (B) and non-smokers (C)] and (3) the prevalence of smoking in England

TABLE 11 *Mortality by age, per 1000*

	Doll *et al.* (1994)[103]			Doll *et al.* (2004)[104]				
Age at death (years)	Current smoker	Former	Non-smoker	Current smoker	Former smoker, by age stopped (years) 35–44	45–54	55–64	Non-smoker
35–44	2.8	2	1.60	2.7				1.6
45–54	8.1	4.9	4.00	8.5	5.4			3.8
55–64	20.3	13.4	9.50	21.4	9.0	16.4		8.4
65–74	47	31.6	23.70	50.7	22.7	31.7	36.4	18.6
75–84	106	77.3	67.40	112.2	53.1	39.1	78.9	51.7
85 +	218.7	179.7	168.60					

Although a later paper by the same authors includes mortality data derived after 10 years' more follow-up of the same doctors' cohort (until 2001),[104] the earlier 1994 paper[103] has been used because this provides annual mortality by smoking habits at age of death. It also provides figures for those aged > 85 years and for former smokers aged < 45 years, which the later 2004 paper[104] does not. This table compares the mortality rates obtained using data from both papers.

TABLE 12 *The prevalence of smoking for men (for women)*

Age (years)	Current cigarette smoker (D1)[a]	Ex-regular cigarette smoker (D2)[a]	Never regularly smoked cigarettes (D3)[a]
16–24	0.25 (0.29)	0.05 (0.07)	0.69 (0.64)
25–34	0.37 (0.28)	0.14 (0.16)	0.49 (0.56)
35–44	0.26 (0.27)	0.21 (0.18)	0.53 (0.55)
45–54	0.25 (0.25)	0.30 (0.24)	0.44 (0.51)
55–64	0.19 (0.20)	0.44 (0.30)	*0.36 (0.50)*
65–74	0.10 (0.13)	0.56 (0.29)	0.34 (0.57)
75 +	0.07 (0.09)	0.61(0.34)	0.32 (0.57)
All ages	0.24 (0.23)	0.29 (0.22)	0.47 (0.56)

a The figures in brackets indicate the female prevalence figures.

and Wales (D) (Appendix 5). These data were used to calculate the prevalence of each comorbidity within current (E), former (F) and non-smokers (G), by ensuring that the following equation was satisfied:

$$(E \times D1) + (F \times D2) + (G \times D3) = A$$

Where E : F = the OR, B; G : F = the OR, C.

This can be illustrated using the example of a 60-year-old person with LC. The prevalence of LC comes from *Table 13*,[106] the RR of LC from *Table 14*[107] and the prevalence of smoking, as above from *Table 12*.[105]

TABLE 13 *Prevalence of lung cancer*

Age (years)	Prevalence
0–44	0.00%
45–64	0.15%
65 +	0.80%
All ages	0.14%

TABLE 14 *Relative risk of lung cancer by smoking status*

	Current smoker	Former	Non-smoker
RR	1	0.44	0.03

- Substituting the prevalence of smoking and the actual prevalence rate:

$$(E \times 0.19) + (F \times 0.44) + (G \times 0.36) = 0.15$$

- Substituting the ORs:

$$(E \times 0.19) + (E \times 0.44 \times 0.44) + (E \times 0.36 \times 0.03) = 0.15\%$$

$$(E) = \frac{0.15\%}{(0.19 + (0.44 \times 0.44) + (0.36 \times 0.03))}$$

$$(E) = 0.0038$$
$$(F) = 0.0017$$
$$(G) = 0.0001$$

This process was repeated for all age and gender categories within each comorbidity. The prevalence of each comorbidity, the RR by smoking status and resulting prevalence by age, gender and smoking status are shown in Appendices 7–11.

Deriving utility weights

Comorbidities within our cohort were each allocated an associated utility and, for every cohort cycle, the number of people with each comorbidity was multiplied by the associated utility and adjusted for the time period spent in the morbid health state. Where someone had more than one comorbidity, we used the lowest utility value, so 'double counting' of morbidities resulting in false multiplicative or additive assumptions would not have occurred. Attaching utilities to morbidities in this way permitted our model to determine estimates for the utilities of morbidities when no intervention was used, enabling comparison of the total QALYs attributable to interventions and 'no intervention'.

The following procedure was used to derive utilities for our cohort. Tengs and Wallace reviewed studies that included original QoL weights with

the aim of compiling a list of QoL weights for 1000 disease areas.[108] A search of Tengs and Wallace's database, the NHS Economic Evaluation Database, MEDLINE and of bibliographies in retrieved papers identified 1100 potential studies, of which, 243 contained potentially relevant information on utilities and 154 reported original data. Tengs and Wallace calculated the average values for utility scores and these were used in our model for LC, CHD, MI and stroke. We did not attempt to combine these with scores from other sources due to a lack of sufficient evidence on the quality of the respective data.

Lung cancer utilities
Six utility values were provided for LC covering the following areas, an average of which was calculated:

- small cell LC with one cycle course of radiation
- small cell LC with one cycle course of cyclophosphamide, doxorubicin and vincristine (CAV) chemotherapy
- small cell LC with one cycle course of etoposide (VP-16)/cisplatin
- small cell LC after disease progression
- small cell LC that is in complete remission
- small cell LC in partial remission of treatment.

Stroke utilities
Tengs and Wallace[108] identified 28 papers with QoL stroke weights, including patients in the following health states:

- Minor stroke:
  - with or without cognitive deficit
  - first year after stroke
  - left with residual cerebral arteriovenous malformations after treatment.
- Moderate stroke:
  - with or without cognitive deficit
  - residual deficit in patients with prior MI
  - language deficit
  - motor deficit.
- Acute requiring hospitalisation.
- Major stroke:
  - with or without the ability to speak
  - first year after stroke
  - left with residual cerebral arteriovenous malformations after treatment
  - severe residual deficit in patients with prior MI
  - with or without cognitive deficit
  - language deficit
  - motor deficit.

Coronary heart disease and myocardial infarction utilities

Tengs and Wallace[108] identified only one paper for CHD (utility = 0.8) and 83 for health status after MI; the MI papers covered the following health states:

- All MIs (no further details provided).
- MI treated with streptokinase or recombinant tissue plasminogen activator, no dyspnoea at rest/on mild exertion or on strenuous exertion.
- MI patients unable to care for themselves.
- MI patients who did not experience a stroke or refraction.
- MI patients where rehabilitation had been provided.

Chronic obstructive pulmonary disease utilities
Rutten-van Molken *et al.*[109] investigated the differences in COPD utility measured in 13 countries using data from a subset of 1235 trial patients (from 6000 participants) who completed a baseline European Quality of Life-5 Dimensions (EQ-5D) questionnaire[110] as part of a double-blind, placebo-RCT investigating whether dopropium reduces the rate of decline in forced expiratory volume. EQ-5D utility score was 0.76 at baseline; scores were split into six groups based on the severity of COPD (moderate, severe and very severe) and location (UK/USA); our model used an average of UK scores for all severities of COPD.

Utility of current and former smoking: no comorbidity
Tillmann and Silcock[111] assessed differences in health status between Scottish current and former smokers (abstinent for > 5 years), registered with nine general medical practices using the EQ-5D, and EQ-5D scores were 0.78 for former and 0.75 for current smokers.

Summary of utility scores used
The utility scores used in the model are shown in *Table 15*. There were insufficient data on how comorbidity severity might be distributed among smokers, former smokers and non-smokers so, as per Tengs and Wallace,[108] we used average utility scores rather than scores intended to reflect varied severity of comorbidity.

Deriving comorbidity costs

Summary of comorbidity costs used in model
For cohort simulations we required a cost attributable to each comorbidity and, to permit

comparisons with 'no intervention', we needed to calculate the annual total costs for each comorbidity. Total annual costs were derived by multiplying, for each cohort cycle, the number of people with each comorbidity and attributable costs; annual comorbidity costs, inflated to 2008 prices, are shown in *Table 16* and explanations of the rationale for deriving these follow.

Rationale for deriving costs attributable to each comorbidity

Lung cancer

The *Health Care Needs Assessment* provides evidence for cost, cost-effectiveness and optimum service configuration for treatment of diseases including LC.[112] The authors acknowledge that there is uncertainty surrounding the cost of palliative and terminal LC care, but estimate it to be between £2000 and £7100 per person (1998 UK sterling); we used average figures in the model, £4550 (£5501 at current prices). It is unclear whether reported costs figure take account of gender differences in the number of people with LC.

Stroke and coronary heart disease

The National Audit Office (NAO)[113] estimated that the direct cost of stroke was £2.8B each year (in 2005). The total cost per person was calculated by dividing the NAO estimated cost by the number of people with stroke in the UK, giving an estimated annual 2006 cost of £2061;[105,114] it was assumed that the same definition of stroke was used for both data sources. A similar approach was used for the cost of CHD with the annual cost provided by the British Heart Foundation;[115] stroke and CHD costs are shown in *Table 17*.

TABLE 15 *Utility scores*

Comorbidity	Utility	Source (reference number)
LC	0.58	107
Stroke	0.48	107
CHD	0.80	107
MI	0.80	107
COPD	0.73	108
No comorbidities	0.75 current smoker 0.78 former smoker	110

TABLE 16 *Annual cost of each comorbidity*

Disease	Average annual cost (2008 £)	Source (reference number)
LC	5501	111
Stroke	2061	104, 112, 113
CHD	1063	104, 113, 114
MI	2175	115, 116, 117
COPD	926	118

TABLE 17 *Annual cost of stroke and coronary heart disease (2008 £)*

	Stroke	CHD
Total cost per year (£)	2,867,200,000	3,809,320,747
Total population (male)	29,668,033	29,668,033
Total population (female)	30,864,468	30,864,468
% with stroke/CHD (male)	2.40	7.00
% with stoke/CHD (female)	2.20	5.00
Average cost per person (£)	2061	1063

Myocardial infarction

The cost of MI has two components; those of the acute event and ongoing annual health-care costs. Event costs were taken from national published databases and the calculation of long-term costs assumed monthly general practitioner (GP) and 3-monthly cardiology follow-up visits, with use of cholesterol lowering drugs.[116–118]

Chronic obstructive pulmonary disease

The annual cost of COPD care was taken from Appendix D of the *Chronic Obstructive Pulmonary Disease: National Clinical Guideline on Management of Chronic Obstructive Pulmonary Disease in Adults in Primary and Secondary Care*.[119] This includes GP visits, medication, oxygen, inpatient stay and emergency admission; it is unclear whether this takes account of the gender distribution amongst people with COPD.

Cohort simulations and model assumptions

The virtual cohort assembled 1000 smokers who had recently started a quit attempt and simulations aimed to determine the cost-effectiveness of RPIs used within this population.

The following assumptions were made in the base-case model:

1. A background (i.e. spontaneous) rate of quitting smoking of 2% among all smokers.
2. RPIs used by this population of smokers would have the same efficacy as in clinical trials.
3. Costs of RPIs were as recorded in the *British National Formulary* (BNF).
4. Age, gender and smoking-specific cohort mortality and morbidity rates are accurately calculated using procedures outlined above.
5. Costs incurred by exposure to morbidities are adequately calculated as described above.

Analysis of intervention effectiveness

For all interventions, the most influential parameter within the model was the proportion abstinent from smoking during each 6-monthly cohort cycle. In all cases, the proportion abstinent at time zero was 100%, because RPIs are provided to smokers who have recently stopped smoking; parameters representing the likely proportions remaining abstinent at 6 and 12 months (*Table 18*, *Figure 11*) are from control and intervention groups within trials included in the Chapter 3 systematic review, conducted to estimate the effectiveness of RPIs for relapse prevention. Model parameters (estimates) representing the effectiveness of bupropion, varenicline and NRT for preventing relapse to smoking amongst abstinent smokers are also from this review.

Trials investigating RPIs have followed up participants for a maximum of 12 months, so we only have data on the effectiveness of interventions over this length of time. However, some relapse to smoking will occur after 1 year and, hence, in the longer term, the impact of RPIs may diminish as time passes if relapse rates are higher in those who have used RPIs. To estimate the potential long-term impact of RPIs, we made three different assumptions about the likely persistence of short-term benefits from use of RPIs and incorporated these into our model. These assumptions were that differences between the RPI-treated and non-treated groups observed after 1 year would:

1. Diminish with the same annual 'background' relapse rate (2% of non-smokers relapsing to smoking each year in 'treated' and 'non-treated' groups).
2. Persist for 10 years but then disappear.
3. Disappear completely after 1 year.

TABLE 18 *Intervention inputs: delivery costs and impact on relapse*

	Bupropion		NRT		Varenicline	
	Bupropion	No intervention	NRT	No intervention	Varenicline	No intervention
Cost of intervention (£)	69	0	100	0	177	0
% abstinent at 0 months	100	100	100	100	100	100
% abstinent at 6 months	50	44	26	18	51	42
% abstinent at 12 months	37	29	23	18	41	36

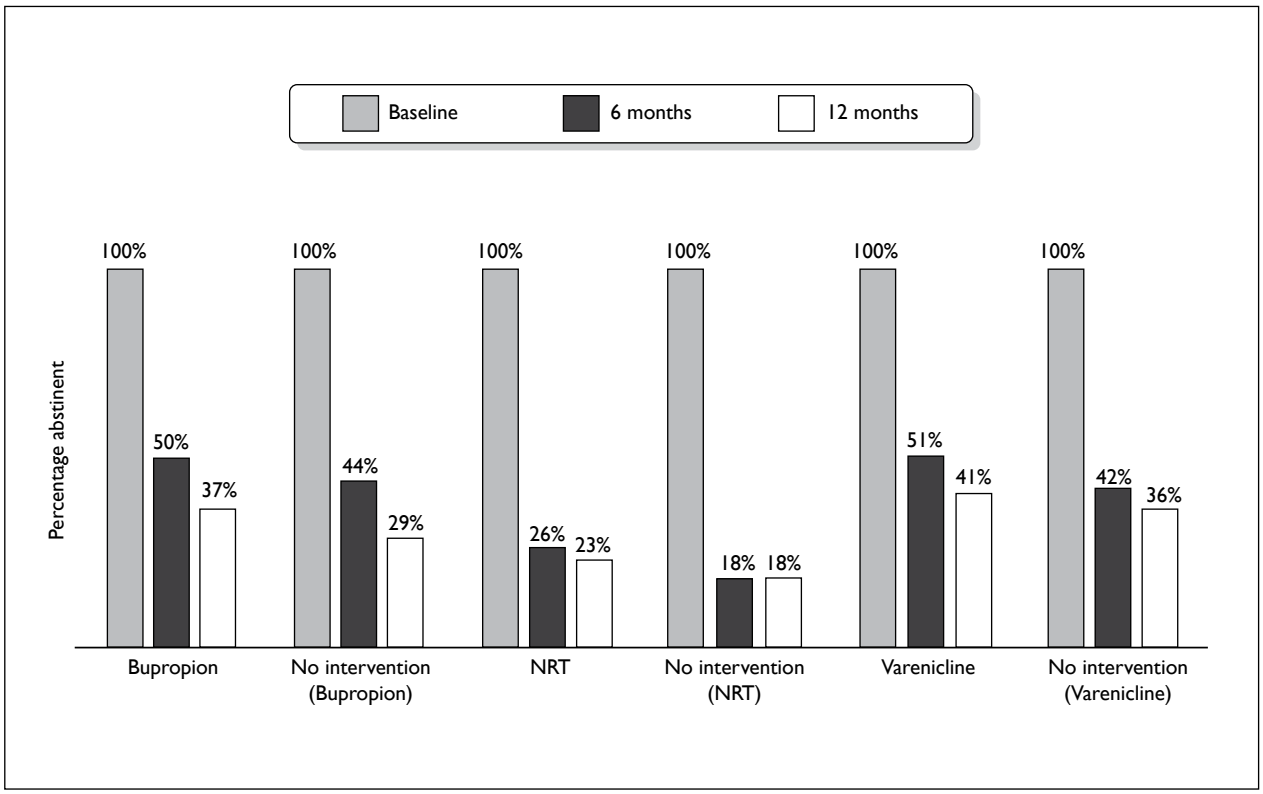

FIGURE 11 *Proportion abstinent at baseline, 6 months and 12 months with relapse prevention intervention and in comparable 'no intervention' groups.*

Assumption 1, above, was used in the base-case scenario and assumptions 2 and 3 were used in sensitivity analyses.

Table 18 gives (1) the estimated costs of delivering interventions (full details explaining calculations follow) and (2) the proportions of smokers abstinent at different time points after quitting, as derived from our review in Chapter 3 that the costs of 'no intervention' accrue with time, as the amount of relapse to smoking increases.

The cost of bupropion was calculated using a price per 150-mg tablet of £0.66[120] with patients receiving one daily tablet for 6 days followed by 150 mg twice daily for a period of 7 weeks. NRT costs were calculated by combining dosing provided in a previous analysis[121] with costs from the BNF[120] and a study by Parrott calculated that smokers received 60.48 units of NRT during a course of treatment.[121] Varenicline was calculated using a cost per initial pack of £27.30, followed by two tablets per day (at a cost of £0.97 per tablet) for a period of 77 days.[120]

For NRT trials, a further sensitivity analysis was undertaken, excluding two trials in which participants had been abstinent from smoking for only very short periods (24 and 48 hours, respectively) prior to NRT being introduced as relapse prevention therapy. As most relapse was expected to occur in the first few days after abstinence, relapse prevention treatments might be expected, therefore, to have lower efficacy amongst participants of these trials. The cost and effectiveness inputs for remaining NRT trials that required longer abstinence periods prior to the onset of relapse prevention treatment are shown in *Table 19*.

Economic evaluation

Cost-effectiveness models are used to assess the relative benefits of a given treatment using patient outcomes and the costs incurred in achieving those outcomes. The calculation of the additional cost per additional unit gain of benefit (i.e. QALYs) is known as the incremental analysis and results are presented as ICERs. After incremental costs and QALYs were estimated, the ICERs were calculated using the following formula:

$$ICER = \frac{Cost_{\text{int}ervention} - Cost_{Comparator}}{Effect_{\text{int}ervention} - Effect_{Comparator}}$$

TABLE 19 *Nicotine replacement therapy trials, excluding those with short abstinence periods: delivery costs and impact on relapse*

	NRT	
	NRT	**No intervention**
Cost of intervention (£)	100	0
% abstinent at 0 months	100	100
% abstinent at 6 months	48.62	31.15
% abstinent at 12 months	25.69	16.39

The incremental cost per QALY is calculated for all the interventions modelled, allowing the user to compare any two interventions.

Discounting

Costs and outcomes were discounted at 3.5% per year.[122]

Sensitivity analyses

Sensitivity analyses were carried out for each intervention to examine the impact of changing model values for:

- background quit rate
- cost and effectiveness
- persistence of intervention benefits.

Model background quit rates of 2% (base case), 1.2% and 2.8% were investigated, as was varying intervention costs between –50% and + 50% of the base-case value. For effectiveness data, the proportion of *additional* abstainers at 6 and 12 months was assessed using a range between 10% and 150% of the original value for *additional* abstainers. For example if, in the control group, the number of abstainers in the control group is 40% and the number of abstainers in the treatment group is 50%, then this equates to an additional 10% of abstainers. Therefore, the sensitivity analysis would assess the impact of changing this value between 1% (i.e. 41% abstaining) and 15% (i.e. 55% abstaining). The persistence of short-term benefits from interventions was investigated as described for the three scenarios outlined above (see Analysis of intervention effectiveness).

Results

Base-case results

Table 20 provides the base-case costs and QALYs, per person, associated with each intervention, using a 2% background cessation rate.

TABLE 20 *Base-case results*

	Background cessation = 2%	
Intervention	**Cost (£)**	**QALY**
Bupropion	6755	12.76
No intervention (bupropion trial)	6822	12.69
NRT	7050	12.63
No intervention (NRT trial)	7039	12.58
Varenicline	6794	12.79
No intervention (varenicline trial)	6704	12.75
No intervention (pooled data)	6981	12.61

All interventions result in increased QALYs compared with 'no intervention' and net costs, including all medical costs incorporated in the model and intervention costs, generally increased, with the exception of bupropion.

Figure 12 illustrates the total cost and total QALYs for all the interventions and 'no intervention'.

Incremental analysis – comparison against 'no intervention' using trial data

Incremental analysis was carried out to compare each intervention to 'no intervention' in terms of the total costs and QALYs. All treatments show a very low cost per QALY (maximum = £2106), therefore, they can be considered cost-effective against a willingness-to-pay threshold of £20,000. However, bupropion is the cheapest and the most effective intervention and, therefore, assuming that the interventions are mutually exclusive it dominates all the other interventions (i.e. is more effective and less costly).

Should any decision maker/health service commissioner wish to choose *between* the different interventions included in the analysis, the *incremental* costs and benefits should be assessed.

For example, if varenicline was compared against, say, bupropion, we can see that it produces an additional 0.03 QALYs at an additional cost of around £45 (*Figure 13*). The ICER for varenicline versus bupropion is, therefore, £1500 per QALY and varenicline would be considered cost-effective compared to bupropion. However, as mentioned below, caution should be taken when comparing results from different trials; robust data comparing interventions is best obtained from head-to-head comparisons are made within studies and none were available for bupropion and varenicline.

Table 21 shows the results of comparing each intervention to 'no intervention'. Note that the effectiveness of 'no intervention' varies, as each treatment was modelled against the relevant 'no intervention' abstinence rate derived from control groups in trials of that treatment. However, as baseline differences may exist between different trial participants, comparisons between drugs are, indirect and need to be treated with caution. Incremental costs and QALYs are shown, as well as the ICER.

When we excluded those NRT trials, which recruited participants who had been abstinent for very short periods and compared remaining trials with 'no intervention', there was very little change in findings for NRT; the incremental QALYs gained were 0.08 (12.66 compared to 12.58) and NRT was also associated with an overall reduction in total costs of £47 (of which, the £100 cost of NRT was offset by £147 savings on other costs). As such, NRT (when used for relapse prevention with smokers who have been abstinent for longer periods) dominated 'no intervention' in terms of cost-effectiveness.

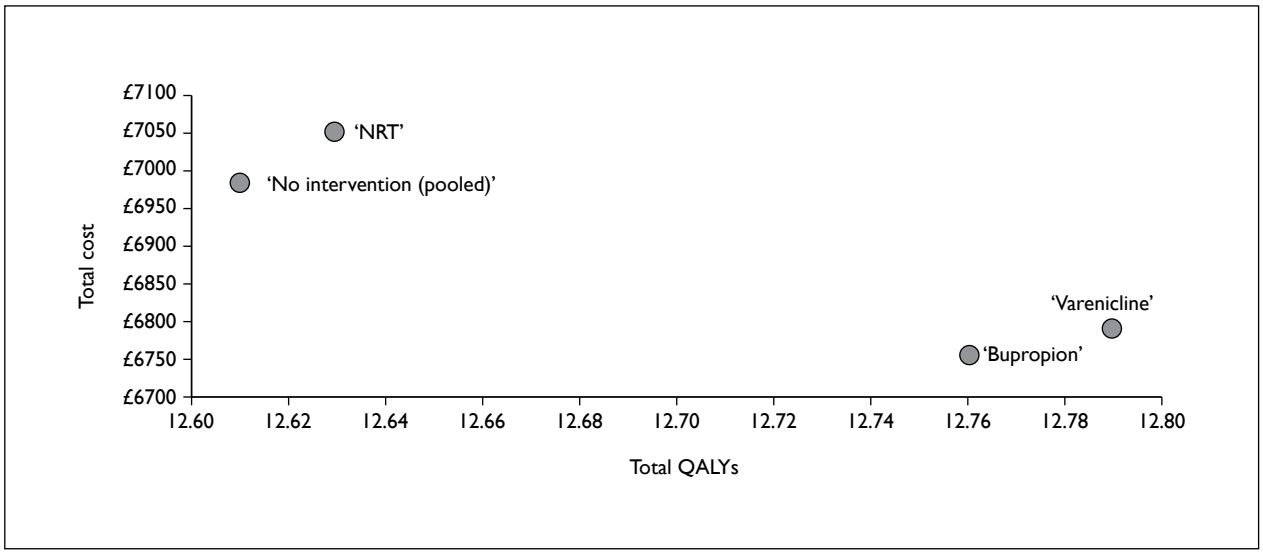

FIGURE 12 *Total cost and total QALY results.*

TABLE 21 *Comparing the interventions to 'no intervention'*

	Background cessation = 2%		
Compared with 'no intervention'	**Incremental cost (£)**	**Incremental QALY**	**ICER (£)**
'Bupropion' vs 'no intervention'[a]	–68	0.07	Dominant[b]
'NRT' vs 'no intervention'	12	0.04	265
'Varenicline' vs 'no intervention'	90	0.04	2106

a 'No intervention' reflects abstinence rate in control groups from intervention trials.
b i.e. treatment is more effective and less costly than 'no intervention'.

Sensitivity analyses

Background quit rate variation

Background quit rate is 1.2% or 2.8%

Table 22 shows the results of comparing each intervention to 'no intervention' with a lower background cessation of 1.2%, but keeping everything else the same; findings are very similar to the base case (2% in the base case). All interventions follow the pattern of the base-case results and can be considered cost-effective against a willingness-to-pay threshold of £20,000 per QALY. Bupropion remains the cheapest and the most effective intervention and dominates all the other interventions (more effective and less costly).

Table 23 demonstrates that all treatments are still cost-effective when compared against 'no intervention' at a background quit rate of 2.8%.

Intervention costs

For each of the three interventions, cost and effectiveness parameters were varied to assess their impact upon the cost-effectiveness results in the model. *Tables 24–26* detail the impact of changing the attributable costs of the three interventions. Bupropion remains dominant, and hence cost-effective at all projected costs (i.e. ± 50% of those included in the base case) while NRT is more sensitive to cost changes, becoming dominant at an intervention cost of £70, which is below that in the base case. At the highest projected intervention cost, varenicline appears less cost-effective; however, all interventions remain cost-effective as judged by the National Institute for Health and Clinical Excellence (NICE) cost-effectiveness benchmark of £20,000 per QALY.

Effectiveness of interventions

Tables 27–29 demonstrate the impact of changing the level of effectiveness of each intervention. As described above, the proportion of *additional* abstainers at 6 and 12 months was assessed using a range between 10% and 150% of the original value for *additional* abstainers. For example if, in the control group, the number of abstainers in the control group was 40% and the number of abstainers in the treatment group was 50%, then this equates to an additional 10% of abstainers. Therefore, the sensitivity analysis would assess the impact of changing this value between 1% (i.e. 41% abstaining) and 15% (i.e. 55% abstaining). Changes in the postulated effectiveness of interventions affects RPIs' cost-effectiveness more than alterations in cost. Bupropion dominates unless hypothesised effectiveness falls below 50% of used in the base case, and cost-effectiveness falls with decreasing effectiveness as shown by an incremental cost-effectiveness ratio of £8831 per QALY at 10% of base-case effectiveness. NRT only dominates when effectiveness is set at a higher level than estimated from clinical trials and used in the base case, but the ICER for NRT would exceed the NICE threshold if this were to fall below 10% of the

TABLE 22 *Background quit rate is 1.2%*

	Background cessation = 1.2%		
Compared with 'no intervention'	**Incremental cost (£)**	**Incremental QALY**	**ICER (£)**
'Bupropion' vs 'no intervention (bupropion trial)'	−85	0.07	Dominant
'NRT' vs 'no intervention (NRT trial)'	1	0.05	11
'Varenicline' vs 'no intervention (varenicline trial)'	79	0.04	1676

TABLE 23 *Background quit rate is 2.8%*

	Background cessation = 2.8%		
Compared with 'no intervention'	**Incremental cost (£)**	**Incremental QALY**	**ICER (£)**
'Bupropion' vs 'no intervention (bupropion trial)'	−54	0.06	Dominant
'NRT' vs 'no intervention (NRT trial)'	21	0.04	520
'Varenicline' vs 'no intervention (varenicline trial)'	99	0.04	2538

TABLE 24 *Sensitivity analysis – varying bupropion costs*

Intervention cost (£)	Incremental cost (£)	Incremental QALYs	ICER
35	–83	0.07	Dominant
41	–76	0.07	Dominant
48	–69	0.07	Dominant
55	–62	0.07	Dominant
62	–55	0.07	Dominant
69	–48	0.07	Dominant
76	–41	0.07	Dominant
83	–35	0.07	Dominant
90	–28	0.07	Dominant
97	–21	0.07	Dominant
104	–14	0.07	Dominant

TABLE 25 *Sensitivity analysis – varying NRT costs*

Intervention cost (£)	Incremental cost (£)	Incremental QALYs	ICER (£)
50	–26	0.04	Dominant
60	–16	0.04	Dominant
70	–6	0.04	Dominant
80	4	0.04	92
90	14	0.04	323
100	24	0.04	554
110	34	0.04	785
120	44	0.04	1016
130	54	0.04	1247
140	64	0.04	1478
150	74	0.04	1710

TABLE 26 *Sensitivity analysis – varying varenicline costs*

Intervention cost (£)	Incremental cost (£)	Incremental QALYs	ICER (£)
89	14	0.04	319
106	31	0.04	734
124	49	0.04	1149
142	67	0.04	1565
159	85	0.04	1980
177	102	0.04	2395
195	120	0.04	2810
212	138	0.04	3226
230	156	0.04	3641
248	173	0.04	4056
266	191	0.04	4472

TABLE 27 *Sensitivity analysis – effectiveness of bupropion*

Increase in abstainers (%)	Incremental cost (£)	Incremental QALYs	ICER (£)
10	57	0.01	8331
20	46	0.01	3376
30	34	0.02	1682
40	22	0.03	826
50	10	0.03	311
60	–1	0.04	Dominant
70	–13	0.05	Dominant
80	–25	0.05	Dominant
90	–37	0.06	Dominant
100	–48	0.07	Dominant
110	–60	0.07	Dominant
120	–72	0.08	Dominant
130	–84	0.09	Dominant
140	–95	0.09	Dominant
150	–107	0.10	Dominant

TABLE 28 *Sensitivity analysis – effectiveness of NRT*

Increase in abstainers (%)	Incremental cost (£)	Incremental QALYs	ICER (£)
10	93	0.00	20,097
20	85	0.01	9533
30	78	0.01	5851
40	70	0.02	3979
50	62	0.02	2845
60	55	0.03	2085
70	47	0.03	1540
80	39	0.03	1130
90	32	0.04	810
100	24	0.04	554
110	16	0.05	344
120	9	0.05	169
130	1	0.06	21
140	–6	0.06	Dominant
150	–14	0.07	Dominant

base-case level. Varenicline is never dominant and although the NICE benchmark is only exceeded when effectiveness falls below 20% of observed, it appears less cost-effective than either NRT or bupropion with consistently higher ICER values throughout the range of effectiveness explored.

Additional analysis: varying persistence of intervention benefits

It is recognised that the benefits of smokers achieving permanent abstinence are greater than those arising from temporary abstinence periods, but there were no available data with which to

TABLE 29 *Sensitivity analysis – effectiveness of varenicline*

Increase in abstainers (%)	Incremental cost (£)	Incremental QALYs	ICER (£)
10	170	0.00	37,909
20	162	0.01	18,600
30	155	0.01	11,933
40	147	0.02	8554
50	140	0.02	6512
60	132	0.03	5145
70	125	0.03	4165
80	117	0.03	3429
90	110	0.04	2855
100	102	0.04	2395
110	95	0.05	2019
120	87	0.05	1705
130	80	0.06	1439
140	72	0.06	1211
150	65	0.06	1013

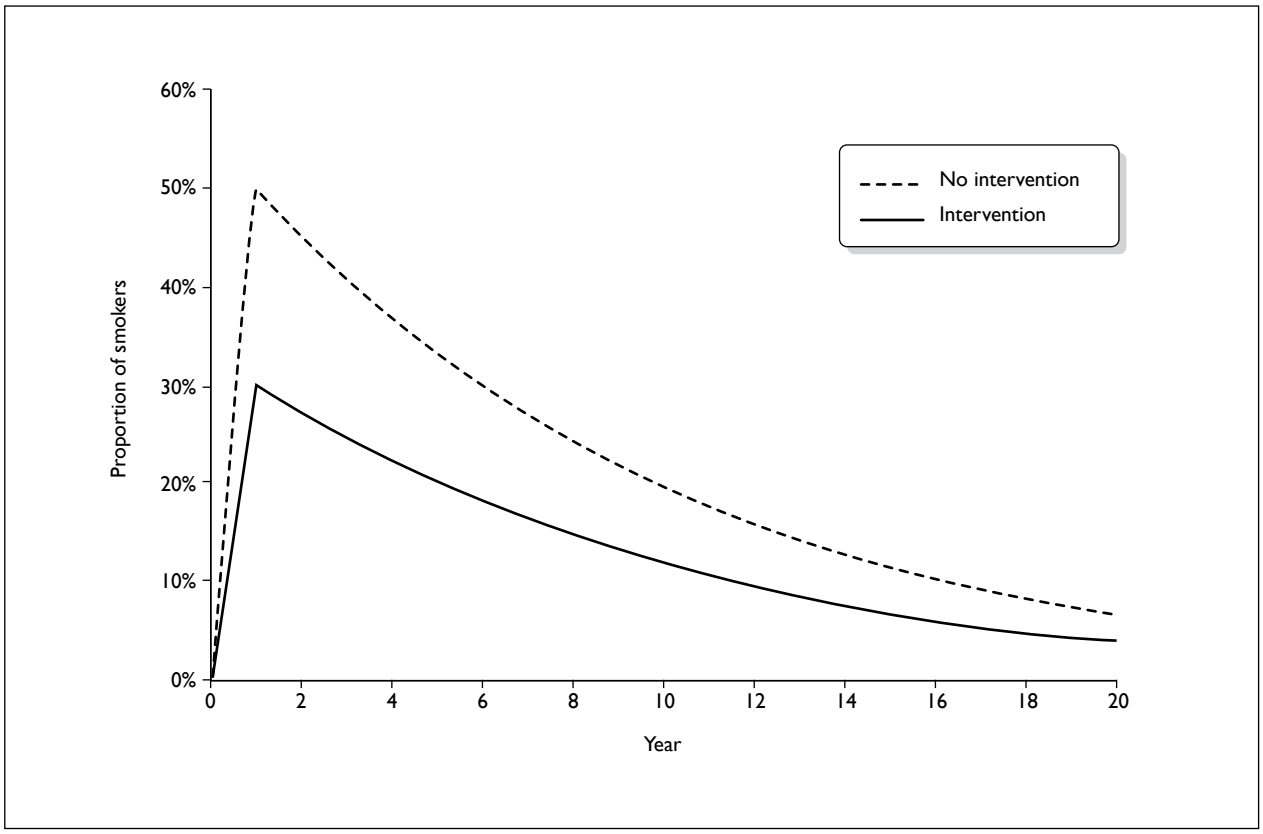

FIGURE 13 *Hypothetical example of long-term benefits (as assumed in 'base-case' model). Assuming abstinence rates observed at 1 year continue for a further 10 years.*

predict the long-term smoking status of those smokers who achieved temporary abstinence but subsequently relapsed to smoking. Consequently, we assessed three different potential scenarios for the persistence of benefits arising from intervention delivery (described above) and findings are related below for the base case (i.e. a constant 'background' relapse rate occurring after all interventions), assuming abstinence rates observed at 1 year continue for a further 10 years and assuming that differences in abstinence rates attributable to interventions persist for only 1 year.

For this analysis, it was assumed that abstinence rates observed at 1 year would continue for a further period of 10 years, after which the 'background' rate would be observed for each treatment arm (*Figure 14*). As expected, increasing the level of effectiveness of the treatments to 10 years increases the cost-effectiveness of each intervention (*Table 30*). However, it should be recognised that abstinence rates usually decline with time,[123] so this scenario is likely to overestimate the cost-effectiveness of treatments.

Assuming abstinence rates at 1 year do not persist beyond this and differences between groups disappear

In this scenario, we assumed that the benefits of an intervention would last only 1 year, after which there would be no differences between intervention and 'no intervention' groups (*Figure 15*). *Table 31*

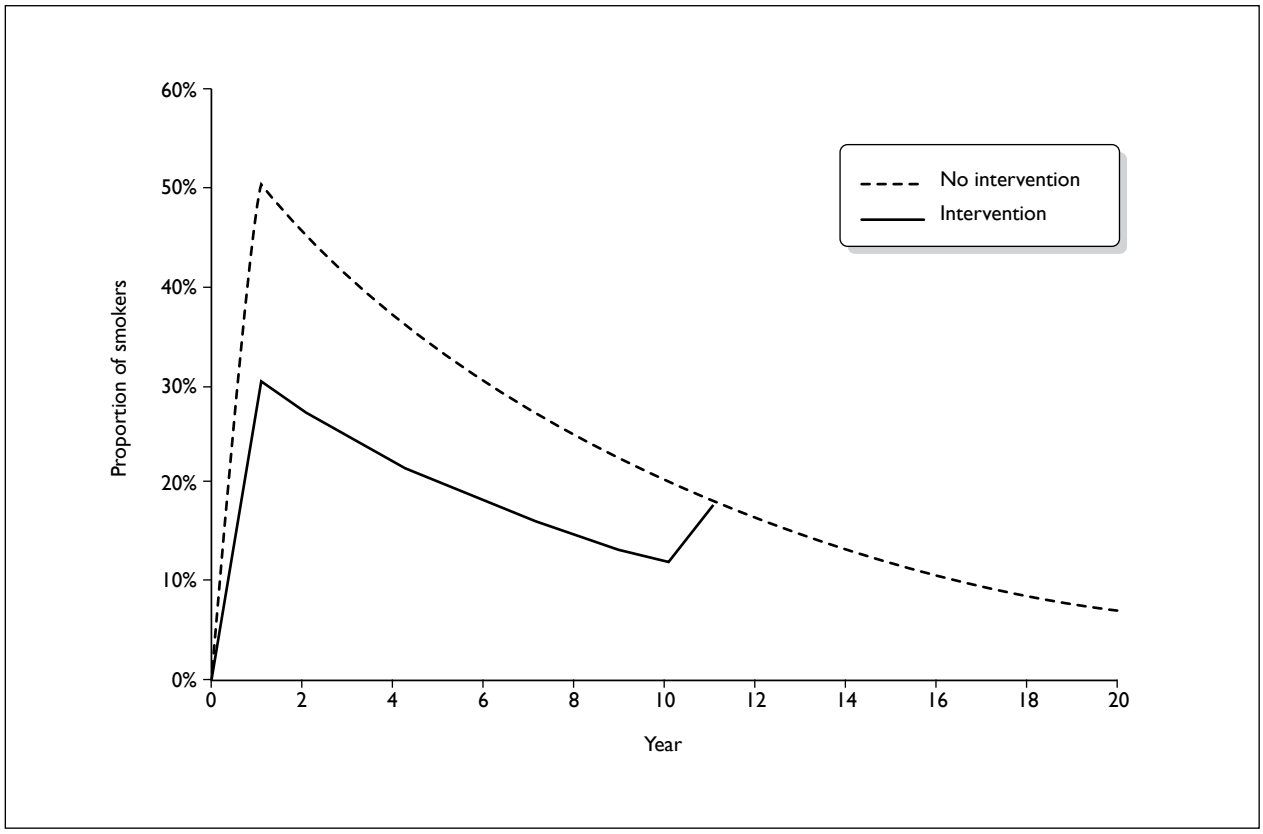

FIGURE 14 *Hypothetical example of benefits remaining for 10 years.*

TABLE 30 *Cost-effectiveness when full benefits last 10 years*

	Background cessation = 2%		
Compared with 'no intervention'	**Incremental cost (£)**	**Incremental QALY**	**ICER (£)**
'Bupropion' vs 'no intervention (bupropion trial)'	–102	0.091	Dominant
'NRT' vs 'no intervention (NRT trial)'	–38	0.074	Dominant
'Varenicline' vs 'no intervention (varenicline trial)'	26	0.081	322

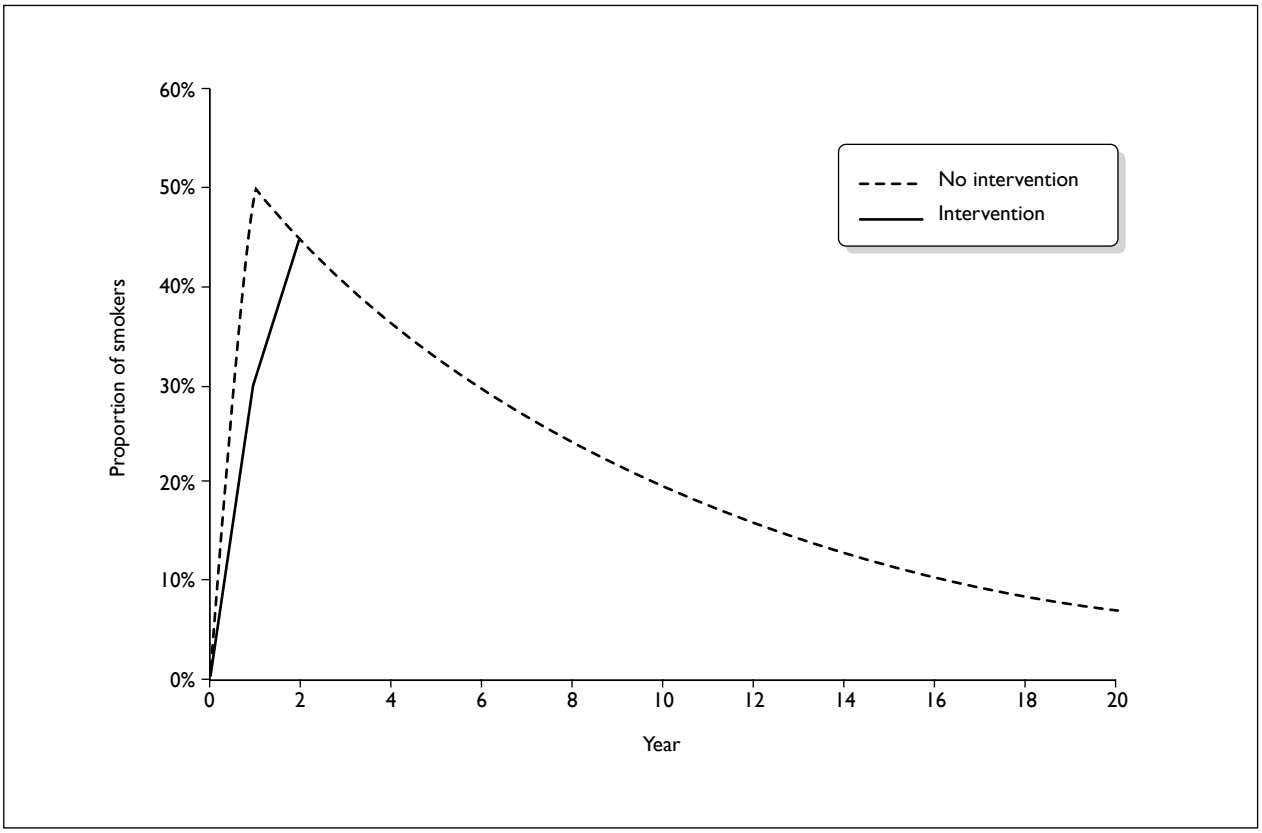

FIGURE 15 *Hypothetical example of benefits remaining for 1 year.*

TABLE 31 *Cost-effectiveness when benefits last only 1 year*

	Background cessation = 2%		
Compared with 'no intervention'	**Incremental cost (£)**	**Incremental QALY**	**ICER (£)**
'Bupropion' vs 'no intervention (bupropion trial)'	59	0.002	25,098
'NRT' vs 'no intervention (NRT trial)'	93	0.002	49,731
'Varenicline' vs 'no intervention (varenicline trial)'	170	0.002	91,189

shows that, in this instance, interventions do not appear to be cost-effective as judged by the usual NICE benchmark. This makes intuitive sense, since the benefits are only accrued for 1 year, while the cost of the intervention has remained at its full amount. However, it is very unlikely that the benefits of averting relapse would not be apparent after the first year and, as such, these results represent a highly unlikely worst-case scenario. Differences in abstinence rates between arms of smoking cessation trials have been observed up to 8 years after randomisation.[123]

Discussion and conclusions

Findings indicate that, in common with other interventions which reduce smoking, RPIs are also likely to be highly cost-effective; the economic and health costs of smoking are so great that reducing this, even moderately, produces substantial benefits. Compared with 'no intervention', using bupropion for relapse prevention resulted in an incremental QALY increase of 0.07 with a concurrent NHS cost saving of £68; for NRT, spending £12 resulted in a 0.04 incremental QALY

increase (see *Table 21*). Varenicline, produced the same incremental QALY increase as NRT, but at over seven times the cost, however, as these figures are derived from a single trial, they, require cautious interpretation and cost-effectiveness estimates for interventions should not be directly compared as they were obtained from different, heterogenic trials conducted in varied populations. Extensive sensitivity analyses demonstrated that cost-effectiveness ratios were more sensitive to variations in RPI effectiveness than cost and that; for bupropion and NRT, cost-effectiveness generally remained, even when input parameters are varied greatly. For varenicline, cost-effectiveness, as judged by the £20,000 per QALY benchmark remained at all but the minimum of the effectiveness range, but ICERs remained substantially higher than for bupropion and NRT throughout the range of costs and effects inputted. Cost-effectiveness was robust to the projected persistence of longer-term benefits from RPIs and base-case cost-effectiveness ratios only exceeded £20,000 per QALY when intervention effects were projected to last for only 1 year (*Table 31*). However, this scenario is highly unlikely as cessation intervention benefits can last for up to 8 years[123] and we can think of no reason why similar patterns of relapse to smoking would not be experienced after RPIs, and the effectiveness of NRT and varenicline is not likely to vary as markedly as was tested in analyses. The results of this study are comparable to those from economic evaluations of smoking cessation interventions; smoking cessation interventions have, in general, also been shown to result in greater benefits at lower or marginally higher costs than 'no intervention'.[121,124,125]

Limitations

There are a number of limitations inherent within the model. A lack of data on how comorbidities varied with smoking status made it impossible to categorise former smokers as achieving either 'recent' or 'long-term' abstinence and the impact of this on our findings is unclear. If at some point after permanently stopping smoking, the probability of developing some or all of the model comorbidities returns to that of non-smokers, the model will have overestimated the numbers of people with comorbidities and, hence, comorbidity costs, resulting in an underestimation of interventions' cost-effectiveness.

The model assumes that smokers use only one type of cessation intervention in any one quit attempt but, in 'real life', some smokers try stopping smoking repeatedly and some use many different cessation methods. However, the incorporation of a background quit rate into the model addresses this limitation, and sensitivity analysis demonstrated that RPIs appeared effective across a wide range of different background rates.

Model estimates for the effectiveness of interventions were taken from RCTs but interventions often show greater efficacy in trials than in routine clinical care and this could have contributed to an overestimation of cost-effectiveness. Also most pharmacotherapy relapse prevention trials required between 2 and 3 months abstinence from smoking before relapse prevention treatments were started and abstinence was generally achieved with the help of evidence-based support, so the model relates primarily to interventions used in this context. NRT trials provide some insight into the potential influences of abstinence period length and the use of support to achieve abstinence on cost-effectiveness. When trials with very short abstinence periods (< 48 hours), achieved without cessation support, were excluded from NRT analyses, NRT appeared to be even more cost-effective. Consequently, the effectiveness and cost-effectiveness of NRT, and perhaps of other RPIs, is likely to be dependent upon abstinent smokers' characteristics, such as how they achieved abstinence and also upon the timing of relapse prevention intervention delivery in relation to the start of any quit attempt. Unfortunately, the model cannot investigate these issues in the absence of sufficient empirical trial data.

Again, due to a lack of available data, the model assumed that, when a person had multiple comorbidities, their QoL was equivalent to that experienced with the most severe of these. From the perspective of assessing the impact of the interventions, this is a conservative assumption as each intervention, by encouraging abstinence from smoking, is likely to reduce the prevalence of *combinations* of comorbidities (e.g. LC and CHD would both become less likely in the event of smoking cessation). Improvements in the QoL experienced by some of those people with more than one comorbidity who remain abstinent would, therefore, be greater than the model predicts; QALY gains from eliminating such comorbidity combinations would be greater than predicted within the model and interventions would appear even more cost-effective.

One interesting aspect of this model is that, as recommended by the UK Treasury, all future costs and health outcomes have been discounted at 3.5% per year. However, it should be noted that the costs of RPIs are borne in the immediate future (i.e. undiscounted), while the benefits are likely to be accrued in the long-term future and hence, discounted. With discounting at 3.5% rate, one QALY today is equivalent to around 0.25 QALYs in 40 years' time and health gains experienced at this future time are, therefore, reduced fourfold. Recommended discount rates vary between different countries and even within countries over time; NICE's recommended rate for health outcomes was 1.5% until 2003. Because the costs of the interventions are accrued in the short-term and the benefits (i.e. reduced comorbidities) occur in the future, the results of this analysis will underestimate the undiscounted outcomes.

Summary

Our model shows that bupropion, NRT and varenicline (based on one trial) used by recently abstinent quitters to prevent relapse to smoking are cost-effective when, compared with 'no intervention' and judged against a 'willingness-to-pay' threshold of £20,000 per QALY. A direct comparison of the incremental cost-effectiveness of these treatments was not possible because data underpinning analyses were generally derived from mutually-exclusive trials, with insufficient data comparing interventions within trials to permit direct comparisons and any comparisons, therefore, must be indirect. All three of these pharmacological interventions for relapse prevention appear to have a similar magnitude of cost-effectiveness as smoking cessation-orientated interventions.

Chapter 5

Systematic review to derive abstinence curves for smokers attempting to stop smoking with the use of evidence-based treatments

Introduction

Understanding relapse patterns for smokers attending the NHS SSS is necessary to help estimate the likely impact that effective RPIs might have, if introduced into routine NHS SSS care. Unfortunately, routinely-available NHS SSS data cannot be used to accurately describe such relapse patterns because, in the NHS, smoking status is recorded at very few times after smokers' start quit attempts.[126,127] However, smokers attempting to quit using evidence-based cessation treatments are likely to have similar relapse behaviours and their patterns can be used as a proxy for those of smokers who use NHS support to assist cessation attempts.

Relapse patterns among smokers who attempt smoking cessation without support, the 'natural history' of relapse, have been described; most such untreated smokers return to smoking within 8 days of starting a quit attempt and only 3–5% are still abstinent at 6–12 months.[128] However, the patterns of relapse among smokers who use optimal, evidence-based treatments, such as those delivered through the NHS SSS, to help them try stopping have not been clearly defined. Individual trials have presented abstinence and/or relapse rates, but no systematic attempt has been made to locate and synthesise data from these diverse studies. Supported quit attempts are more successful than unsupported ones;[129] trials of pharmacotherapies and behavioural support for smoking cessation and their delivery in routine health-care result in higher 1 year abstinence rates of around 25%[130–133] and 18%[127] respectively. Relapse is, therefore, less frequent in supported quit attempts, but we currently do not know how smoking cessation treatments might exert effects on relapse. For example, cessation treatments may make relapse less frequent without affecting the actual process of relapse itself; in this situation, variations over time in relapse rates of untreated and treated smokers would be identical and, hence, the shapes of relapse curves for both would be the same. However, the proportion of smokers remaining abstinent from smoking at any given time after quitting would be higher after cessation had been achieved with treatment. Alternatively, if cessation treatments affected the processes involved in relapse to smoking, then relapse curves for treated smokers would have different shapes to those derived for untreated ones.

Only two studies have investigated relapse patterns after cessation had been achieved, using evidence-based treatments. A systematic review investigated relapse to smoking after use of NRT, but did not adequately describe relapse patterns immediately after smokers' quit dates when relapse rates are highest.[134] Also, a non-systematic review has, using data from a small number of trials, qualitatively compared relapse curves after cessation with NRT and behavioural support; the authors hypothesised that most variation in relapse patterns or rates of relapse happened in the very early stages of quit attempts and that such differences were attributable to different cessation treatments used.[135] Clearly more rigorous synthesis of available data would determine whether such hypotheses are valid. To investigate patterns of relapse among smokers who have used cessation support, we conducted a systematic review to determine the timing and rate of relapse among smokers who attempt to stop smoking while accessing evidence-based support, and derived relapse curves reflecting their experiences. We define 'relapse' in this chapter to mean any return to smoking after quit date.

Aim

To derive 'relapse to smoking' (abstinence) curves for smoking cessation attempts made with NHS SSS using (1) prolonged and (2) point abstinence from smoking as outcome measures.

Objectives

1. To systematically search for and identify RCTs in which intervention group smokers receive evidence-based interventions similar to those provided by NHS SSS, including trials of NRT, bupropion varenicline and nortriptyline delivered with behavioural support.
2. To select from identified trials, those including sufficient data for accurate relapse curves, reflecting relapse patterns in the first year after smokers' quit dates, to be drawn; those involving adult smokers with a clearly reported quit date and at least 12 months' subsequent follow-up, with smoking status being recorded at least three times in the first month after quitting.
3. To extract and synthesise smoking status data from intervention groups of selected trials, above enabling relapse curves to be drawn.

Methods

Rationale for studies' inclusion

We anticipated that the most robust data on the frequency of relapse by smokers in quit attempts would be collected during clinical trials and used the following considerations to decide which clinical trials were appropriate for consideration.

Interventions

We wanted to derive a relapse curve for smokers receiving optimal, evidence-based smoking cessation support and used Cochrane Collaboration systematic review evidence to define this. Cochrane reviews show that behavioural support provided outside of routine clinical care is effective for smoking cessation[136,137] as are NRT,[138] bupropion,[139] varenicline[140] and nortriptyline.[139] Consequently, we defined optimal, evidence-based smoking cessation support as the following two interventions combined, being provided in addition to routine clinical health care: (1) if behavioural support, defined as either the duration of time spent with a smoker (including assessment for trial entry), exceeded 30 minutes at the initial consultation and the number of further assessment and re-enforcement visits exceeded two or at least four appointments in total occurred in which brief support (5–10 minutes' duration) was given plus (2) any single pharmacotherapy treatment for which there was Cochrane review evidence for efficacy and a side effect profile which has enabled it to have widespread use in at least one country; eligible pharmacotherapies were NRT, bupropion, varenicline and nortriptyline. We excluded trials that assessed relapse prevention.

Relapse curves

Although we wanted to derive a 'survival'-type relapse curve, we anticipated some difficulty in obtaining data for this. A 'survival'-type relapse curve uses the exact date that a smoker returns to smoking to plot the proportion remaining abstinent from smoking over time,[128,141] but such plots or the data to draw them are not often reported.[128] Many trials either provide line graphs connecting the percentage or number of participants still abstinent at different time points or data with which these can be drawn[142] and due to a lack of 'survival'-type relapse curves and data in trial reports, these were used in a recent attempt to derive a relapse curve for 'untreated' smokers.[128] Consequently, for estimating our relapse curve, we decided to use trial reports which included both types of curve or data from which either could be derived.

Smoking outcomes and frequency of ascertainment

In smoking cessation trials, participants usually set a target quit date and have abstinence from smoking recorded as point prevalence or prolonged measures[143] at set time points afterwards; trials do not usually identify those participants who fail to stop smoking on the intended quit date (i.e. who quit for < 24 hours). Ideally, for constructing relapse curves, one would use a continuous or prolonged measure of smoking abstinence, but we anticipated that, in many trials, such measures would not be available and repeated point prevalence was more likely to be recorded at multiple follow-up points. We therefore decided to use trials which reported either prolonged or point prevalence abstinence from smoking, but present curves for these separately. Also, we anticipated, as has been found in 'untreated' smokers, that a large proportion of relapse would occur soon into any quit attempt,[128] so we sought trials which ascertained smoking status at least three times in the month following smokers' quit dates (preferably recorded at 2, 3 and 4 weeks after the start of treatment) and which had a final follow-up point at least 12 months after randomisation by which time most relapse to smoking would have occurred.

Process for identifying studies

The Cochrane Database of Systematic Reviews was searched in December 2009 to identify all reviews that potentially assessed

the impact of smoking cessation treatments using the term 'smoking cessation'. Forty-one systematic reviews were identified, of which 12 focused on pharmacotherapies for smoking cessation.[138–140,144–152] The 12 systematic reviews were screened to identify studies that assessed specific pharmacotherapies with evidence of effectiveness. The full texts of the papers identified from the included Cochrane reviews were then screened independently by two authors (JL-B and SA or AMcN and TC) using a specially designed data extraction form to assess whether they fulfilled the pre-specified inclusion criteria (see *Box 7*, *Figure 16*).

Assessment of methodological quality

Two authors (JL-B and SA) independently assessed the methodological quality of the eligible primary trials. The quality assessment for each trial included an evaluation of the method of generation of the randomisation sequence, the method of allocation concealment, whether blinding was used, percentage of participants lost to follow-up in the treatment group, and whether the participants were analysed using the intention to treat principle.

Data extraction

Two authors (JL-B and SA) performed data extraction independently and any differences were resolved through discussion. To derive curves for relapse to smoking by smokers using optimal, evidence-based smoking cessation treatments (as defined above), the following data were extracted from the arms of all included trials in which participants used such support:

(a) Where survival curves were reported, these were converted to abstinence rates at the pre-specified time points using visual assessment.
(b) Proportion of trial participants reporting continuous abstinence from smoking at all pre-specified time points between quit date and final follow-up.
(c) Proportion of trial participants reporting point abstinence from smoking at pre-specified time points between quit date and final follow-up.
(d) Number enrolled into the pharmacotherapy treatment group at randomisation.

The standard error for the prevalence of abstinence from smoking was estimated using the following formula:

$$\text{standard error} = \frac{\sqrt{\left[\text{prevalence} \times \left(100 - \text{prevalence}\right)\right]}}{\text{Number of participants in study arm}}$$

If possible, missing data were obtained by contacting the authors of the primary papers. One author (JL-B) entered the data, and double-checking was performed by another author (SA).

Statistical analysis

Meta-analyses were performed to calculate a weighted prevalence of abstinence in the cessation treatment groups across trials using a random effect model (DerSimonian and Laird model) at each pre-specified time point to allow for heterogeneity being anticipated between the studies. The results are presented as prevalence of abstinence estimates with 95% CIs. Statistical heterogeneity between the trials was quantified using I^2.[153] Separate pooled analyses were conducted based on the method used to report abstinence from smoking (point prevalence or continuous abstinence) were performed. Sensitivity analyses were conducted to assess the effect of excluding trials which yielded heterogeneous findings. The pooled estimates were then plotted to derive relapse curves for prolonged/continuous abstinence, and abstinence curves for point prevalence abstinence. Meta-analyses were conducted using REVIEW MANAGER 5.

Results

Three Cochrane systematic reviews that assessed pharmacotherapy trials for evidence of effectiveness were identified;[138–140] these included 202 articles and provided strong evidence that NRT, bupropion, varenicline and nortryptiline are all effective for smoking cessation (*Box 7*, *Figure 16*). Eleven trials were excluded due to having assessed a pharmacotherapy for which there was no evidence of effectiveness or one with a side effect profile that precluded its widespread use in at least one country (fluoxetine, $n = 2$; paroxetine, $n = 1$; sertraline, $n = 1$; moclobemide, $n = 1$; selegilline, $n = 2$; venlafaxine, $n = 1$; cytisine, $n = 1$;) or having assessed combinations of cessation treatments for which there was no evidence of effectiveness ($n = 2$). From the remaining 191 studies, 175 were excluded, in the following order, for not being described as a cessation trial ($n = 7$), not incorporating an intensive behavioural support component ($n = 45$), not having at least 12 months

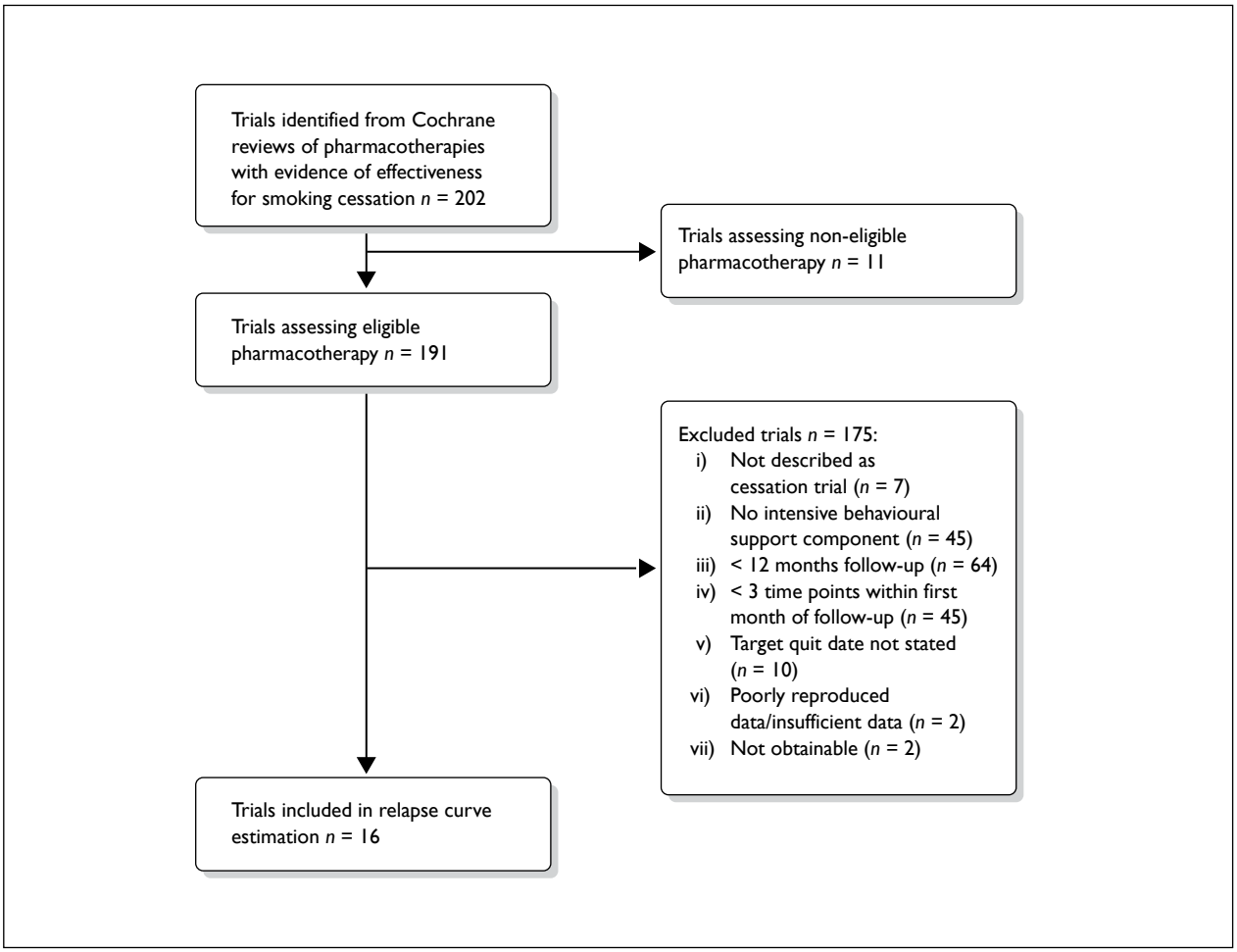

FIGURE 16 *Flow chart for included studies.*

BOX 7 *Criteria for studies inclusion*

Types of studies

RCTs

Types of participants

Adult daily smokers with a clearly defined quit date

Types of interventions

Intensive behavioural support [defined as either the duration of time spent with a smoker (including assessment for the trial) exceeded 30 minutes at the initial consultation and the number of further assessment and re-enforcement visits exceeds two; or a large number of visits to clinic/trial centre (at least four) where often brief (5–10 minutes) support is given over an extended period during treatment and follow-up], in addition to NRT, bupropion, varenicline, or nortriptyline

Frequency of smoking outcome ascertainment

A minimum follow-up period of 12 months and at least three follow-up points in the first month after quit date

Nature of smoking outcomes

Self-reported, prolonged or point prevalence abstinence from smoking between a quit date and follow-up points, where possible verified by biochemical assessment

follow-up ($n = 64$), not having at least three time points measured in the first month since quit date ($n = 45$), not having stated using a target quit date ($n = 10$), insufficient/poorly reproduced data presented to allow data extraction ($n = 2$), or not being obtainable through interlibrary loan ($n = 2$). Thus 16 RCTs were included[130–133,154–165] (*Table 32*, *Figure 17*) and 8679 participants were included in analyses. Ten trials were conducted in the USA, one in the UK, three in Iceland, one in Japan, and the remaining study was conducted in both the UK and the USA.

All included studies were published and assessed the individual effects of NRT,[132,133,157,160,161,163–165] bupropion,[130,131,154,155,162,164] or varenicline;[130,154,156,158,159] no eligible nortriptyline studies were identified. Eight trials used a two-arm, parallel group design and eight had multiple arms; four of which assessed the effect of two cessation treatments[130,131,154,164] and four trials were dose-ranging studies.[156,157,159,162]

Definition of abstinence

The majority of the included trials used point prevalence estimates to ascertain abstinence from smoking; 3-day point prevalence was used by one trial,[131] 7-day point prevalence by six,[130,154,156,158,159,161] and three did not report a minimum abstinence period required for point prevalence to be considered achieved.[163–165] Four trials used continuous abstinence from quit date,[132,133,157,160] one trial used continuous abstinence for the first month of follow-up followed by 7-day point prevalence,[162] and the remaining trial used 7-day point prevalence for all time points, except at 12 months when prolonged abstinence was reported.[155] None of the four trials reporting continuous abstinence reported point prevalence abstinence.[132,133,157,160] All of the included studies used biochemical verification to confirm non-smoking status.

Behavioural support

In addition to drug treatments, all included trials provided behavioural support (see definition above) outside of routine clinical care; four used group-based sessions and remaining studies used individual consultations to deliver this support. Further details are given in *Table 33*.

Risk of bias in included studies

Of the 16 included trials, eight reported methods used to generate their randomisation sequence, with five using computer-generated lists,[130,132,133,159,160] one stratified randomisation[162] and two block randomisation.[131,154] Only seven studies reported using an adequate method for allocation concealment, using centrally performed systems.[130,132,133,154,155,159,160] Thirteen studies used double-blinding,[130–133,154–157,159,160,162,163,165] all studies reported the proportion of loss to follow-up, and 11 stated using an intention-to-treat analysis.[130,131,154–159,161,162,164]

Pooled estimates for prevalences of abstinence by treatment

Nine estimates of prevalence from eight studies contributed to a pooled analysis which assessed the prevalence of abstinence from smoking after using NRT as a smoking cessation treatment; five assessed continuous/prolonged abstinence and the remaining four assessed point prevalence abstinence. In studies that reported continuous/prolonged estimates, abstinence decreased over time from 86% (95% CI 79% to 92%) at the first time point in the first month to 20% (95% CI 16% to 24%) at 12 months' follow-up (*Table 34*, *Figure 18*). Very high levels of heterogeneity were seen in the analyses conducted at the first three time points within the first month ($I^2 = 93\%$, 94% and 93%, respectively). In studies that reported point prevalence estimates, smaller reductions in abstinence were seen over time, which decreased from 51% (95% CI 42% to 61%) at the first time point in the first month to 30% (95% CI 17% to 42%; *Figure 19*). Substantially lower levels of heterogeneity were seen between the studies. Studies that reported continuous abstinence for all timings showed higher abstinence rates than studies which reported point prevalence abstinence rates. This is slightly unusual because point prevalence estimates for smoking cessation are usually higher than prolonged/continuous ones, however, these abstinence estimates were obtained from different trials, so comparisons are indirect and must be made cautiously because outcome differences may reflect the different characteristics of smokers within and settings of trials.

Six trials provided eight point prevalence of abstinence estimates that contributed to the pooled analysis assessing relapse after using bupropion; abstinence decreased over time from 35% (95% CI 21% to 49%) at the first time point within the first month to 22% (95% CI 17% to 27%) at 12 months' follow-up (*Figure 20*). Very high levels of heterogeneity were seen in

TABLE 32 *Included studies: abstinence curve review*

Trial	Pharmacotherapy and dose	Duration of pharmacotherapy treatment	Setting, number and characteristics of participants	Time points used within first month of follow-up			Verification method for abstinence	Ascertainment of abstinence
Blondal *et al.* (1997)[160]	NRT: 1-mg nicotine vapour maximum 5 doses/day	Recommended 3-month use	Iceland, *n* = 79 (40 male), mean (range) age = 42 years (22–67), mean (range) CPD = 26 (4–50), mean (range) FTQ score = 7.1 (3–10), mean (range) exhaled CO (p.p.m.) = 29 (3–80)	6 days	15 days	22 days	CO < 10 p.p.m.	Continuous
Blondal *et al.* (1999a)[132]	NRT: 0.5-mg nicotine spray/dose and 15 mg patch	Spray: 1 year Patch: 5 months	Iceland, *n* = 120 (43 male), mean (range) age = 41 years (23–62), mean (SD) grammes tobacco per day = 25.6 (15.7), mean FTQ score = 5.7, mean (SD) exhaled CO (p.p.m.) = 24.6 (12.3)	1 day	15 days	43 days	CO < 10 p.p.m.	Continuous
Blondal *et al.* (1999b)[133]	NRT: 15-µg nicotine vapour 6–12 times/day	Recommended maximum of 6 months	Iceland, *n* = 52 (21 male), mean (range) age = 42 years (25 –63), CPD mean (SE) = 29 (1) mean (SE) FTND = 6.5 (0.22)	15 days	22 days	43 days	CO < 10 p.p.m.	Continuous
Gonzales *et al.* (2001)[155]	Bupropion SR: 150 mg twice/day	12 weeks	USA, *n* = 226 (48% female), mean (SD) age 44.5 years (11.8), mean (SD) FTQ = 7.0 (1.7)	2 weeks	3 weeks	4 weeks	CO ≤ 10 p.p.m.	7-day PP (only reports continuous at 12 months)
Gonzales *et al.* (2006)[154]	Varenicline: 1 mg twice/day Bupropion SR: 150 mg twice/day	12 weeks	US study Varenicline arm: *n* = 352 (176 male – 50%), mean (SD) age = 42.5 years (11.1), mean (SD) CPD = 21.1 (9.47), mean (SD) FTND = 5.18 (2.16) Bupropion arm: *n* = 329 (192 male – 58.4%), mean (SD) age = 42.0 years (11.7), mean (SD) CPD = 21.0 (8.52), mean (SD) FTND = 5.19 (2.08)	2 weeks	3 weeks	4 weeks	CO < 10 p.p.m.	7-day PP
Hurt *et al.* (1994)[161]	NRT: 22-mg patch	8 weeks	USA, *n* = 120 (51.7% female), mean (SD) age = 42.8 years (11.1), mean (SD) CPD = 28.8 (9.4), mean (SD) FTQ = 7 (1.8), FTND = 6.3 (2), mean (SD) exhaled CO (p.p.m.) = 28.1 (11.7)	2 weeks	3 weeks	4 weeks	CO ≤ 8 p.p.m.	7-day PP

Trial	Pharmacotherapy and dose	Duration of pharmacotherapy treatment	Setting, number and characteristics of participants	Time points used within first month of follow-up			Verification method for abstinence	Ascertainment of abstinence
Hurt *et al.* (1997)[162]	Bupropion SR: 50 mg twice/day 150 mg once/day 150 mg twice/day	7 weeks	US study 50 mg twice/day arm: *n* = 153 (58.2% female), mean (SD) age = 44.1 years (10.5), mean (SD) CPD = 26.2 (8.5), mean (SD) FTQ = 7.3 (1.6) 150 mg once/day arm: *n* = 153 (50.3% female), mean (SD) age = 42.3 years (11.3), mean (SD) CPD = 27.5 (9.6), mean (SD) FTQ = 7.3 (1.6) 150 mg twice/day arm: *n* = 156 (50.6% female), mean (SD) age = 45.0 years (11.8), mean (SD) CPD = 27.2 (10.8), mean (SD) FTQ = 7.1 (1.7)	2 weeks	3 weeks	4 weeks	CO ≤ 10 p.p.m.	Continuous (first month), then 7 day PP
Jarvis *et al.* (1982)[163]	NRT: 2-mg gum	Recommended minimum of 3 months	UK, *n* = 58 (29/50% male), mean age = 41.0 years, mean CPD = 30.9. No nicotine addiction measure reported	1 week	2 weeks	4 weeks	Not used	PP (days not specified)
Jorenby *et al.* (1999)[164]	NRT: 21-mg patch Bupropion SR: 150 mg twice/day	Patch: 8 weeks Tablets: 9 weeks	US study NRT arm: *n* = 244 (51.6% female), mean (SD) age 44.0 years (10.9), mean (SD) CPD = 26.5 (9.4), mean (SD) FTQ = 7.4 (1.7), mean (SD) exhaled CO (p.p.m.) = 28.3 (9.9) Bupropion arm: *n* = 244 (51.6% female), mean (SD) age = 42.3 years (10.2), mean (SD) CPD = 25.5 (8.8), mean (SD) FTQ = 7.4 (1.6), mean (SD) exhaled CO (p.p.m.) = 28.4 (11.1)	2 weeks	3 weeks	4 weeks	CO < 10 p.p.m.	PP (days not specified)
Jorenby *et al.* (2006)[130]	Bupropion SR: 150 mg twice/day Varenicline: 1 mg twice/day	12 weeks	US study Bupropion arm: *n* = 342 (60.2% male), mean (SD) age = 42.9 years (11.9), mean (SD) CPD = 21.8 (8.7), mean (SD) FTND = 5.39 (2.19) Varenicline arm: *n* = 344 (55.2% male), mean (SD) age = 44.6 years (11.4), mean (SD) CPD = 27.1 (11.5), mean (SD) FTND = 5.39 (2.21)	2 weeks	3 weeks	4 weeks	CO ≤ 10 p.p.m.	7-day PP

continued

TABLE 32 *Included studies: abstinence curve review (continued)*

Trial	Pharmacotherapy and dose	Duration of pharmacotherapy treatment	Setting, number and characteristics of participants	Time points used within first month of follow-up			Verification method for abstinence	Ascertainment of abstinence
Nakamura *et al.* (2007)[159]	Varenicline: 0.25 mg twice/day 0.5 mg twice/day 1 mg twice/day	12 weeks	Japan study 0.25 mg twice/day arm: *n* = 153 (93 male – 72.7%), mean (SD) age = 40.2 years (12.3), mean (SD) CPD = 24.9 (10.3), mean (SD) FTND = 5.6 (2.1) 0.5 mg twice/day arm: *n* = 128 (91 male – 71.1%), mean (SD) age = 39.0 years (12.0), mean (SD) CPD = 23.8 (10.5), mean (SD) FTND = 5.5 (2.1) 1.0 mg twice/day arm: *n* = 130 (103 male – 79.2%), mean (SD) age = 40.1 years (11.6), mean (SD) CPD = 24.0 (9.8), mean (SD) FTND = 5.4 (2.1)	2 weeks	3 weeks	4 weeks	CO ≤ 10 p.p.m.	7-day PP
Oncken *et al.* (2006)[156]	Varenicline: 0.5 mg twice/day (non-titrated) 0.5 mg twice/day (titrated) 1.0 mg twice/day (non-titrated) 1.0 mg twice/day (titrated)	12 weeks	US study 0.5 mg twice/day (non-titrated) arm: *n* = 129 (45.0% male), mean (SD) age = 42.9 years (10.1), mean (SD) CPD = 20.9 (8.1), mean (SD) FTND = 5.5 (2.0) 0.5 mg twice/day (titrated) arm: *n* = 130 (53.1% male), mean (SD) age = 43.5 years (10.5), mean (SD) CPD = 21.3 (8.1), mean (SD) FTND = 5.4 (1.9) 1.0 mg twice/day (non-titrated) arm: *n* = 129 (48.8% male), mean (SD) age = 43.7 years (10.0), mean (SD) CPD = 20.8 (10.1), mean (SD) FTND = 5.5 (2.0) 1.0 mg twice/day (titrated) arm: *n* = 130 (48.5% male), mean (SD) age = 42.2 years (10.7), mean (SD) CPD = 20.9 (7.0), mean (SD) FTND = 5.3 (2.1)	2 weeks	3 weeks	4 weeks	CO ≤ 10 p.p.m.	7-day PP
Piper *et al.* (2007)[131]	Bupropion: 150 mg twice/day plus placebo gum	8 weeks	USA, *n* = 224 (135 female – 60.3%), mean (SD) age = 42.3 years (11.4), mean (SD) CPD = 23.4 (10.8), mean (SD) FTND = 5.7 (2.04), mean (SD) exhaled CO (p.p.m.) = 27.3 (11.2)	2 weeks	3 weeks	4 weeks	CO at 6 and 12 months only	3 consecutive day PP

Trial	Pharmacotherapy and dose	Duration of pharmacotherapy treatment	Setting, number and characteristics of participants	Time points used within first month of follow-up			Verification method for abstinence	Ascertainment of abstinence
Schneider *et al.* (1983)[165]	NRT: 2-mg gum	Ad lib, up to 1 year	USA, *n* = 30 (17 female – 57%), mean age = 40 years, mean CPD = 35. No nicotine addiction measure reported	2 weeks	3 weeks	4 weeks	CO at 4, 6 and 12 months only	PP (days not specified)
Shiffman *et al.* (2002)[157]	NRT: 4-mg gum NRT: 2-mg gum	12 weeks, but could extend to 24 weeks if required	UK and US study 4-mg gum arm: *n* = 450 (43.3% male), mean (SD) age = 44.28 years (11.78), mean (SD) CPD = 26.3 (11.2), mean (SD) FTND = 6.1 (1.8), mean (SD) exhaled CO (p.p.m.) = 27.16 (13.83) 2-mg gum arm: *n* = 459 (42.9% male), mean (SD) age 41.11 years (12.06), mean (SD) CPD = 17.7 (8.2), mean (SD) FTND = 2.6 (1.8), mean (SD) exhaled CO (p.p.m.) = 19.36 (12.02)	2 weeks	3 weeks	4 weeks	CO ≤ 10 p.p.m.	Continuous, had to be abstinent during first 2 weeks of follow-up to be eligible as abstinent at further follow-up
Williams *et al.* (2007)[158]	Varenicline: 1 mg twice/day	52 weeks	USA, *n* = 251 (127 male – 50.6%), mean (SD) age 48.2 years (12.3), mean (range) CPD = 23.2 (10–90), mean (SD) FTND = 5.50 (2.07)	2 weeks	3 weeks	4 weeks	CO ≤ 10 p.p.m.	7-day PP

CO, carbon monoxide; CPD, cigarettes smoked per day; FTND, Fagerstrom test for nicotine dependence; FTQ, Fagerstrom Tolerance Questionnaire; PP, point prevalence of abstinence; SD, standard deviation; SE standard error; SR, sustained release.

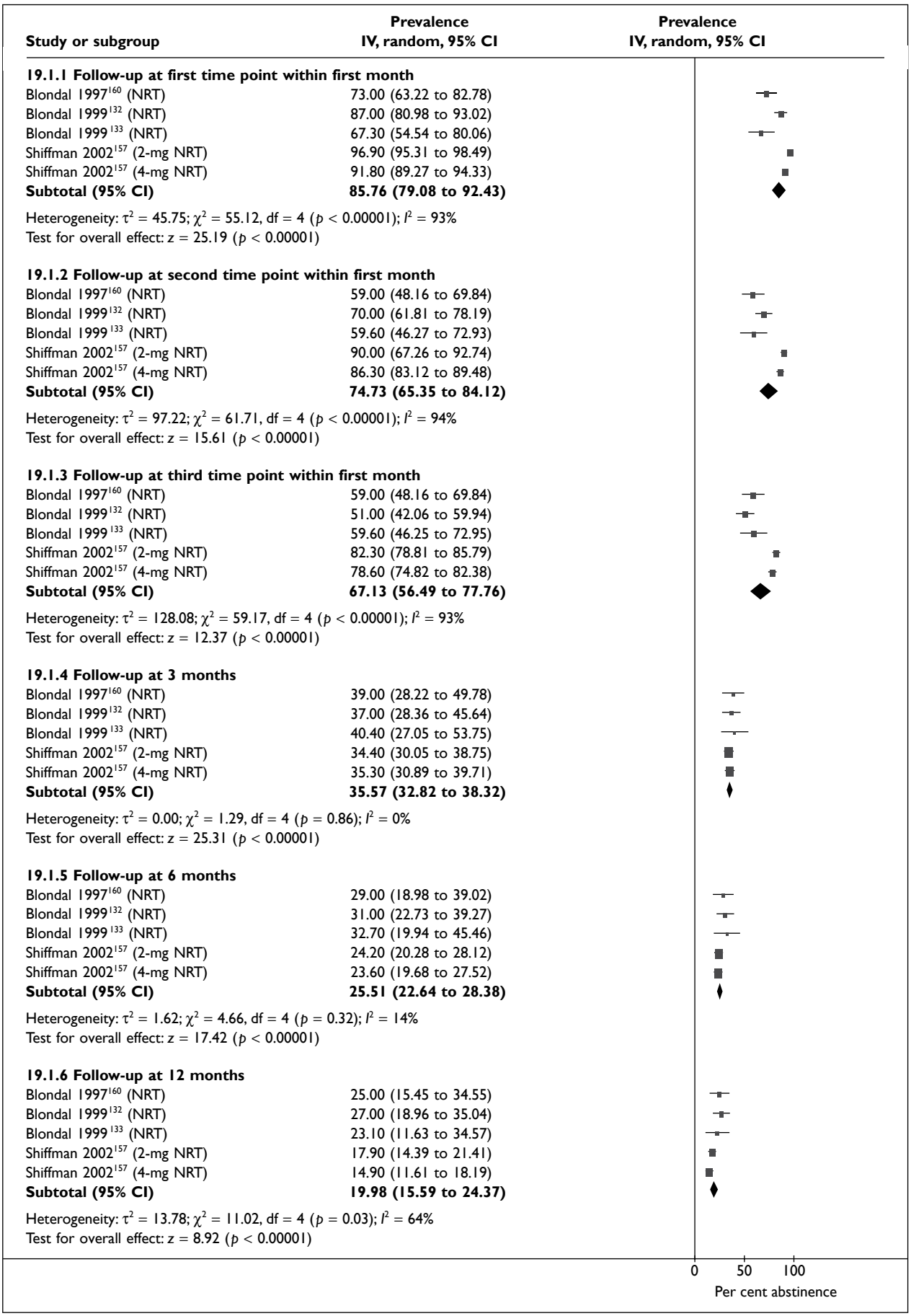

FIGURE 17 *Prevalence of continuous/prolonged abstinence after using NRT for smoking cessation in addition to behavioural support using a meta-analysis of RCTs. Data are presented as prevalence of abstinence and are pooled using random effect models. Squares represent the point estimate and the horizontal lines denote 95% CIs. Size of the data markers correspond to the weight of the study in the meta-analysis.*

TABLE 33 *Characteristics of the included studies*

Trial	Details of behavioural support
Blondal *et al.* (1997)[160]	Group sessions. Each session 60 minutes. Six sessions over 43 days. Supportive treatment emphasised change in attitude towards smoking, discussion of various methods to remain smoker free and how to cope with difficult situations. Instructional booklet on how to stop smoking
Blondal *et al.* (1999)[132]	Group sessions. Supportive meetings attended on days 1, 8, 15 and 22 days post-quit
Blondal *et al.* (1999)[133]	Group sessions. Each session 60 minutes. Five sessions up to day 22 post-quit. Support delivered by two therapists experienced in smoking cessation. Change in self-image from a smoker to a non-smoker was emphasised and coping strategies
Gonzales *et al.* (2001)[155]	Individual sessions. Brief counselling from trained research counsellors based on a standard intervention to encourage smoking cessation and to prevent relapse for nine visits to week 12
Gonzales *et al.* (2006)[154]	Individual sessions. Up to 10 minutes of brief standardised counselling to assist in problem solving and skills training for relapse prevention for 12 weeks
Hurt *et al.* (1994)[161]	Individual sessions. Brief counselling by study nurse then weekly telephone calls for counselling to week 12, further follow-up visits with counselling made at 6, 9 and 12 months
Hurt *et al.* (1997)[162]	Individual sessions. Each session 10–15 minutes lead by study assistant
Jarvis *et al.* (1982)[163]	Group sessions. Each session 60 minutes. Weekly meeting for 6 weeks
Jorenby *et al.* (1999)[164]	Individual sessions. Each session up to 15 minutes. Weekly sessions. Motivation, identification of smoking triggers, coping responses, weight management, use of medications, using standardised treatment. Supportive telephone call from counsellor approximately 3 days post-quit date
Jorenby *et al.* (2006)[130]	Individual sessions. Up to 10 minutes of brief smoking-cessation counselling at each clinic visit for 12 weeks. Up to 5 minute telephone call 3 days post-target quit date
Nakamura *et al.* (2007)[159]	Individual sessions. Up to 10 minutes of brief smoking-cessation counselling at each clinic visit for 12 weeks. Up to 5 minute telephone call 3 days post-target quit date
Oncken *et al.* (2006)[156]	Individual sessions. Up to 10 minutes of brief smoking-cessation counselling at each clinic visit for 12 weeks. Up to 5 minute telephone call 3 days post-target quit date
Piper *et al.* (2007)[131]	Individual sessions. Participants attended one session per week for 4 weeks then two more sessions every other week. Brief counselling at quit date and first post-quit session for a total of three 10-minute counselling sessions over 3 weeks
Schneider (1983)[165]	Individual sessions. Each session approximately 45 minutes. Clinic support system. Discussed daily progress and problems
Shiffman *et al.* (2002)[157]	Individual sessions. Each session 5–10 minutes for first four weekly visits. Study co-ordinator reviewed behavioural tips and directing participant's attention to user guide
Williams *et al.* (2007)[158]	Individual sessions. Each session up to 10 minutes of brief counselling at randomisation and at each visit

the analyses conducted for the three follow-up points within the first month, at 3 months' and 12 months' follow-up (I^2 = 98%, 95%, 95%, 85%, 88%, respectively). A subgroup analysis based on studies that reported continuous abstinence for all timings could not be performed as all of the included studies reported point prevalence of abstinence only. However, when a sensitivity analysis based on excluding outlier results[131,155,164] was performed, the estimates for pooled prevalence were generally less heterogeneous and abstinence rates were lower (first month: first time point = 30%, second time point = 30%, third time point = 29%; 3 months = 31%; 6 months = 26%; 12 months = 23%).

Five trials provided 10-point prevalence of abstinence estimates that contributed to the analysis-assessing relapse after varenicline use. Abstinence did not decrease appreciably over time; it was 36% (95% CI 32% to 40%) at the first time point within the first month and 31% (95% CI 28% to 35%) at 12-month follow-up (*Figure 21*) with moderate levels of heterogeneity in analyses. A sensitivity analysis based on methods of ascertainment of smoking cessation outcome was not possible because all studies reported only point prevalence abstinence, and a sensitivity analysis excluding 'outliers' was not performed as no studies were deemed to have outlier results.

TABLE 34 *Details of behavioural support given in the included studies*

	Pooled point prevalence of abstinence (95% CI, I^2)			
	NRT	**Bupropion sustained release**	**Varenicline**	**Combined**
Number of trials included	5	6	5	16
First time point within first month	51.1 (41.7 to 60.5, I^2 = 67%)	34.7 (20.7 to 48.8, I^2 = 98%)	35.9 (32.2 to 39.6, I^2 = 64%)	47.0 (33.7 to 60.3, I^2 = 99%)
Second time point within first month	54.0 (46.0 to 62.0, I^2 = 59%)	37.0 (27.6 to 46.3, I^2 = 95%)	46.0 (43.1 to 48.8, I^2 = 32%)	49.8 (40.7 to 58.8, I^2 = 98%)
Third time point within first month	50.3 (45.2 to 55.5, I^2 = 13%)	37.3 (27.3 to 47.3, I^2 = 95%)	48.5 (45.0 to 52.0, I^2 = 55%)	49.0 (41.7 to 56.3, I^2 = 97%)
3 months	40.8 (34.4 to 47.3, I^2 = 40%)	34.8 (29.1 to 40.4, I^2 = 85%)	55.3 (49.9 to 60.6, I^2 = 82%)	43.9 (39.6 to 48.2, I^2 = 90%)
6 months	32.2 (21.8 to 42.6, I^2 = 79%)	27.2 (24.0 to 34.3, I^2 = 57%)	35.1 (30.6 to 37.0, I^2 = 77%)	30.6 (27.9 to 33.3, I^2 = 77%)
12 months	29.3 (16.6 to 42.0, I^2 = 87%)	21.9 (16.6 to 27.2, I^2 = 88%)	31.4 (27.5 to 35.2, I^2 = 69%)	26.2 (22.9 to 29.4, I^2 = 87%)

Comparison of relapse patterns, measured by point prevalence, for different cessation treatments

The smoking abstinence patterns for NRT, bupropion and varenicline, as measured by point prevalence estimation, differed markedly over the first 3 months after quitting, became similar after this and showed a similar pattern of steady decline from 6 months onwards (*Figure 21*). One caveat was that, when drawing smoking abstinence curves from point prevalence estimates, imputation of data between the discrete time points at which prevalence's were obtained is necessary. However, *Figure 21* summarises the best currently available data for considering smoking abstinence patterns after supported cessation attempts.

Treatment with NRT resulted in most abstinence at the first follow-up point after quitting; approximately 51% of those receiving NRT were abstinent at around 2 weeks into quit attempts, compared with approximately 35% of those receiving bupropion and varenicline. The abstinence rate with NRT then remained fairly constant, and much higher than with other treatments, for the rest of the first month after quitting, followed by a smooth decline for the remainder of the year. In contrast, the proportion abstinent with bupropion changed little over the initial 3 months and subsequently followed a near-identical pattern of decline to that with NRT.

Abstinence patterns with varenicline were different again; varenicline treatment resulted in a sharp increase in the proportion abstinent within the first month of treatment followed by a slower rate of increase in abstinence until around 3 months, when over half were abstinent (55%). After 3 months, point prevalence abstinence rates after varenicline began declining and did so at a similar rate to those after treatment with on bupropion and NRT, but with higher overall abstinence rates recorded. This is demonstrated by the varenicline curve having a very similar shape to others after the 3-month point, but being higher in relation to the *y*-axis.

Discussion

We have described, for the first time, abstinence patterns over 12 months after quitting with NRT, bupropion or varenicline; the three cessation treatments used most frequently used by NHS SSS; combined with behavioural support. Abstinence rates differed markedly initially but became comparable after 3 months. For NRT, the complete abstinence curve followed a similar trajectory to untreated smokers' relapse curves[128] with highest abstinence rates at the very start of smokers' quit attempts; for bupropion minimal smoking occurred before 3 months and, for varenicline, little return to smoking occurred in the whole 12-month period. Compared to untreated smokers' curves,[128] those derived in this study suggest that

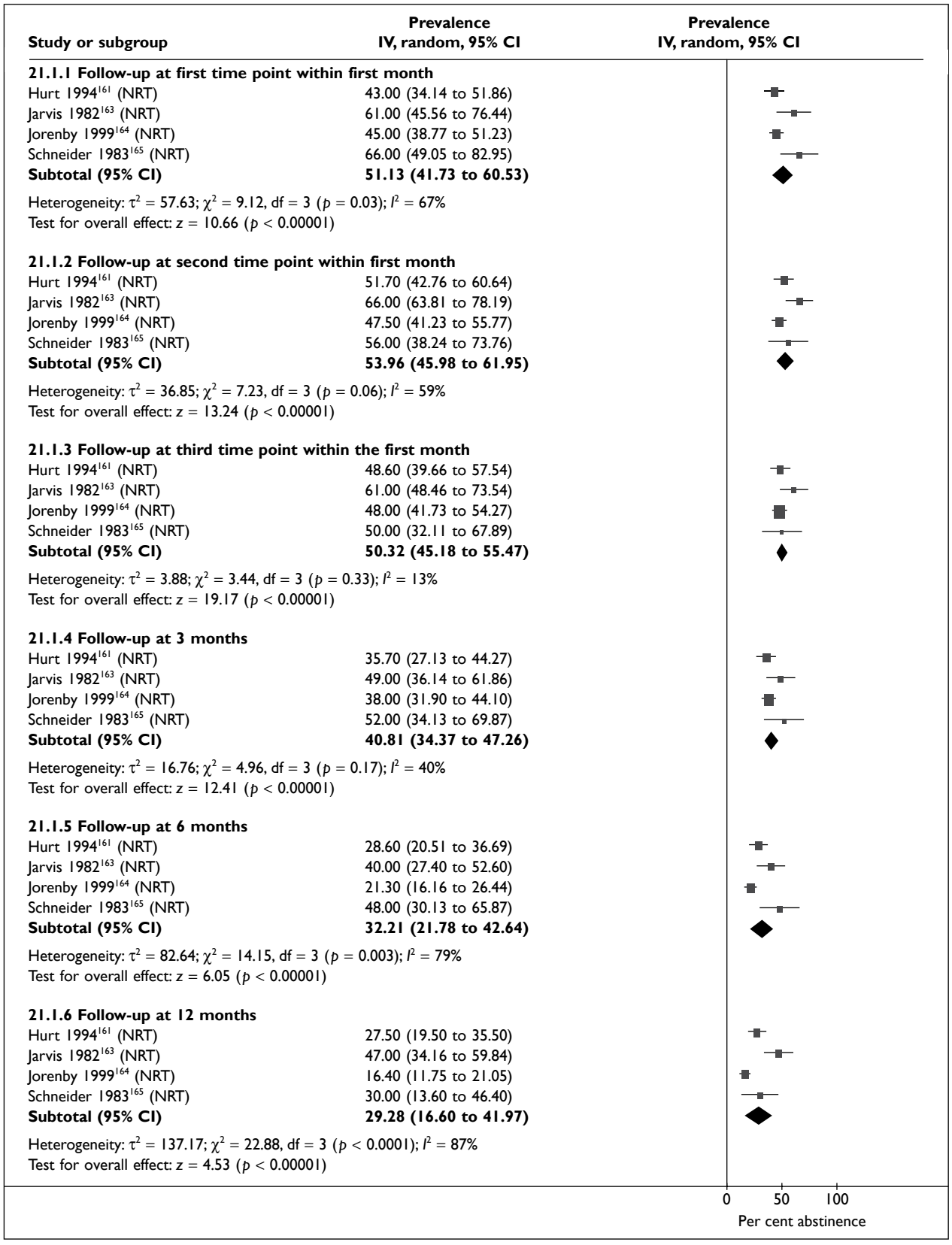

FIGURE 18 *Prevalence of point abstinence after using NRT for smoking cessation in addition to behavioural support using a meta-analysis of RCTs. Data are presented as prevalence of abstinence and are pooled using random effect models. Squares represent the point estimate and the horizontal lines denote 95% CIs. Size of the data markers correspond to the weight of the study in the meta-analysis.*

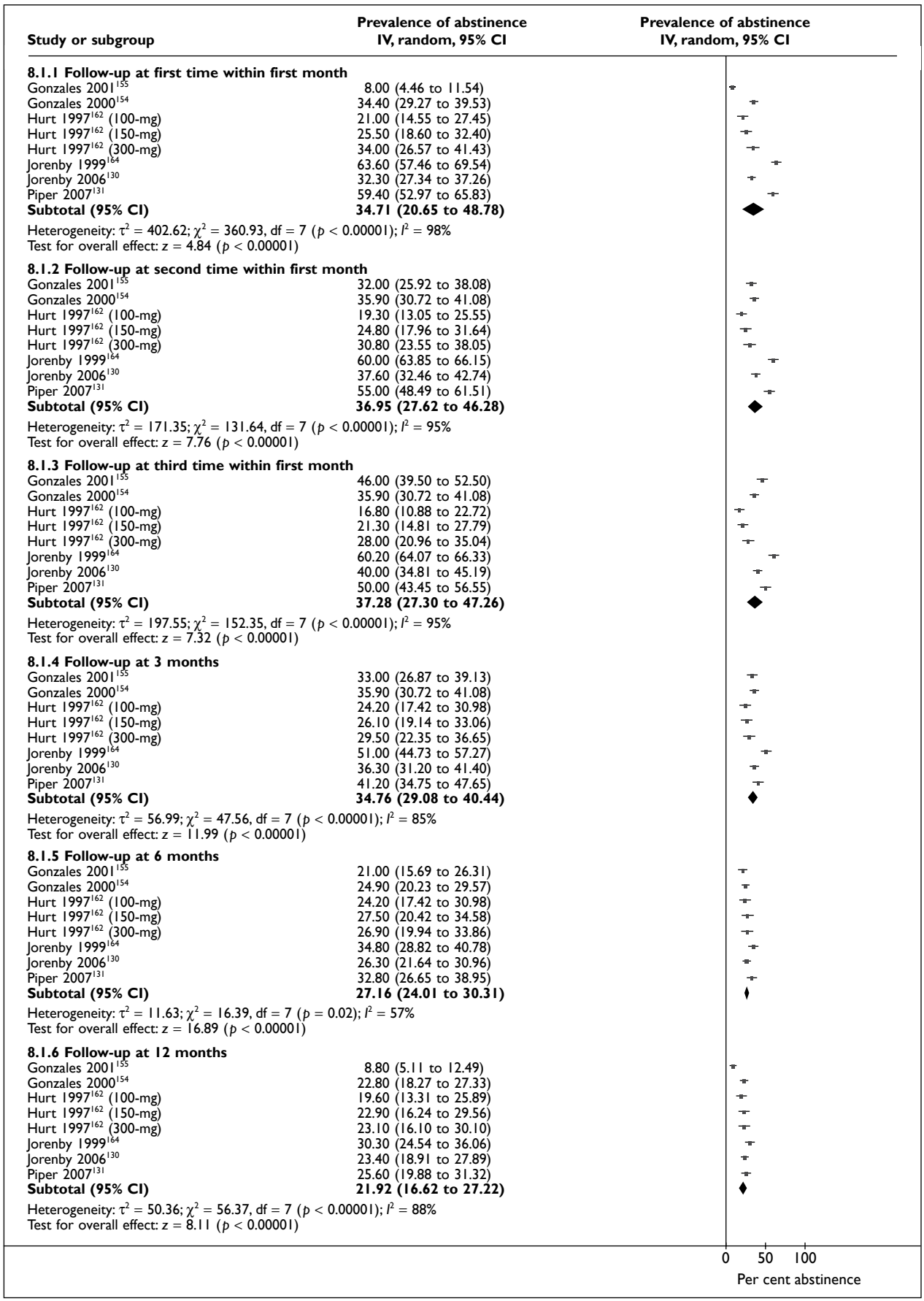

FIGURE 19 *Prevalence of point abstinence after using bupropion SR for smoking cessation in addition to behavioural support using a meta-analysis of RCTs. Data are presented as prevalence of abstinence and are pooled using random effect models. Squares represent the point estimate and the horizontal lines denote 95% CIs. Size of the data markers correspond to the weight of the study in the meta-analysis.*

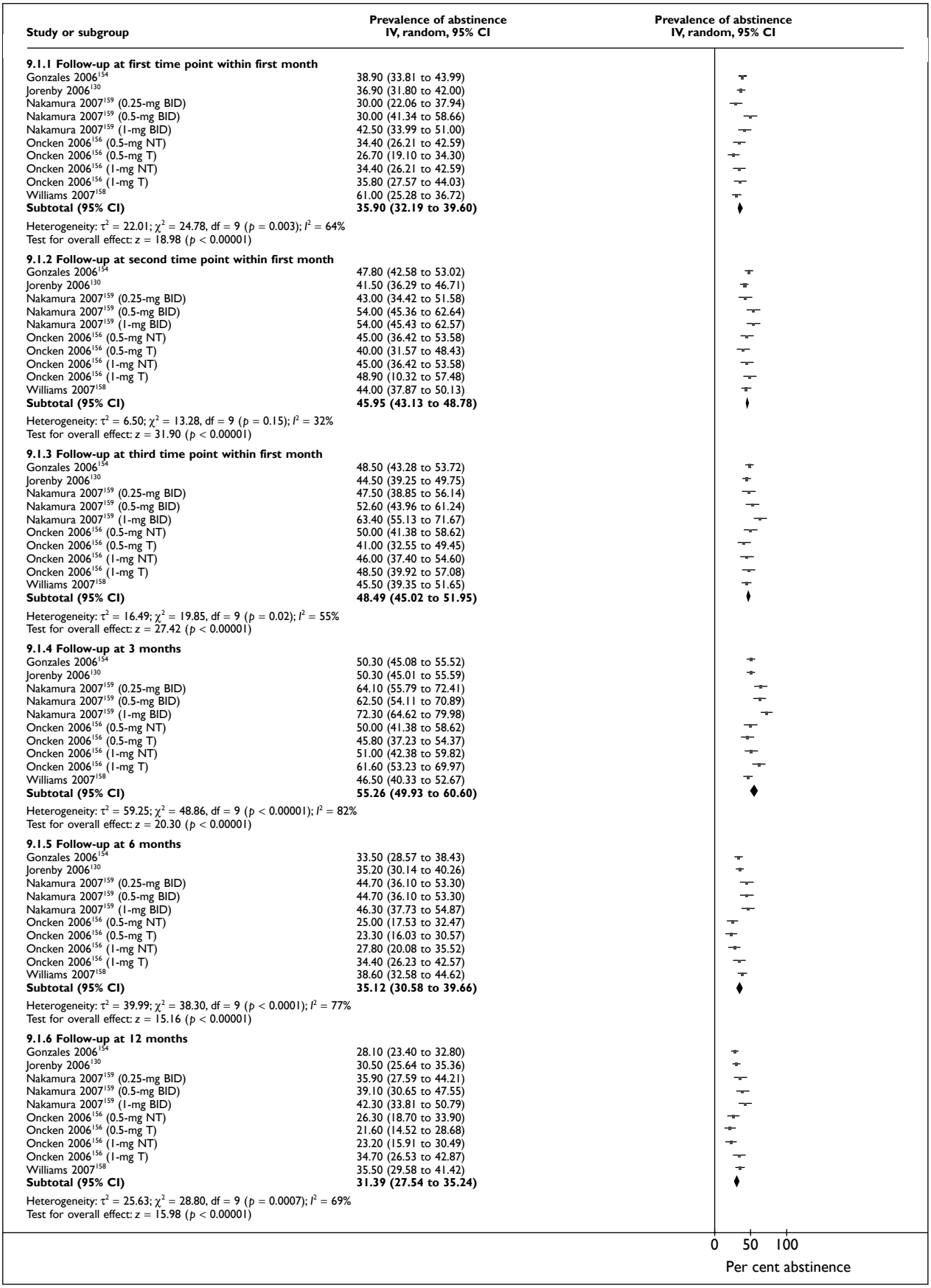

FIGURE 20 *Prevalence of point abstinence after using varenicline for smoking cessation in addition to behavioural support using a meta-analysis of RCTs. Data are presented as prevalence of abstinence and are pooled using random effect models. Squares represent the point estimate and the horizontal lines denote 95% CIs. Size of the data markers correspond to the weight of the study in the meta-analysis. BID, twice per day; NT, non-titrated; T, titrated.*

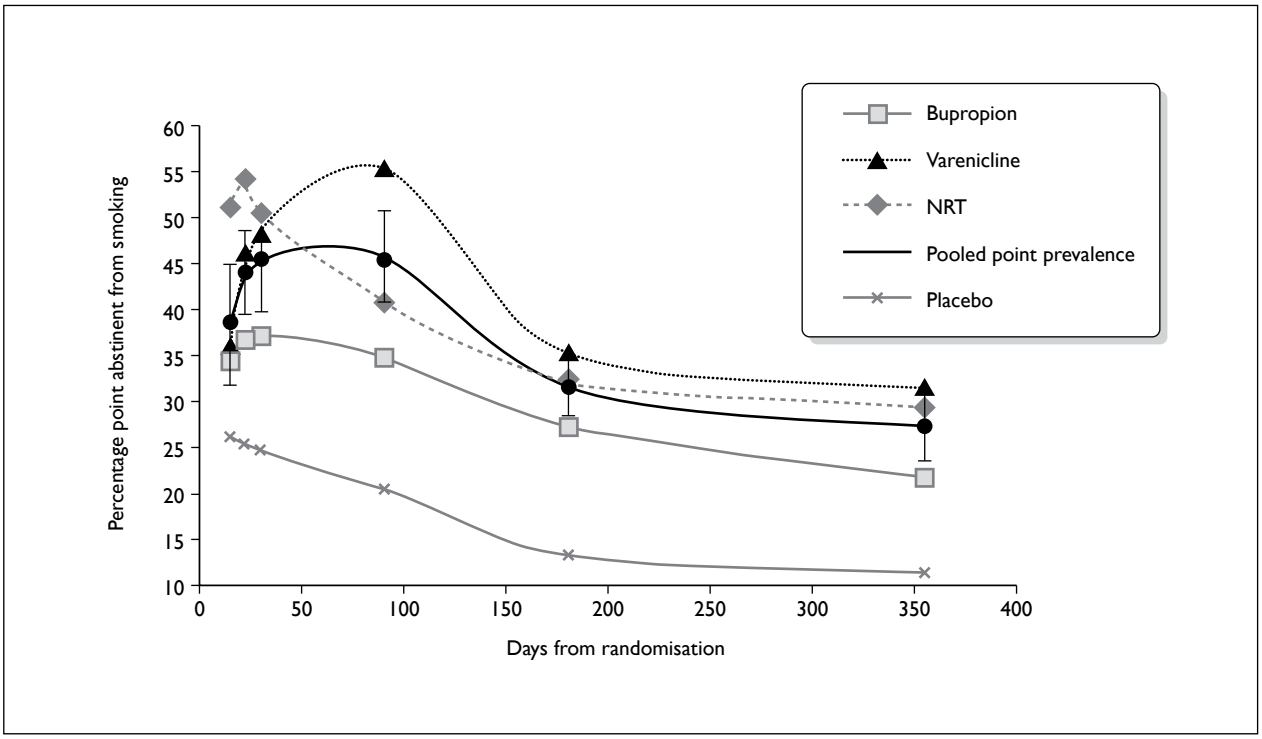

FIGURE 21 *Abstinence curves (shown as line graph) in participants from the included trials of evidence-based smoking cessation treatments using pooled estimates of point prevalence of abstinence from meta-analyses of RCTs. Crosses represent the point estimates for NRT, squares represent the point estimates for bupropion, triangles represent the point estimates for varenicline, and stars represent the point estimate for the combined medications derived from the meta-analyses. Horizontal lines denote the 95% CIs for the combined medications estimate at each of the pre-specified points of follow-up.*

evidence-based cessation treatments postpone returning to smoking; returning to smoking continued throughout the first year of treated quit attempts but in untreated ones almost all returning to smoking occurs within 3 months.

Limitations

Comparisons across treatments require caution because most studies used only point prevalence measures to ascertain smoking status and few trials reported prolonged abstinence measures, such as continuous cessation between quit dates and follow-up points. Point prevalence measures can be more volatile than continuous or prolonged measures of abstinence and the latter are more appropriate for deriving relapse curves, however, in the absence of continuous outcome data being reported at all time points we have been restricted to using point prevalence to derive our abstinent curve. We have only been able to contrast curves derived from prolonged and point prevalence abstinence measures for NRT trials and curves presented are derived from different trials as, within individual studies, continuous and point prevalence outcome measures were often not reported for simultaneous follow-up points. However, apart from within the first month where an increase in abstinence was seen in the abstinence curves, the curves derived using these two different outcome measures had broadly similar shapes. When comparing the shapes of the abstinent curves derived using prevalence data, very different relapse patterns are seen within the first 3 months of quit attempts assisted by bupropion or varenicline as compared to NRT. This difference may be real and due to differences in the responses of patients to these treatments or perhaps in the characteristics of smokers using them. Another caveat is that 14 of the 16 included studies assumed participants with missing outcome data or who were lost to follow-up had returned to smoking; this could have had an impact on our findings by artificially lowering the abstinence rates at the later follow-up time points since the percentage of participants not completing the studies ranged from 0% to 50%, although a third of studies had less than 10% non-completers.

A further caveat is that no trials reported the proportion of participants who did not attempt to

stop smoking on their quit date and none explicitly reported that patients must attempt cessation on their intended quit dates (though this is implied in many cessation studies). Consequently, by including in our analyses those who fail to stop smoking at all, our relapse curves may overestimate initial relapse rates at the outset of cessation attempts; future trials should consider reporting such data. Findings should be seen as preliminary due to observed heterogeneity between some prevalence estimates. By only including trials that satisfied Cochrane review standards, heterogeneity attributable to interventions employed is likely to have been minimised, but different doses of drug treatments and/or intensities of behavioural support may still have contributed towards this, as there were no striking differences in participants' demographic characteristics or nicotine addiction levels to help explain it. We believe that most heterogeneity has arisen from trials' use of slightly different follow-up time points within the first month after quitting which explains the more acceptable heterogeneity levels observed at the later, more uniform follow-up time points. We attempted to account for heterogeneity by using random effect models in analyses, though these methods may still result in confidence intervals which are too narrow and hence insufficiently conservative.[166] However, it is unlikely that bias was introduced into the meta-analysis since we identified eligible studies from published Cochrane reviews and included only relevant RCTs which collect data prospectively and are the most robust form of research evidence. Finally, the generalisibility of our findings to NHS SSS might be questioned; while all three pharmacotherapies studied are used frequently by NHS SSS, treatment protocols for the delivery of behavioural support are likely to differ and interventions used in clinical trials often demonstrate less effectiveness when translated into routine care.

A key finding of this review is that, irrespective of what happens in the very early stages of quit attempts, for all three treatments considered, substantial relapse occurs after 3 months and most cessation treatments will have been discontinued either prior to or at this time point. Eliminating relapse after 3 months could potentially increase 12-month quit rates by 13%, 14% and 19% for NRT, bupropion and varenicline respectively (estimates taken from *Figures 2*, *4* and *5* but are preliminary due to heterogeneity levels). This illustrates the potential impact of extending cessation treatment and complements the findings from Chapter 3 in which we demonstrated the efficacy, for smoking cessation, of extending the provision of smoking cessation medications beyond the usual acute cessation treatment period. Clearly, for the three treatments considered here and in Chapter 3, an extension of therapy periods, as previously suggested for NRT[134] might reduce relapse to smoking, facilitating higher rates of permanent smoking cessation. Additionally, as the rate of relapse early in quit attempts involving NRT is so rapid, any relapse prevention treatments that have an adjunctive impact at this time could have the substantial effects.

Chapter 6
Discussion

The strengths and weaknesses of the methodologies used in this review have been discussed within the chapters in which research methods were described; here we summarise the findings from the individual studies and discuss their implications, with particular reference to the potential integration of RPIs with smoking cessation support currently delivered by the NHS SSS.

Qualitative work and survey

Qualitative research with 16 health professionals working in NHS SSS indicated that there was no shared understanding of what relapse prevention meant or the kinds of interventions that should be used for this. Despite this, managers were positively orientated towards their use and indicated a willingness to provide them within the routine care delivered by their services. In the online survey, 96 NHS SSS managers from across the UK returned completed survey questionnaires (52% response rate). Of these, 58.3% ($n = 56$) reported running services that already provided RPIs for clients (RPI definition provided within survey), despite the absence of evidence for RPI effectiveness at the time of survey completion. The most commonly provided RPIs were behavioural support delivered by telephone (77%), in group settings (73%), or to individuals (54%). Pharmacotherapy was less frequently used for relapse prevention; just under half of managers reported that their services offered NRT (48%, $n = 27$) and 21.4% ($n = 12$) bupropion. Performance management targets for NHS SSS that focus on achieving relatively short (4-week) periods of cessation and inadequate funding for provision of RPIs were reported barriers to introducing such interventions into routine care.

Effectiveness of relapse prevention interventions

The systematic review that investigated the effectiveness of RPIs included 36 studies that randomised and delivered interventions to smokers who had recently achieved abstinence ('abstainers'). 'Self-help' behavioural interventions delivered to abstainers who had become abstinent without using any form of cessation support were effective for preventing relapse to smoking at long-term follow-up (OR 1.52, 95% CI 1.15 to 2.01). The following pharmacotherapies were also effective as RPIs after their successful use as cessation treatments: bupropion at long-term follow-up (pooled OR 1.49, 95% CI 1.10 to 2.01); NRT at medium- (pooled OR 1.56, 95% CI 1.16 to 2.11) and long-term follow-ups (pooled OR 1.33, 95% CI 1.08 to 1.63) and one trial of varenicline also indicated effectiveness. Eighteen studies randomised smokers and delivered behavioural RPIs to them as additional components to cessation treatment. Although a few individual trials reported some statistically significant findings, where pooled analyses were possible there was no evidence for the effectiveness of any interventions delivered at this time.

Cost-effectiveness of relapse prevention interventions

We conducted a health economic analysis for those interventions which, in our effectiveness review, appeared effective at preventing relapse when used by smokers who had achieved abstinence in 'supported' quit attempts, as would occur in routine NHS SSS care. We found that, in common with other interventions that reduce smoking, RPIs are highly cost-effective. Compared with 'no intervention'; using bupropion resulted in an incremental QALY increase of 0.07, with a concurrent NHS cost saving of £68; for NRT, spending £12 resulted in a 0.04 incremental QALY increase; varenicline resulted in a similar QALY increase as NRT but at almost seven times the cost; however, findings were derived from a single trial and require cautious interpretation. Extensive sensitivity analyses demonstrated that cost-effectiveness ratios were more sensitive to variations in effectiveness than cost and that, for bupropion and NRT, cost-effectiveness generally remained, even when input parameters are varied greatly, suggesting that this will be apparent in routine clinical practice. Varenicline also generally demonstrated cost-effectiveness at a 'willingness-to-

pay' threshold of £20,000 per QALY, but exceeded this when inputted values for potential effectiveness were at the lower end of the range explored. With available data, only indirect comparisons between RPIs are possible and, therefore, assessments of their relative cost-effectiveness should only be made with caution.

Relapse curves for smokers in supported quit attempts

There were no data available from smokers attending NHS SSS which could be used to draw relapse curves to reflect their experiences of relapse to smoking; curves derived were therefore based entirely on data from cessation trials in which smokers received interventions similar to those delivered by NHS SSS. Systematic searching and consideration of retrieved articles identified 16 RCTs meeting all review inclusion criteria and these investigated NRT, bupropion or varenicline combined with intensive behavioural support. For all drugs, there was substantial relapse to smoking after treatment courses had finished (i.e. between 3 and 12 months into quit attempts). Eliminating such relapse would improve cessation rates at 12 months by 13%, 14% and 19% for NRT, bupropion and varenicline respectively (though these figures are derived using some pooled abstinence estimates which have substantial heterogeneity). Quit attempts involving NRT appeared to have the highest early relapse rates, when trial participants would be expected to still be on treatment, but for those involving bupropion and varenicline little relapse was apparent during this time. However, this observation could have arisen because bupropion and varenicline trials assessed smoking cessation by repeatedly assessing short periods of abstinence from smoking, rather than asking about continuous cessation between participants' quit dates and all follow-up points.

Interpretation

Research with health professionals and managers working in the NHS SSS across the UK, indicated that a small majority were already providing RPIs, and there was a keenness to continue to do so or, in services which did not currently offer RPIs, to start to provide such interventions in the future. However, a lack of a shared understanding of what relapse prevention meant and a lack of evidence for the effectiveness of RPIs at the time of the survey meant that RPIs provided at that time were being delivered in the absence of any convincing evidence for their effectiveness. Additionally, in our efficacy review, we found no evidence that the most frequently-provided RPIs (counselling by telephone or in person) by the NHS SSS have any positive impacts. Should the NHS decide to fund RPI delivery by the NHS SSS, clear guidance on the kinds of interventions which should be delivered and which is informed by this report is required. Additionally, performance-management of NHS SSS would need altering, such that importance of sustaining quit attempts beyond 4 weeks is incentivised.

Our refined approach to reviewing the effectiveness of RPIs, found evidence for long-term effectiveness of bupropion, NRT and varenicline which had not previously been apparent. These medications are commonly used in NHS SSS and introducing them as relapse prevention treatments after a period of sustained abstinence reflects how relapse prevention would be likely to work within NHS SSS. Findings for bupropion are probably the most robust and the most generalisable to potential RPI use in the NHS as all the bupropion trials employed this model of 'extended treatment' after prolonged abstinence achieved with support. Greater caution is needed with respect to NRT because two of the four NRT trials, began relapse treatment with NRT after very short periods of unsupported abstinence (maximum 48 hours); it is not clear how generalisable findings from these trials are to the NHS SSS. Also as varenicline findings are based on only one trial, these should also be seen as preliminary, although since our review searches were conducted, further varenicline relapse prevention trials have also reported positively. It's worth noting that, none of the pharmacotherapy studies were conducted in countries which, like the UK, have had organised smoking cessation services for some years; it is possible that RPIs might be less effective in the UK where more 'resistant' smokers avail themselves for support. Self-help RPIs were also found to be effective for unsupported quitters and it is possible that these interventions could also be effective for smokers, like those accessing NHS SSS, who are supported in cessation attempts. However, this needs formal testing as it is entirely possible for self-help materials to have a much smaller treatment effect for preventing relapse when used by smokers who, early in quit attempts, are also receiving either pharmaceutical of behavioural treatments to try to stop smoking.

As might be expected for interventions which reduce smoking; NRT, bupropion and varenicline all appear very cost-effective as judged by the £20,000 per QALY, NICE benchmark and, for bupropion and NRT, with highly favourable cost-effectiveness ratios generally being maintained in the face of substantial sensitivity analyses, such that this is very likely to be maintained in routine clinical practice. Our economic analyses were limited by the empirical data from trials included in the RPI effectiveness review and, as such, there were too few direct comparisons between the different RPIs to enable comparisons about their relative cost efficacy to be made; available comparisons are indirect and must be viewed with caution. Similarly, most interventions were introduced after 2–3 months of supported abstinence, so it is not possible to be confident about the optimal time after quit attempts begin for relapse prevention treatments to be introduced. However, the relapse curves that were drawn as proxies for the relapse experiences of NHS SSS users suggest that merely extending treatment periods could have a significant impact. Additionally, the sensitivity analysis for NRT trials in the cost-effectiveness analysis suggests that RPIs delivered to supported quitters after longer abstinence periods might be more cost-effective than those delivered to unsupported smokers who have maintained only very short abstinences; this supports a model of extending treatment periods beyond currently delivered smoking cessation treatments in the NHS SSS.

To our knowledge, this is the first systematic attempt to describe relapse patterns for supported quit attempts; although relapse curves were not produced from routine NHS SSS data, they are the most appropriate to NHS SSS users' experiences yet produced. Curves show that initial patterns of relapse while smokers are likely to be on either NRT, bupropion or varenicline, differ markedly, but rates of relapse became comparable, and then converge after 3 months when most users are no longer being treated. Extended treatment periods with these medications past the 3-month point could potentially increase 12-month quit rates by between 10% and 20%. Given the uncertainties in some of our prevalence estimates, further research is needed to explore whether the varied trajectories observed early in quit attempts on different treatments are real or, alternatively, an artefact of how cessation was measured. However, as the high rates of relapse that were observed early in quit attempts using NRT appear independent of how trials assessed smoking cessation, the use of non-drug, behavioural RPIs, alongside NRT and behavioural support in such attempts, merits research.

Conclusions

In summary, our findings have identified that RPIs are likely to be very good value for money if incorporated into routine treatment within the NHS SSS. While staff within the NHS SSS were largely favourably inclined towards providing RPIs, guidance would be needed to encourage the adoption of the most effective RPIs as would incentives that focused on the importance of sustaining quit attempts beyond the currently monitored 4-week targets.

Recommendations

Research

1. Further research investigating the use of NRT, bupropion and varenicline (the three pharmacotherapies used in the NHS SSS) for relapse prevention is required, including the following:
   i. Placebo RCTs to investigate the (cost) effectiveness of these RPIs as an extension to current NHS SSS cessation support – most review trials were conducted in countries without organised cessation services and, hence relapse prevention interventions may have different outcomes in the UK.
   ii. Studies of the acceptability of extended use of pharmacotherapies for relapse prevention in NHS SSS users, and particularly of bupropion, which is the least frequently used cessation therapy in England; the acceptability of these pharmacotherapies for relapse prevention will influence their uptake.
   iii. Whether or not the addition of behavioural relapse prevention interventions, delivered in the early stages of quit attempts using NRT can have an adjunctive, positive impact on cessation rates.
   iv. Confirmation of whether the different trajectories of relapse that we observed for NRT, bupropion and varenicline are valid (i.e. a more rapid relapse rate for users of NRT in the first month compared with the other two drug treatments) and occur

when these treatments are used in routine NHS SSS clinical practice.

2. The following research into behavioural relapse prevention interventions is required:
   i. RCTs to confirm or refute the finding that self-help interventions, delivered to smokers who have achieved abstinence unsupported, have long-term effectiveness for preventing relapse to smoking.
   ii. RCTs to investigate whether or not self-help interventions delivered to smokers who have achieved abstinence with NHS SSS support are effective.
   iii. Further research to refine interventions that showed potential in our effectiveness review, such as individual counselling for pregnant women and the use of telephone support after cessation treatment and test whether or not these might have long-term effectiveness.
3. Methodological standardisation: among relapse prevention trials identified for this report, there was huge variation in the definition of RPIs, the characteristics of smokers these were delivered to, follow-up periodicity, and outcome measurement after randomisation. Also among cessation trials used to derive relapse curves, reporting of outcomes seriously restricted the data available. In order to permit coherent synthesis of future research findings in this important field, we recommend that practitioners and researchers investigating this field agree common standards for:
   i. The definition of RPI: in particular, consensus is needed as to whether behavioural RPIs, delivered alongside smoking cessation interventions to smokers either prior to or soon after quit attempts have started *can* or *should* be categorised as different to smoking cessation interventions. If there is consensus about such interventions being different, clear definitions for both are required.
   ii. Methodological standards for the conduct and reporting of behavioural and pharmacological relapse prevention trials.
   iii. Cessation trials should report the percentage of participants who make no attempt to stop smoking on target quit dates and should report continuous and point prevalence smoking cessation measures simultaneously at all follow-ups.

Implications for health care

Some NHS SSS are providing RPIs, but where this occurs, those with the weakest evidence base are generally used, illustrating a requirement for the emerging evidence base, and guidance, to be made available as soon as possible. Should the NHS decide to encourage and fund the use of RPIs for smokers who have become abstinent with NHS SSS support, new incentives are likely to be required before NHS SSS will substantially adopt their use. Currently, NHS SSS are performance-managed on their ability to achieve targets set for short-term (i.e. 4-week) periods of cessation; managers perceived these targets were a clear disincentive to spending on interventions such as RPIs, which might enhance longer term abstinence but not their clients' initial, monitored cessation rates. Any integration of RPIs into NHS SSS care should include sufficient monitoring such that an assessment of their cost-effectiveness in routine use can be made.

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Contribution of authors

Tim Coleman was the lead applicant at funding stage and participated in design, conduct, analysis and write up of all studies within report. Shade Agboola led the design, conduct analysis and write up of the qualitative and survey research and effectiveness review and participated in the conduct, analysis and write up of the systematic review. Jo Leonardi-Bee was a co-applicant at funding stage, participated in design, conduct, analysis and write up of systematic reviews and survey work, and led the 'relapse curves' review. Matthew Taylor designed, led, conducted and wrote up the health economic aspects of the report. Andy McEwan participated in design, conduct, analysis and write up of survey work. Ann McNeill was a co-applicant at funding stage, was the project manager following the grant award, and participated in design, conduct, analysis and write up of all studies within the report.

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Appendix 1
Interview questions (Chapter 2)

1. What interventions are currently being used by your service to help smokers who wish to stop smoking?

2. In your experience, at what point do smokers who have quit smoking most often relapse to smoking?

3. What do you understand by smoking relapse prevention interventions?

Experiences of delivering relapse prevention interventions within Stop Smoking Services

4. Do you routinely provide relapse prevention interventions to smokers in your service?

5. What types? (Content)

6. To whom, is it to those who have already relapsed or to all smokers after the four week quit date, regardless of smoking status at the time?

7. For how long is the relapse prevention intervention provided for? (Duration)

8. What percentage of smokers who relapse to smoking take advantage of relapse prevention treatments? (Uptake)

9. Are your staff trained to provide relapse prevention support?

10. Do you collect any data so as to monitor the effectiveness of relapse prevention support you provide?

Feasibility

11. What do you think about the effectiveness of…? Varenicline (champix); bupropion (zyban); extended treatment with NRT; behavioural sessions after the 4 week quit date; extended telephone contact after the 4 week quit date (*This question depends on the answer to question 4*)

Challenges experienced

12. Is it difficult to get smokers to attend any clinics or sessions after the 4-week quit date?

13. Are there any groups of smokers who pose a challenge in particular?

14. What other challenges do you face with respect to preventing relapse in smokers?

Service provision

15. What is the nature and number of sessions offered?

16. What is the length and timing of these sessions?

17. What is the actual uptake of these treatment sessions by smokers?

18. What kind of staff are involved in providing these services for smokers who wish to quit?

Appendix 2

Relapse prevention intervention questionnaire

This anonymous questionnaire seeks information about Relapse Prevention Interventions (which are also known as Relapse Prevention Treatments) that your smoking cessation service (SCS) currently offers or has previously offered. It should be completed by the person who manages or runs this service within your Primary Care Trust (PCT). If you are not the service manager/coordinator, then please pass this on to him or her.

Before we can ask questions about Relapse Prevention Interventions we need to ask you a few questions about your current service provision to put your answers in context (i.e. support you currently provide to help smokers quit).

Section 1: Provision of Smoking Cessation Interventions

1. What types of behavioural smoking cessation interventions are delivered by your SCS?

(tick all that apply)

Individual behavioural counselling…….. ☐

Group behavioural counselling…….. ☐

Self-directed sessions using computer software…….. ☐

Telephone advice/counselling……..... ☐

Self-help materials (i. e. booklets)…….. ☐

Peer led sessions……..... ☐

Other (specify below)……... ☐

……
…….

2. If your service delivers advice/counselling in groups what types of group treatments does your service provide?

(tick all that apply)

Open groups (clients can join and leave at any time)…… ☐

Closed groups (fixed number of sessions that run sequentially; usually only joined at the first one)…….. ☐

Other (specify below)…… ☐

……
…….

3. If your service delivers advice/counselling in groups, on average how long are group sessions?

… … …. .. ...…….*Minutes*

4. Is there a specific number of group sessionsthat constitutes a complete course of treatment?

Yes……..... ☐

No…… ☐

If your answer above is 'yes', please go to question5. If 'no', go to question 6

5. How many sessions constitute a complete course of treatment?

...……*Sessions*

6. If your service delivers advice/counselling to individuals, on average how long are individual sessions?

…….Minutes

7. If your service provides individual counselling, is there a specific number of individual sessions that constitutes a complete course of treatment?

Yes…….. ☐

No……... ☐

If your answer above is 'yes', please go to question 8. If 'no' go to question 9

8. How many individual sessions constitute a complete course of treatment?

....…….....*Sessions*

9. Roughly, what percentages of clients attending your service receive individual or group support?

Clients receiving group support……. %

Clients receiving individual support…… %

Bupropion…….. ☐

10. Which of the following drugs does your service recommend to clients?

(***tick all that apply)***

Varenicline…… ☐

Nicotine replacement therapy……... ☐

Combination NRT e.g. patch+oral product)…… ☐

…….....
.....

11. Which of the following drugs can be issued directly to clients attending your service (e.g. by PGD, voucher or prescription)?

(tick all that apply)

Bupropion……... ☐

Varenicline……. ☐

Nicotine replacement therapy ……. ☐

Other (specify below)……. ☐

……
……

Section 2: Provision of Relapse Prevention Interventions

This section asks about relapse prevention treatments provided by your service to abstinent quitters.

Relapse Prevention Interventions (or Relapse Prevention Treatments) are behavioural or drug therapies delivered after acute smoking cessation treatment has ended and resulted in abstinence from smoking. Relapse Prevention Interventions therefore seek to reduce relapse to smoking among abstinent smokers. We are distinguishing relapse prevention interventions from interventions that aim to prevent a lapse becoming a full relapse to smoking (such interventions are addressed in questions 19 and 20)

12. Does your service provide relapse prevention interventions to **abstinent quitters?**

Yes……. ☐

No…….. ☐

If answer above is 'yes' go to question 15 if 'no', go to question 13

13. Has your service ever provided relapse prevention interventions to **abstinent quitters** in the past?

Yes……. ☐

No…….. ☐

If answer above is yes, please go to question 14, if 'no' go to question 19

14. Please indicate the reasons why you no longer provide relapse prevention interventions.

(tick all that apply)

Poor client attendance……. ☐

Lack of relapse prevention training courses for staff…….. ☐

Inadequate funding…….. ☐

Relapse prevention treatments are not effective…… ☐

Pressure to meet Department of Health Targets…….. ☐

Other (specify below)……... ☐

……
…….

Now go to question 19.

15. What types of relapse prevention interventions do you

provide to **abstinent quitters**?

(tick all that apply)

NRT……... ☐

Bupropion……. ☐

Varenicline……... ☐

Individual behavioural counselling……... ☐

Group behavioural counselling ☐

Telephone contact…….. ☐

Self-help materials…… ☐

Regular motivational letters enquiring as to progress… ☐

Other (specify below)……... ☐

……
…….

16. How soon after completion of the acute smoking cessation treatment can an **abstinent quitter** access relapse prevention interventions from your service?

(tick one box)

Immediately ☐

After a period of time has elapsed ☐

17. If you ticked "*after a period of time has elapsed*", please specify the length of this period
…….*Weeks*

18. For how long are relapse prevention interventions offered to **abstinent quitters** who received smoking cessation treatment from your service?

(tick one box)

3 months or less……... ☐

Greater than 3 months and up to 6months……... ☐

Indefinitely……. ☐

Other (specify below)…… ☐

……
…….

19. Does your service offer any

Yes…….. ☐

intervention for someone who has experienced a brief lapse to smoking to prevent full blown relapse?

No…… ☐

20. If yes, please state what intervention is offered?

……
……

Section 3: Feasibility of relapse prevention interventions

This section asks about the feasibility and potential challenges of introducing / continuing to provide relapse prevention interventions within the routine care provided by your SCS. ***Relapse prevention interventions seek to reduce relapse to smoking among abstinent smokers.***

21. If you are currently offering relapse prevention interventions, under current circumstances, how likely is it that your stop smoking service might continue to provide relapse prevention interventions to abstinent quitters?

(tick one box)

Very likely…… ☐
Likely……... ☐
Not sure……... ☐
Unlikely……... ☐
Definitely not…….. …. ☐

22. If you are currently offering relapse prevention interventions, under current circumstances, how likely is it that your stop smoking service might start to provide relapse prevention interventions to abstinent quitters?

(tick one box)

Very likely…… ☐
Likely……... ☐
Not sure……... ☐
Unlikely……... ☐
Definitely not…….. …. ☐

If your answer to either question 21 or 22 above is 'not sure', 'unlikely' or' definitely not', please go to question 23, otherwise you are now finished.

Inadequate funding…….. ☐

23. Please indicate the reasons why you are not sure or do not believe it likely that relapse prevention interventions will be provided by your service in the future.

(tick all that apply)

DOH focus on four-week quits, rather than long term cessation…... ☐

Clients usually relapse before they contact the service…… ☐

Few clients contact the service after acute smoking cessation treatment whilst still abstinent……. ☐

Inability to provide drug treatment within the service…… ☐

Other (specify below)…….. ☐

24. Assuming that the above issues were resolved, how likely is it that the following interventions **could** be offered to abstinent quitters who have completed smoking cessation treatment -as a form of relapse prevention in your service?

Intervention	***Very likely***	***Likely***	***Not sure***	***Unlikely***	***Definitely not***
NRT	☐	☐	☐	☐	☐
Varenicline	☐	☐	☐	☐	☐
Bupropion	☐	☐	☐	☐	☐
Group counselling	☐	☐	☐	☐	☐
Individual counselling	☐	☐	☐	☐	☐
NRT combinations	☐	☐	☐	☐	☐
Other relapse prevention interventions(explain below)	☐	☐	☐	☐	☐

……
…….

25. If you answered 'probably not' or 'definitely not', for any of the listed interventions please provide reasons below.

…….

…….

…….

You are now finished. Thank you very much for your help.

Appendix 3

Search strategies and results

MEDLINE (Ovid Web); 2004–7/ August week 1; 8 August 2007

579 records were retrieved.

1. Smoking Cessation/
2. "Tobacco Use Disorder"/
3. Tobacco/
4. Nicotine/
5. Tobacco, Smokeless/
6. Smoking/pc, th
7. ((quit$or stop$or ceas$or giv$) adj smok$).ti,ab.
8. Tobacco Smoke Pollution/
9. or/1-8
10. Randomised controlled trial.pt.
11. controlled clinical trial.pt.
12. Randomised Controlled Trials/
13. Random Allocation/
14. Double-Blind Method/
15. Single-Blind Method/
16. clinical trial.pt.
17. exp Clinical Trials/
18. (clin$adj trial$).ti,ab.
19. Placebos/
20. placebo$.ti,ab.
21. random$.ti,ab.
22. Research Design/
23. ((singl$or doubl$or trebl$or tripl$) adj (blind$or mask$)).ti,ab.
24. (volunteer$or prospectiv$).ti,ab.
25. exp Evaluation Studies/
26. exp Cross-Sectional Studies/
27. Prospective Studies/
28. Retrospective Studies/
29. Follow-Up Studies/
30. exp Health Education/
31. exp Health Behaviour/
32. exp Community Health Services/
33. Health Promotion/
34. exp Behaviour Therapy/
35. or/10-34
36. Recurrence/
37. (relaps$or recurr$).ti,ab.
38. (resum$or restart$or re start$or lapse$).ti,ab.
39. maintenance.ti,ab.
40. (maintain$or sustain$).ti,ab.
41. or/36-40
42. 9 and 35 and 41
43. Animals/
44. Humans/
45. 43 not (43 and 44)
46. 42 not 45
47. (2004$or 2005$or 2006$or 2007$).ed.
48. 46 and 47

EMBASE (Ovid Web); 2004–7/ week 31; 8 August 2007

406 records were retrieved.

1. (random$or factorial$or crossover$or cross over$or cross-over$or placebo$or (doubl$adj blind$) or (singl$adj blind$) or assign$or allocat$or volunteer$).ti,ab.
2. crossover procedure/or double-blind procedure/or Randomised controlled trial/or single-blind procedure/
3. 1 or 2
4. smoking cessation.mp.
5. exp Smoking Cessation/
6. exp SMOKING/
7. ((quit$or stop$or ceas$or giv$or prevent$) adj smok$).mp.
8. exp Passive Smoking/or exp Smoking Habit/or exp Cigarette Smoking/
9. or/4-8
10. Relapse/
11. (relaps$or recurr$).ti,ab.
12. (resum$or restart$or re start$or lapse$).ti,ab.
13. maintenance therapy/
14. maintenance.ti,ab.
15. (maintain$or sustain$).ti,ab.
16. or/10-15
17. 3 and 9 and 16
18. exp animal/
19. Nonhuman/
20. (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dogs or dog or cats or bovine or sheep or ovine or pig or pigs or porcine).ti,ab, sh.
21. or/18-20
22. exp human/or exp human experiment/
23. 21 not (21 and 22)
24. 17 not 23
25. (2004$or 2005$or 2006$or 2007$).em.
26. 24 and 25

CENTRAL (Cochrane Library/ Wiley); 2007:3; 8 August 2007

228 records were retrieved.

#1 MeSH descriptor Tobacco Use Disorder explode all trees
#2 MeSH descriptor Tobacco, Smokeless explode all trees
#3 MeSH descriptor Tobacco Smoke Pollution explode all trees
#4 MeSH descriptor Tobacco Use Cessation explode all trees
#5 MeSH descriptor Nicotine explode all trees
#6 (smoking AND cessation)
#7 (antismok*)
#8 (quit*):ti
#9 (smok*):ti
#10 (cigar*):ti
#11 (tobacco):ti
#12 (nicotine):ti
#13 MeSH descriptor Smoking explode all trees
#14 (#1 OR #2 OR #3 OR #4 OR #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13)
#15 MeSH descriptor Recurrence explode all trees
#16 (relaps* or recurr*)
#17 (resum* or restart* or (re start*) or lapse*)
#18 (maintenance)
#19 (maintain* or sustain*)
#20 (#15 OR #16 OR #17 or #18 or #19)
#21 (#14 AND #20), from 2004 to 2007

PsycINFO (Ovid Web); 2004–7/ July week 5; 8 August 2007

555 records were retrieved.

1. smoking cessation.mp. or exp Smoking Cessation/
2. (antismoking or anti-smoking).mp.
3. (quit$or cessat$).mp.
4. (abstin$or abstain$).mp.
5. (control$adj smok$).mp. [mp = title, abstract, heading word, table of contents, key concepts]
6. exp Behaviour Modification/
7. 2 or 3 or 4 or 5 or 6
8. exp Tobacco Smoking/
9. (smok$or cigar$or tobacco$).mp.
10. exp Prevention/
11. 8 or 9
12. 7 and 11
13. 10 and 11
14. 1 or 12 or 13
15. relapse prevention/
16. exp Maintenance Therapy/
17. (relaps$or recurr$).ti,ab.
18. (resum$or restart$or re start$or lapse$).ti,ab.
19. maintenance.ti,ab.
20. (maintain$or sustain$).ti,ab.
21. or/15-20
22. 14 and 21
23. (2004$or 2005$or 2006$or 2007$).up.
24. 22 and 23

Science Citation and Social Science Citation Index (ISI Web of Science); 2004–7/August 8; 8 August 2007

646 records were retrieved.

(((smoking cessation) OR (smok* SAME (quit or stop or prevent*))) AND (random* or trial or control* or (study same smok*)) AND (relaps* or recur* or resum* or restart* or (re start*) or lapse* or maintenance or maintain or sustain)) NOT (rat or rats or mouse or mice or hamster or hamsters or animal or animals or dogs or dog or cats or bovine or sheep or ovine or pig or pigs or porcine)

Time span = 2004–7

Appendix 4

Population weights

TABLE 35 *Population weights*

Age (years)	Total (%)	Male (%)	Female (%)
16	0.87	0.43	0.44
17	0.87	0.43	0.44
18	0.87	0.43	0.44
19	0.87	0.43	0.44
20	0.87	0.43	0.44
21	0.87	0.43	0.44
22	0.87	0.43	0.44
23	0.87	0.43	0.44
24	0.87	0.43	0.44
25	1.85	0.93	0.93
26	1.85	0.93	0.93
27	1.85	0.93	0.93
28	1.85	0.93	0.93
29	1.85	0.93	0.93
30	2.10	1.05	1.05
31	2.10	1.05	1.05
32	2.10	1.05	1.05
33	2.10	1.05	1.05
34	2.10	1.05	1.05
35	2.09	1.03	1.05
36	2.09	1.03	1.05
37	2.09	1.03	1.05
38	2.09	1.03	1.05
39	2.09	1.03	1.05
40	1.84	0.92	0.92
41	1.84	0.92	0.92
42	1.84	0.92	0.92
43	1.84	0.92	0.92
44	1.84	0.92	0.92
45	1.69	0.84	0.85
46	1.69	0.84	0.85
47	1.69	0.84	0.85
48	1.69	0.84	0.85
49	1.69	0.84	0.85
50	1.83	0.91	0.92
51	1.83	0.91	0.92
52	1.83	0.91	0.92
53	1.83	0.91	0.92
54	1.83	0.91	0.92
55	1.48	0.73	0.75

TABLE 35 *Population weights (continued)*

Age (years)	Total (%)	Male (%)	Female (%)
56	1.48	0.73	0.75
57	1.48	0.73	0.75
58	1.48	0.73	0.75
59	1.48	0.73	0.75
60	1.31	0.64	0.67
61	1.31	0.64	0.67
62	1.31	0.64	0.67
63	1.31	0.64	0.67
64	1.31	0.64	0.67
65	1.18	0.56	0.61
66	1.18	0.56	0.61
67	1.18	0.56	0.61
68	1.18	0.56	0.61
69	1.18	0.56	0.61
70	1.06	0.48	0.58
71	1.06	0.48	0.58
72	1.06	0.48	0.58
73	1.06	0.48	0.58
74	1.06	0.48	0.58
75	0.92	0.38	0.54
76	0.92	0.38	0.54
77	0.92	0.38	0.54
78	0.92	0.38	0.54
79	0.92	0.38	0.54
80	0.57	0.21	0.36
81	0.57	0.21	0.36
82	0.57	0.21	0.36
83	0.57	0.21	0.36
84	0.57	0.21	0.36
85	0.35	0.10	0.24
86	0.35	0.10	0.24
87	0.35	0.10	0.24
88	0.35	0.10	0.24
89	0.35	0.10	0.24
90	0.08	0.02	0.06
91	0.08	0.02	0.06
92	0.08	0.02	0.06
93	0.08	0.02	0.06
94	0.08	0.02	0.06
95	0.08	0.02	0.06
96	0.08	0.02	0.06
97	0.08	0.02	0.06
98	0.08	0.02	0.06
99	0.08	0.02	0.06
100	0.08	0.02	0.06
Total	100.00	48.00	52.00

Appendix 5
Search strategies

Productivity losses and absenteeism

MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations; 2000–6/Sep week 3; searched 2 October 2006

1. Smoking/
2. (smoke or smoker or smokers or smoking).ti,ab.
3. (tobacco or cigar$).ti,ab.
4. or/1-3
5. ((loss$or lost or reduc$) adj3 productivity).ti,ab.
6. ((loss$or lost or reduc$) adj3 output$).ti,ab.
7. 5 or 6
8. 4 and 7
9. Absenteeism/
10. Sick Leave/
11. (sick$adj3 (certificat$or absence or leave or work)).ti,ab.
12. absenteeism.ti,ab.
13. or/9-12
14. 4 and 13
15. 18 or 14

EMBASE; 2000–6/week 39; searched 2 October 2006

1. SMOKING/
2. (smoke or smoker or smokers or smoking).ti,ab.
3. (tobacco or cigar$).ti,ab.
4. or/1-3
5. PRODUCTIVITY/
6. ((loss$or lost or reduc$) adj3 productivity).ti,ab.
7. ((loss$or lost or reduc$) adj3 output$).ti,ab.
8. or/5-7
9. 4 and 8
10. ABSENTEEISM/
11. Medical Leave/
12. (sick$adj3 (certificat$or absence or leave or work)).ti,ab.
13. absenteeism.ti,ab.
14. or/10-13
15. 4 and 14
16. 9 or 15

CINAHL; 2000–6/Sep week 4; searched 2 October 2006

1. SMOKING/
2. (smoke or smoker or smokers or smoking).ti,ab.
3. (tobacco or cigar$).ti,ab.
4. or/1-3
5. ((loss$or lost or reduc$) adj3 productivity).ti,ab.
6. ((loss$or lost or reduc$) adj3 output$).ti,ab.
7. PRODUCTIVITY/
8. or/5-7
9. 4 and 8
10. ABSENTEEISM/
11. Sick Leave/
12. (sick$adj3 (certificat$or absence or leave or work)).ti,ab.
13. absenteeism.ti,ab.
14. or/10-13
15. 4 and 14
16. 9 or 15

Health Management Information Consortium (HMIC); 2000–6/September; searched 2 October 2006

1. exp SMOKING/
2. (smoke or smoker or smokers or smoking).ti,ab.
3. (tobacco or cigar$).ti,ab.
4. or/1-3
5. exp PRODUCTIVITY/
6. ((loss$or lost or reduc$) adj3 productivity).ti,ab.
7. ((loss$or lost or reduc$) adj3 output$).ti,ab.
8. or/5-7
9. 4 and 8
10. exp ABSENTEEISM/
11. exp SICK LEAVE/
12. (sick$adj3 (certificat$or absence or leave or work)).ti,ab.
13. absenteeism.ti,ab.
14. or/10-13
15. 4 and 14
16. 9 or 15

NHS Economic Evaluation Database (NHS EED); CRD internal database; 2000–6/September; searched 2 October 2006

s smoke or smoker or smokers or smoking
s tobacco or cigar$
s s1 or s2
s (loss$or lost or reduc$)(w3)productivity
s (loss$or lost or reduc$)(w3)output$
s s4 or s5
s s3 and s6
s sick$(w3)(certificat$or absence or leave or work)
s absenteeism

s s8 or s9
s s3 and s10

Annual costs of lung cancer and stroke in the UK

Lung cancer
Sanderson H, Spiro S. *Cancer of the lung.* In. Stevens A, Raftery J, Mant J, Simpson S. Health care needs assessment: the epidemiologically based needs assessment reviews: Volume 1. Second Edition. Abingdon: Radcliffe Publishing, 2004. pp. 503–48.

Stroke
Mant J, Wade D, Winner S. *Stroke.* In. Stevens A, Raftery J, Mant J, Simpson S. Health care needs assessment: the epidemiologically based needs assessment reviews: Volume 1. Second Edition. Abingdon: Radcliffe Publishing, 2004. pp. 141–244.

National Audit Office. *Reducing brain damage: faster access to better stroke care.* London: Stationery Office, 2005.

Utilities: myocardial infarction; chronic obstructive pulmonary disease; lung cancer; coronary heart disease; and stroke

MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations; 1996–2006/November week 1; searched 15 November 2006

1. exp Quality-Adjusted Life Years/
2. quality adjusted life year$.ti,ab.
3. qaly$.ti,ab.
4. (utility or utilities).ti,ab.
5. (preference or preferences).ti,ab.
6. (time adj2 trade).ti,ab.
7. standard gamble.ti,ab.
8. rating scale.ti,ab.
9. or/1-8
10. *Myocardial Infarction/
11. 9 and 10
12. *Pulmonary Disease, Chronic Obstructive/
13. 9 and 12
14. *Lung Neoplasms/
15. 9 and 14
16. *Coronary Disease/
17. 9 and 16
18. *Cerebrovascular Accident/
19. 9 and 18

EMBASE; 1996–2006/week 45; searched 15 November 2006

1. exp quality adjusted life year/
2. quality adjusted life year$.ti,ab.
3. qaly$.ti,ab.
4. (utility or utilities).ti,ab.
5. (preference or preferences).ti,ab.
6. standard gamble.ti,ab.
7. rating scale.ti,ab.
8. or/1-7
9. *Heart Infarction/
10. 8 and 9
11. *Chronic Obstructive Lung Disease/
12. 8 and 11
13. *Lung Cancer/
14. 8 and 13
15. *Ischemic Heart Disease/
16. 8 and 15
17. *STROKE/
18. 8 and 17

NHS Economic Evaluation Database (NHS EED); CRD internal database. 2006/October; searched 15 November 2006

s quality(w)adjusted(w)life(w)year$
s qaly$
s utility or utilities
s preference or preferences
s time(w2)trade
s standard(w)gamble
s rating(w)scale
s s1 or s2 or s3 or s4 or s5 or s6 or s7
s myocardial(w)infarct$
s s8 and s9
s chronic(w)obstructive(w)pulmonary(w)disease$or COPD
s s8 and s11
s lung(w)(cancer$or neoplasm$)
s s8 and s13
s coronary(w2)disease or CHD
s s8 and s15
s stroke
s s8 and s17

Health Economic Evaluation Database (HEED); CD-ROM; September 2006; searched 15 November 2006

AX = (quality adjusted life year) or (quality adjusted life years)
AX = qaly or qalys
AX = utility or utilities
AX = preference or preferences
AX = (time trade off)

AX = (standard gamble)
AX = (rating scale)
CS = 1 or 2 or 3 or 4 or 5 or 6 or 7
AX = (myocardial infarction)
CS = 8 and 9
AX = (chronic obstructive pulmonary disease) or COPD
CS = 8 and 11
AX = (lung cancer) or (lung cancers) or (lung neoplasm) or (lung neoplasms)
CS = 8 and 13
AX = "coronary disease" within 2 OR CHD
CS = 8 and 15
AX = stroke
CS = 8 and 17

The Cost-Effectiveness (CEA) Registry. Internet. Comprehensive Table of Cost-Utility Ratios 2002–2003 and Comprehensive Table of Cost-Utility Ratios 1976–2001. Searched 15 November 2006

Association between smoking and COPD/stroke: separated into current, former and never smokers

MEDLINE and MEDLINE In-Process & Other Non-Indexed Citations; 1996–2006/November week 2; searched 20 November 2006

1. Smoking/
2. (former$and never and current$).ti,ab.
3. (smoking status).ti,ab.
4. 1 and (2 or 3)
5. Pulmonary Disease, Chronic Obstructive/
6. ((chronic adj2 pulmon$) or copd).ti,ab.
7. 5 or 6
8. 4 and 7
9. Cerebrovascular Accident/
10. stroke.ti,ab.
11. 9 or 10
12. 4 and 11

EMBASE; 1996–2006/week 46; searched 20 November 2006

1. SMOKING/
2. (former$and never and current$).ti,ab.
3. smoking status.ti,ab.
4. 1 and (2 or 3)
5. Chronic Obstructive Lung Disease/
6. ((chronic adj2 pulmon$) or copd).ti,ab.
7. 5 or 6
8. 4 and 7
9. STROKE/
10. stroke.ti,ab.
11. 9 or 10
12. 4 and 11

NHS Economic Evaluation Database (NHS EED); CRD internal database; 2006/October; searched 20 November 2006

s smoking
s former$and never and current$
s smoking(w)status
s s1 and (s2 or s3)
s chronic(w2)pulmon$or copd
s s4 and s5
s stroke
s s4 and s7

Health Economic Evaluation Database (HEED); CD-ROM; October 2006; searched 20 November 2006

AX = smoking
AX = (former and never and current)
AX = (smoking status)
CS = 1 and (2 or 3)
AX = "chronic pulmonary" within 2 OR COPD
CS = 4 and 5
AX = stroke
CS = 4 and 7

Appendix 6

Male mortality in the general population

TABLE 36 *Male mortality in the general population*

Age (years)	Mortality
0	0.005709
1	0.000414
2	0.000243
3	0.000182
4	0.000145
5	0.000114
6	0.000122
7	0.000101
8	0.000106
9	0.000117
10	0.000106
11	0.000122
12	0.000142
13	0.000173
14	0.000192
15	0.000254
16	0.000321
17	0.000486
18	0.000644
19	0.000612
20	0.000738
21	0.000665
22	0.000778
23	0.000759
24	0.000716
25	0.000820
26	0.000786
27	0.000765
28	0.000815
29	0.000851
30	0.000923
31	0.000937
32	0.001037
33	0.001027
34	0.001052
35	0.001124
36	0.001217
37	0.001302
38	0.001279
39	0.001457
40	0.001595
41	0.001648
42	0.001822
43	0.002132
44	0.002144
45	0.002345
46	0.002623
47	0.002956
48	0.003201
49	0.003554
50	0.003901
51	0.004234
52	0.004641
53	0.004968
54	0.005386
55	0.005915
56	0.006354
57	0.007306
58	0.007891
59	0.008734
60	0.010033
61	0.010965
62	0.012447
63	0.013166
64	0.014799
65	0.016079
66	0.017600
67	0.019556
68	0.021774
69	0.024228
70	0.026342
71	0.029574
72	0.032947
73	0.036459
74	0.040973
75	0.045751
76	0.050710
77	0.056151

TABLE 36 *Male mortality in the general population (continued)*

Age (years)	Mortality
78	0.061724
79	0.069489
80	0.075742
81	0.083605
82	0.091501
83	0.097921
84	0.106861
85	0.118207
86	0.135494
87	0.148454
88	0.161954
89	0.175991
90	0.185602
91	0.200472
92	0.220085
93	0.239483
94	0.251598
95	0.280321
96	0.292331
97	0.310996
98	0.331163
99	0.345437
100	0.362748

Appendix 7

Lung cancer

TABLE 37 *Prevalence of lung cancer*[15]

Age (years)	Prevalence (%)
0–44	0.00
45–64	0.15
65 +	0.80
All ages	0.14

TABLE 38 *Relative risk of lung cancer by smoking status*[16]

Gender	Current smoker	Former	Non-smoker
Men	1	0.44	0.03
Women	1	0.21	0.05

TABLE 39 *Prevalence of lung cancer by smoking status*

	Men			Women		
Age (years)	Current smoker	Former	Non-smoker	Current smoker	Former	Non-smoker
16	0.00007	0.00003	0.00000	0.00006	0.00001	0.00000
17	0.00007	0.00003	0.00000	0.00006	0.00001	0.00000
18	0.00007	0.00003	0.00000	0.00006	0.00001	0.00000
19	0.00007	0.00003	0.00000	0.00006	0.00001	0.00000
20	0.00007	0.00003	0.00000	0.00006	0.00001	0.00000
21	0.00007	0.00003	0.00000	0.00006	0.00001	0.00000
22	0.00007	0.00003	0.00000	0.00006	0.00001	0.00000
23	0.00007	0.00003	0.00000	0.00006	0.00001	0.00000
24	0.00007	0.00003	0.00000	0.00006	0.00001	0.00000
25	0.00005	0.00002	0.00000	0.00006	0.00001	0.00000
26	0.00005	0.00002	0.00000	0.00006	0.00001	0.00000
27	0.00005	0.00002	0.00000	0.00006	0.00001	0.00000
28	0.00005	0.00002	0.00000	0.00006	0.00001	0.00000
29	0.00005	0.00002	0.00000	0.00006	0.00001	0.00000
30	0.00005	0.00002	0.00000	0.00006	0.00001	0.00000
31	0.00005	0.00002	0.00000	0.00006	0.00001	0.00000
32	0.00005	0.00002	0.00000	0.00006	0.00001	0.00000
33	0.00005	0.00002	0.00000	0.00006	0.00001	0.00000
34	0.00005	0.00002	0.00000	0.00006	0.00001	0.00000
35	0.00005	0.00002	0.00000	0.00006	0.00001	0.00000
36	0.00005	0.00002	0.00000	0.00006	0.00001	0.00000
37	0.00005	0.00002	0.00000	0.00006	0.00001	0.00000
38	0.00005	0.00002	0.00000	0.00006	0.00001	0.00000
39	0.00005	0.00002	0.00000	0.00006	0.00001	0.00000
40	0.00005	0.00002	0.00000	0.00006	0.00001	0.00000
41	0.00005	0.00002	0.00000	0.00006	0.00001	0.00000
42	0.00005	0.00002	0.00000	0.00006	0.00001	0.00000
43	0.00005	0.00002	0.00000	0.00006	0.00001	0.00000

TABLE 39 *Prevalence of lung cancer by smoking status (continued)*

	Men			Women		
Age (years)	Current smoker	Former	Non-smoker	Current smoker	Former	Non-smoker
44	0.00005	0.00002	0.00000	0.00006	0.00001	0.00000
45	0.00383	0.00169	0.00012	0.00214	0.00045	0.00011
46	0.00383	0.00169	0.00012	0.00214	0.00045	0.00011
47	0.00383	0.00169	0.00012	0.00214	0.00045	0.00011
48	0.00383	0.00169	0.00012	0.00214	0.00045	0.00011
49	0.00383	0.00169	0.00012	0.00214	0.00045	0.00011
50	0.00383	0.00169	0.00012	0.00214	0.00045	0.00011
51	0.00383	0.00169	0.00012	0.00214	0.00045	0.00011
52	0.00383	0.00169	0.00012	0.00214	0.00045	0.00011
53	0.00383	0.00169	0.00012	0.00214	0.00045	0.00011
54	0.00383	0.00169	0.00012	0.00214	0.00045	0.00011
55	0.00384	0.00169	0.00012	0.00241	0.00051	0.00012
56	0.00384	0.00169	0.00012	0.00241	0.00051	0.00012
57	0.00384	0.00169	0.00012	0.00241	0.00051	0.00012
58	0.00384	0.00169	0.00012	0.00241	0.00051	0.00012
59	0.00384	0.00169	0.00012	0.00241	0.00051	0.00012
60	0.00384	0.00169	0.00012	0.00241	0.00051	0.00012
61	0.00384	0.00169	0.00012	0.00241	0.00051	0.00012
62	0.00384	0.00169	0.00012	0.00241	0.00051	0.00012
63	0.00384	0.00169	0.00012	0.00241	0.00051	0.00012
64	0.00384	0.00169	0.00012	0.00241	0.00051	0.00012
65	0.02236	0.00984	0.00067	0.01007	0.00211	0.00050
66	0.02236	0.00984	0.00067	0.01007	0.00211	0.00050
67	0.02236	0.00984	0.00067	0.01007	0.00211	0.00050
68	0.02236	0.00984	0.00067	0.01007	0.00211	0.00050
69	0.02236	0.00984	0.00067	0.01007	0.00211	0.00050
70	0.02236	0.00984	0.00067	0.01007	0.00211	0.00050
71	0.02236	0.00984	0.00067	0.01007	0.00211	0.00050
72	0.02236	0.00984	0.00067	0.01007	0.00211	0.00050
73	0.02236	0.00984	0.00067	0.01007	0.00211	0.00050
74	0.02236	0.00984	0.00067	0.01007	0.00211	0.00050
75	0.02304	0.01014	0.00069	0.01167	0.00245	0.00058
76	0.02304	0.01014	0.00069	0.01167	0.00245	0.00058
77	0.02304	0.01014	0.00069	0.01167	0.00245	0.00058
78	0.02304	0.01014	0.00069	0.01167	0.00245	0.00058
79	0.02304	0.01014	0.00069	0.01167	0.00245	0.00058
80	0.02304	0.01014	0.00069	0.01167	0.00245	0.00058
81	0.02304	0.01014	0.00069	0.01167	0.00245	0.00058
82	0.02304	0.01014	0.00069	0.01167	0.00245	0.00058
83	0.02304	0.01014	0.00069	0.01167	0.00245	0.00058
84	0.02304	0.01014	0.00069	0.01167	0.00245	0.00058
85	0.02304	0.01014	0.00069	0.01167	0.00245	0.00058
86	0.02304	0.01014	0.00069	0.01167	0.00245	0.00058

	Men			Women		
Age (years)	Current smoker	Former	Non-smoker	Current smoker	Former	Non-smoker
87	0.02304	0.01014	0.00069	0.01167	0.00245	0.00058
88	0.02304	0.01014	0.00069	0.01167	0.00245	0.00058
89	0.02304	0.01014	0.00069	0.01167	0.00245	0.00058
90	0.02304	0.01014	0.00069	0.01167	0.00245	0.00058
91	0.02304	0.01014	0.00069	0.01167	0.00245	0.00058
92	0.02304	0.01014	0.00069	0.01167	0.00245	0.00058
93	0.02304	0.01014	0.00069	0.01167	0.00245	0.00058
94	0.02304	0.01014	0.00069	0.01167	0.00245	0.00058
95	0.02304	0.01014	0.00069	0.01167	0.00245	0.00058
96	0.02304	0.01014	0.00069	0.01167	0.00245	0.00058
97	0.02304	0.01014	0.00069	0.01167	0.00245	0.00058
98	0.02304	0.01014	0.00069	0.01167	0.00245	0.00058
99	0.02304	0.01014	0.00069	0.01167	0.00245	0.00058
100	0.02304	0.01014	0.00069	0.01167	0.00245	0.00058

Appendix 8

Coronary heart disease

TABLE 40 *Prevalence of coronary heart disease*[17]

Age (years)	Prevalence (%)
16–24	0.00
25–34	0.00
35–44	0.90
45–54	3.50
55–64	11.10
65–74	21.50
75+	26.40

TABLE 41 *Relative risk of coronary heart disease by smoking status*[18]

	Current smoker	Former	Non-smoker
RR	3.12	1.55	1

TABLE 42 *Prevalence of coronary heart disease by smoking status*

	Men			Women		
Age (years)	Current smoker	Former	Non-smoker	Current smoker	Former	Non-smoker
16	0.00000	0.00000	0.00000	0.00378	0.00188	0.00121
17	0.00000	0.00000	0.00000	0.00378	0.00188	0.00121
18	0.00000	0.00000	0.00000	0.00378	0.00188	0.00121
19	0.00000	0.00000	0.00000	0.00378	0.00188	0.00121
20	0.00000	0.00000	0.00000	0.00378	0.00188	0.00121
21	0.00000	0.00000	0.00000	0.00378	0.00188	0.00121
22	0.00000	0.00000	0.00000	0.00378	0.00188	0.00121
23	0.00000	0.00000	0.00000	0.00378	0.00188	0.00121
24	0.00000	0.00000	0.00000	0.00378	0.00188	0.00121
25	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
26	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
27	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
28	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
29	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
30	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
31	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
32	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
33	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
34	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
35	0.01677	0.00833	0.00538	0.00747	0.00371	0.00239
36	0.01677	0.00833	0.00538	0.00747	0.00371	0.00239
37	0.01677	0.00833	0.00538	0.00747	0.00371	0.00239
38	0.01677	0.00833	0.00538	0.00747	0.00371	0.00239
39	0.01677	0.00833	0.00538	0.00747	0.00371	0.00239
40	0.01677	0.00833	0.00538	0.00747	0.00371	0.00239

TABLE 42 *Prevalence of coronary heart disease by smoking status (continued)*

	Men			Women		
Age (years)	Current smoker	Former	Non-smoker	Current smoker	Former	Non-smoker
41	0.01677	0.00833	0.00538	0.00747	0.00371	0.00239
42	0.01677	0.00833	0.00538	0.00747	0.00371	0.00239
43	0.01677	0.00833	0.00538	0.00747	0.00371	0.00239
44	0.01677	0.00833	0.00538	0.00747	0.00371	0.00239
45	0.06416	0.03188	0.02057	0.03767	0.01871	0.01207
46	0.06416	0.03188	0.02057	0.03767	0.01871	0.01207
47	0.06416	0.03188	0.02057	0.03767	0.01871	0.01207
48	0.06416	0.03188	0.02057	0.03767	0.01871	0.01207
49	0.06416	0.03188	0.02057	0.03767	0.01871	0.01207
50	0.06416	0.03188	0.02057	0.03767	0.01871	0.01207
51	0.06416	0.03188	0.02057	0.03767	0.01871	0.01207
52	0.06416	0.03188	0.02057	0.03767	0.01871	0.01207
53	0.06416	0.03188	0.02057	0.03767	0.01871	0.01207
54	0.06416	0.03188	0.02057	0.03767	0.01871	0.01207
55	0.20977	0.10421	0.06724	0.11597	0.05761	0.03717
56	0.20977	0.10421	0.06724	0.11597	0.05761	0.03717
57	0.20977	0.10421	0.06724	0.11597	0.05761	0.03717
58	0.20977	0.10421	0.06724	0.11597	0.05761	0.03717
59	0.20977	0.10421	0.06724	0.11597	0.05761	0.03717
60	0.20977	0.10421	0.06724	0.11597	0.05761	0.03717
61	0.20977	0.10421	0.06724	0.11597	0.05761	0.03717
62	0.20977	0.10421	0.06724	0.11597	0.05761	0.03717
63	0.20977	0.10421	0.06724	0.11597	0.05761	0.03717
64	0.20977	0.10421	0.06724	0.11597	0.05761	0.03717
65	0.44038	0.21878	0.14115	0.20962	0.10414	0.06718
66	0.44038	0.21878	0.14115	0.20962	0.10414	0.06718
67	0.44038	0.21878	0.14115	0.20962	0.10414	0.06718
68	0.44038	0.21878	0.14115	0.20962	0.10414	0.06718
69	0.44038	0.21878	0.14115	0.20962	0.10414	0.06718
70	0.44038	0.21878	0.14115	0.20962	0.10414	0.06718
71	0.44038	0.21878	0.14115	0.20962	0.10414	0.06718
72	0.44038	0.21878	0.14115	0.20962	0.10414	0.06718
73	0.44038	0.21878	0.14115	0.20962	0.10414	0.06718
74	0.44038	0.21878	0.14115	0.20962	0.10414	0.06718
75	0.55568	0.27606	0.17810	0.41478	0.20606	0.13294
76	0.55568	0.27606	0.17810	0.41478	0.20606	0.13294
77	0.55568	0.27606	0.17810	0.41478	0.20606	0.13294
78	0.55568	0.27606	0.17810	0.41478	0.20606	0.13294
79	0.55568	0.27606	0.17810	0.41478	0.20606	0.13294
80	0.55568	0.27606	0.17810	0.41478	0.20606	0.13294
81	0.55568	0.27606	0.17810	0.41478	0.20606	0.13294
82	0.55568	0.27606	0.17810	0.41478	0.20606	0.13294
83	0.55568	0.27606	0.17810	0.41478	0.20606	0.13294

	Men			Women		
Age (years)	Current smoker	Former	Non-smoker	Current smoker	Former	Non-smoker
84	0.55568	0.27606	0.17810	0.41478	0.20606	0.13294
85	0.55568	0.27606	0.17810	0.41478	0.20606	0.13294
86	0.55568	0.27606	0.17810	0.41478	0.20606	0.13294
87	0.55568	0.27606	0.17810	0.41478	0.20606	0.13294
88	0.55568	0.27606	0.17810	0.41478	0.20606	0.13294
89	0.55568	0.27606	0.17810	0.41478	0.20606	0.13294
90	0.55568	0.27606	0.17810	0.41478	0.20606	0.13294
91	0.55568	0.27606	0.17810	0.41478	0.20606	0.13294
92	0.55568	0.27606	0.17810	0.41478	0.20606	0.13294
93	0.55568	0.27606	0.17810	0.41478	0.20606	0.13294
94	0.55568	0.27606	0.17810	0.41478	0.20606	0.13294
95	0.55568	0.27606	0.17810	0.41478	0.20606	0.13294
96	0.55568	0.27606	0.17810	0.41478	0.20606	0.13294
97	0.55568	0.27606	0.17810	0.41478	0.20606	0.13294
98	0.55568	0.27606	0.17810	0.41478	0.20606	0.13294
99	0.55568	0.27606	0.17810	0.41478	0.20606	0.13294
100	0.55568	0.27606	0.17810	0.41478	0.20606	0.13294

Appendix 9

Chronic obstructive pulmonary disease

TABLE 43 *Prevalence of chronic obstructive pulmonary disease*[19]

Age (years)	Prevalence (%)
0–64	1.00
65–74	5.00
75 +	10.00

TABLE 44 *Relative risk of chronic obstructive pulmonary disease by smoking status. This is the association between smoking and the risk of acute respiratory illness used as a proxy for chronic obstructive pulmonary disease*[18]

	Current smoker	Former	Non-smoker
Men	1	0.84	0.68
Women	1	0.96	0.92

TABLE 45 *Prevalence of chronic obstructive pulmonary disease by smoking status*

	Men			Women		
Age (years)	Current smoker	Former	Non-smoker	Current smoker	Former	Non-smoker
16	0.01299	0.01091	0.00883	0.01057	0.01015	0.00973
17	0.01299	0.01091	0.00883	0.01057	0.01015	0.00973
18	0.01299	0.01091	0.00883	0.01057	0.01015	0.00973
19	0.01299	0.01091	0.00883	0.01057	0.01015	0.00973
20	0.01299	0.01091	0.00883	0.01057	0.01015	0.00973
21	0.01299	0.01091	0.00883	0.01057	0.01015	0.00973
22	0.01299	0.01091	0.00883	0.01057	0.01015	0.00973
23	0.01299	0.01091	0.00883	0.01057	0.01015	0.00973
24	0.01299	0.01091	0.00883	0.01057	0.01015	0.00973
25	0.01216	0.01022	0.00827	0.01054	0.01012	0.00970
26	0.01216	0.01022	0.00827	0.01054	0.01012	0.00970
27	0.01216	0.01022	0.00827	0.01054	0.01012	0.00970
28	0.01216	0.01022	0.00827	0.01054	0.01012	0.00970
29	0.01216	0.01022	0.00827	0.01054	0.01012	0.00970
30	0.01216	0.01022	0.00827	0.01054	0.01012	0.00970
31	0.01216	0.01022	0.00827	0.01054	0.01012	0.00970
32	0.01216	0.01022	0.00827	0.01054	0.01012	0.00970
33	0.01216	0.01022	0.00827	0.01054	0.01012	0.00970
34	0.01216	0.01022	0.00827	0.01054	0.01012	0.00970
35	0.01254	0.01053	0.00853	0.01054	0.01012	0.00970
36	0.01254	0.01053	0.00853	0.01054	0.01012	0.00970
37	0.01254	0.01053	0.00853	0.01054	0.01012	0.00970
38	0.01254	0.01053	0.00853	0.01054	0.01012	0.00970
39	0.01254	0.01053	0.00853	0.01054	0.01012	0.00970
40	0.01254	0.01053	0.00853	0.01054	0.01012	0.00970
41	0.01254	0.01053	0.00853	0.01054	0.01012	0.00970
42	0.01254	0.01053	0.00853	0.01054	0.01012	0.00970

TABLE 45 *Prevalence of chronic obstructive pulmonary disease by smoking status (continued)*

	Men			Women		
Age (years)	Current smoker	Former	Non-smoker	Current smoker	Former	Non-smoker
43	0.01254	0.01053	0.00853	0.01054	0.01012	0.00970
44	0.01254	0.01053	0.00853	0.01054	0.01012	0.00970
45	0.01236	0.01038	0.00840	0.01053	0.01011	0.00969
46	0.01236	0.01038	0.00840	0.01053	0.01011	0.00969
47	0.01236	0.01038	0.00840	0.01053	0.01011	0.00969
48	0.01236	0.01038	0.00840	0.01053	0.01011	0.00969
49	0.01236	0.01038	0.00840	0.01053	0.01011	0.00969
50	0.01236	0.01038	0.00840	0.01053	0.01011	0.00969
51	0.01236	0.01038	0.00840	0.01053	0.01011	0.00969
52	0.01236	0.01038	0.00840	0.01053	0.01011	0.00969
53	0.01236	0.01038	0.00840	0.01053	0.01011	0.00969
54	0.01236	0.01038	0.00840	0.01053	0.01011	0.00969
55	0.01231	0.01034	0.00837	0.01055	0.01013	0.00971
56	0.01231	0.01034	0.00837	0.01055	0.01013	0.00971
57	0.01231	0.01034	0.00837	0.01055	0.01013	0.00971
58	0.01231	0.01034	0.00837	0.01055	0.01013	0.00971
59	0.01231	0.01034	0.00837	0.01055	0.01013	0.00971
60	0.01231	0.01034	0.00837	0.01055	0.01013	0.00971
61	0.01231	0.01034	0.00837	0.01055	0.01013	0.00971
62	0.01231	0.01034	0.00837	0.01055	0.01013	0.00971
63	0.01231	0.01034	0.00837	0.01055	0.01013	0.00971
64	0.01231	0.01034	0.00837	0.01055	0.01013	0.00971
65	0.06235	0.05237	0.04240	0.05306	0.05093	0.04881
66	0.06235	0.05237	0.04240	0.05306	0.05093	0.04881
67	0.06235	0.05237	0.04240	0.05306	0.05093	0.04881
68	0.06235	0.05237	0.04240	0.05306	0.05093	0.04881
69	0.06235	0.05237	0.04240	0.05306	0.05093	0.04881
70	0.06235	0.05237	0.04240	0.05306	0.05093	0.04881
71	0.06235	0.05237	0.04240	0.05306	0.05093	0.04881
72	0.06235	0.05237	0.04240	0.05306	0.05093	0.04881
73	0.06235	0.05237	0.04240	0.05306	0.05093	0.04881
74	0.06235	0.05237	0.04240	0.05306	0.05093	0.04881
75	0.12504	0.10504	0.08503	0.10627	0.10202	0.09777
76	0.12504	0.10504	0.08503	0.10627	0.10202	0.09777
77	0.12504	0.10504	0.08503	0.10627	0.10202	0.09777
78	0.12504	0.10504	0.08503	0.10627	0.10202	0.09777
79	0.12504	0.10504	0.08503	0.10627	0.10202	0.09777
80	0.12504	0.10504	0.08503	0.10627	0.10202	0.09777
81	0.12504	0.10504	0.08503	0.10627	0.10202	0.09777
82	0.12504	0.10504	0.08503	0.10627	0.10202	0.09777
83	0.12504	0.10504	0.08503	0.10627	0.10202	0.09777
84	0.12504	0.10504	0.08503	0.10627	0.10202	0.09777
85	0.12504	0.10504	0.08503	0.10627	0.10202	0.09777

	Men			Women		
Age (years)	Current smoker	Former	Non-smoker	Current smoker	Former	Non-smoker
86	0.12504	0.10504	0.08503	0.10627	0.10202	0.09777
87	0.12504	0.10504	0.08503	0.10627	0.10202	0.09777
88	0.12504	0.10504	0.08503	0.10627	0.10202	0.09777
89	0.12504	0.10504	0.08503	0.10627	0.10202	0.09777
90	0.12504	0.10504	0.08503	0.10627	0.10202	0.09777
91	0.12504	0.10504	0.08503	0.10627	0.10202	0.09777
92	0.12504	0.10504	0.08503	0.10627	0.10202	0.09777
93	0.12504	0.10504	0.08503	0.10627	0.10202	0.09777
94	0.12504	0.10504	0.08503	0.10627	0.10202	0.09777
95	0.12504	0.10504	0.08503	0.10627	0.10202	0.09777
96	0.12504	0.10504	0.08503	0.10627	0.10202	0.09777
97	0.12504	0.10504	0.08503	0.10627	0.10202	0.09777
98	0.12504	0.10504	0.08503	0.10627	0.10202	0.09777
99	0.12504	0.10504	0.08503	0.10627	0.10202	0.09777
100	0.12504	0.10504	0.08503	0.10627	0.10202	0.09777

Appendix 10

Myocardial infarction

TABLE 46 *Prevalence of MI*[17]

Age (years)	Prevalence (%)
0–54	0.00
55–64	6.70
65–74	12.10

TABLE 47 *Relative risk of MI by smoking status*[18]

	Current smoker	Former	Non-smoker
Men	1.6	1.11	1.00
Women	2.76	1.05	1

TABLE 48 *Prevalence of MI by smoking status*

	Men			Women		
Age (years)	Current smoker	Former	Non-smoker	Current smoker	Former	Non-smoker
16	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
17	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
18	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
19	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
20	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
21	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
22	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
23	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
24	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
25	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
26	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
27	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
28	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
29	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
30	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
31	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
32	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
33	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
34	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
35	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
36	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
37	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
38	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
39	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
40	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
41	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
42	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
43	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
44	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000

TABLE 48 *Prevalence of MI by smoking status (continued)*

	Men			Women		
Age (years)	Current smoker	Former	Non-smoker	Current smoker	Former	Non-smoker
45	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
46	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
47	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
48	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
49	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
50	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
51	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
52	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
53	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
54	0.00000	0.00000	0.00000	0.00000	0.00000	0.00000
55	0.09210	0.06390	0.05756	0.04250	0.01617	0.01540
56	0.09210	0.06390	0.05756	0.04250	0.01617	0.01540
57	0.09210	0.06390	0.05756	0.04250	0.01617	0.01540
58	0.09210	0.06390	0.05756	0.04250	0.01617	0.01540
59	0.09210	0.06390	0.05756	0.04250	0.01617	0.01540
60	0.09210	0.06390	0.05756	0.04250	0.01617	0.01540
61	0.09210	0.06390	0.05756	0.04250	0.01617	0.01540
62	0.09210	0.06390	0.05756	0.04250	0.01617	0.01540
63	0.09210	0.06390	0.05756	0.04250	0.01617	0.01540
64	0.09210	0.06390	0.05756	0.04250	0.01617	0.01540
65	0.17246	0.11965	0.10779	0.09283	0.03532	0.03363
66	0.17246	0.11965	0.10779	0.09283	0.03532	0.03363
67	0.17246	0.11965	0.10779	0.09283	0.03532	0.03363
68	0.17246	0.11965	0.10779	0.09283	0.03532	0.03363
69	0.17246	0.11965	0.10779	0.09283	0.03532	0.03363
70	0.17246	0.11965	0.10779	0.09283	0.03532	0.03363
71	0.17246	0.11965	0.10779	0.09283	0.03532	0.03363
72	0.17246	0.11965	0.10779	0.09283	0.03532	0.03363
73	0.17246	0.11965	0.10779	0.09283	0.03532	0.03363
74	0.17246	0.11965	0.10779	0.09283	0.03532	0.03363
75	0.17463	0.12115	0.10914	0.09811	0.03732	0.03555
76	0.17463	0.12115	0.10914	0.09811	0.03732	0.03555
77	0.17463	0.12115	0.10914	0.09811	0.03732	0.03555
78	0.17463	0.12115	0.10914	0.09811	0.03732	0.03555
79	0.17463	0.12115	0.10914	0.09811	0.03732	0.03555
80	0.17463	0.12115	0.10914	0.09811	0.03732	0.03555
81	0.17463	0.12115	0.10914	0.09811	0.03732	0.03555
82	0.17463	0.12115	0.10914	0.09811	0.03732	0.03555
83	0.17463	0.12115	0.10914	0.09811	0.03732	0.03555
84	0.17463	0.12115	0.10914	0.09811	0.03732	0.03555
85	0.17463	0.12115	0.10914	0.09811	0.03732	0.03555
86	0.17463	0.12115	0.10914	0.09811	0.03732	0.03555
87	0.17463	0.12115	0.10914	0.09811	0.03732	0.03555

	Men			Women		
Age (years)	Current smoker	Former	Non-smoker	Current smoker	Former	Non-smoker
88	0.17463	0.12115	0.10914	0.09811	0.03732	0.03555
89	0.17463	0.12115	0.10914	0.09811	0.03732	0.03555
90	0.17463	0.12115	0.10914	0.09811	0.03732	0.03555
91	0.17463	0.12115	0.10914	0.09811	0.03732	0.03555
92	0.17463	0.12115	0.10914	0.09811	0.03732	0.03555
93	0.17463	0.12115	0.10914	0.09811	0.03732	0.03555
94	0.17463	0.12115	0.10914	0.09811	0.03732	0.03555
95	0.17463	0.12115	0.10914	0.09811	0.03732	0.03555
96	0.17463	0.12115	0.10914	0.09811	0.03732	0.03555
97	0.17463	0.12115	0.10914	0.09811	0.03732	0.03555
98	0.17463	0.12115	0.10914	0.09811	0.03732	0.03555
99	0.17463	0.12115	0.10914	0.09811	0.03732	0.03555
100	0.17463	0.12115	0.10914	0.09811	0.03732	0.03555

Appendix 11

Stroke

TABLE 49 *Prevalence of stroke*[17]

Age (years)	Prevalence (%)
16–24	0.00
25–34	0.00
35–44	0.30
45–54	1.20
55–64	2.20
65–74	7.60
75+	13.30

TABLE 50 *Relative risk of stroke by smoking status*[18]

	Current smoker	Former	Non-smoker
RR	1.37	1.11	1.00

TABLE 51 *Prevalence of stroke by smoking status*

	Men			Women		
Age (years)	Current smoker	Former	Non-smoker	Current smoker	Former	Non-smoker
16	0.00125	0.00101	0.00091	0.00246	0.00199	0.00179
17	0.00125	0.00101	0.00091	0.00246	0.00199	0.00179
18	0.00125	0.00101	0.00091	0.00246	0.00199	0.00179
19	0.00125	0.00101	0.00091	0.00246	0.00199	0.00179
20	0.00125	0.00101	0.00091	0.00246	0.00199	0.00179
21	0.00125	0.00101	0.00091	0.00246	0.00199	0.00179
22	0.00125	0.00101	0.00091	0.00246	0.00199	0.00179
23	0.00125	0.00101	0.00091	0.00246	0.00199	0.00179
24	0.00125	0.00101	0.00091	0.00246	0.00199	0.00179
25	0.00475	0.00385	0.00347	0.00367	0.00297	0.00268
26	0.00475	0.00385	0.00347	0.00367	0.00297	0.00268
27	0.00475	0.00385	0.00347	0.00367	0.00297	0.00268
28	0.00475	0.00385	0.00347	0.00367	0.00297	0.00268
29	0.00475	0.00385	0.00347	0.00367	0.00297	0.00268
30	0.00475	0.00385	0.00347	0.00367	0.00297	0.00268
31	0.00475	0.00385	0.00347	0.00367	0.00297	0.00268
32	0.00475	0.00385	0.00347	0.00367	0.00297	0.00268
33	0.00475	0.00385	0.00347	0.00367	0.00297	0.00268
34	0.00475	0.00385	0.00347	0.00367	0.00297	0.00268
35	0.00367	0.00297	0.00268	0.00734	0.00595	0.00536
36	0.00367	0.00297	0.00268	0.00734	0.00595	0.00536
37	0.00367	0.00297	0.00268	0.00734	0.00595	0.00536
38	0.00367	0.00297	0.00268	0.00734	0.00595	0.00536
39	0.00367	0.00297	0.00268	0.00734	0.00595	0.00536
40	0.00367	0.00297	0.00268	0.00734	0.00595	0.00536

TABLE 51 *Prevalence of stroke by smoking status (continued)*

	Men			Women		
Age (years)	Current smoker	Former	Non-smoker	Current smoker	Former	Non-smoker
41	0.00367	0.00297	0.00268	0.00734	0.00595	0.00536
42	0.00367	0.00297	0.00268	0.00734	0.00595	0.00536
43	0.00367	0.00297	0.00268	0.00734	0.00595	0.00536
44	0.00367	0.00297	0.00268	0.00734	0.00595	0.00536
45	0.01459	0.01182	0.01065	0.01103	0.00894	0.00805
46	0.01459	0.01182	0.01065	0.01103	0.00894	0.00805
47	0.01459	0.01182	0.01065	0.01103	0.00894	0.00805
48	0.01459	0.01182	0.01065	0.01103	0.00894	0.00805
49	0.01459	0.01182	0.01065	0.01103	0.00894	0.00805
50	0.01459	0.01182	0.01065	0.01103	0.00894	0.00805
51	0.01459	0.01182	0.01065	0.01103	0.00894	0.00805
52	0.01459	0.01182	0.01065	0.01103	0.00894	0.00805
53	0.01459	0.01182	0.01065	0.01103	0.00894	0.00805
54	0.01459	0.01182	0.01065	0.01103	0.00894	0.00805
55	0.02691	0.02181	0.01965	0.03095	0.02507	0.02259
56	0.02691	0.02181	0.01965	0.03095	0.02507	0.02259
57	0.02691	0.02181	0.01965	0.03095	0.02507	0.02259
58	0.02691	0.02181	0.01965	0.03095	0.02507	0.02259
59	0.02691	0.02181	0.01965	0.03095	0.02507	0.02259
60	0.02691	0.02181	0.01965	0.03095	0.02507	0.02259
61	0.02691	0.02181	0.01965	0.03095	0.02507	0.02259
62	0.02691	0.02181	0.01965	0.03095	0.02507	0.02259
63	0.02691	0.02181	0.01965	0.03095	0.02507	0.02259
64	0.02691	0.02181	0.01965	0.03095	0.02507	0.02259
65	0.09473	0.07675	0.06914	0.06840	0.05542	0.04993
66	0.09473	0.07675	0.06914	0.06840	0.05542	0.04993
67	0.09473	0.07675	0.06914	0.06840	0.05542	0.04993
68	0.09473	0.07675	0.06914	0.06840	0.05542	0.04993
69	0.09473	0.07675	0.06914	0.06840	0.05542	0.04993
70	0.09473	0.07675	0.06914	0.06840	0.05542	0.04993
71	0.09473	0.07675	0.06914	0.06840	0.05542	0.04993
72	0.09473	0.07675	0.06914	0.06840	0.05542	0.04993
73	0.09473	0.07675	0.06914	0.06840	0.05542	0.04993
74	0.09473	0.07675	0.06914	0.06840	0.05542	0.04993
75	0.16675	0.13510	0.12172	0.11377	0.09218	0.08304
76	0.16675	0.13510	0.12172	0.11377	0.09218	0.08304
77	0.16675	0.13510	0.12172	0.11377	0.09218	0.08304
78	0.16675	0.13510	0.12172	0.11377	0.09218	0.08304
79	0.16675	0.13510	0.12172	0.11377	0.09218	0.08304
80	0.16675	0.13510	0.12172	0.11377	0.09218	0.08304
81	0.16675	0.13510	0.12172	0.11377	0.09218	0.08304
82	0.16675	0.13510	0.12172	0.11377	0.09218	0.08304
83	0.16675	0.13510	0.12172	0.11377	0.09218	0.08304

	Men			Women		
Age (years)	Current smoker	Former	Non-smoker	Current smoker	Former	Non-smoker
84	0.16675	0.13510	0.12172	0.11377	0.09218	0.08304
85	0.16675	0.13510	0.12172	0.11377	0.09218	0.08304
86	0.16675	0.13510	0.12172	0.11377	0.09218	0.08304
87	0.16675	0.13510	0.12172	0.11377	0.09218	0.08304
88	0.16675	0.13510	0.12172	0.11377	0.09218	0.08304
89	0.16675	0.13510	0.12172	0.11377	0.09218	0.08304
90	0.16675	0.13510	0.12172	0.11377	0.09218	0.08304
91	0.16675	0.13510	0.12172	0.11377	0.09218	0.08304
92	0.16675	0.13510	0.12172	0.11377	0.09218	0.08304
93	0.16675	0.13510	0.12172	0.11377	0.09218	0.08304
94	0.16675	0.13510	0.12172	0.11377	0.09218	0.08304
95	0.16675	0.13510	0.12172	0.11377	0.09218	0.08304
96	0.16675	0.13510	0.12172	0.11377	0.09218	0.08304
97	0.16675	0.13510	0.12172	0.11377	0.09218	0.08304
98	0.16675	0.13510	0.12172	0.11377	0.09218	0.08304
99	0.16675	0.13510	0.12172	0.11377	0.09218	0.08304
100	0.16675	0.13510	0.12172	0.11377	0.09218	0.08304

Appendix 12

Protocol submitted for study funding

1 TITLE: Relapse prevention in UK Stop Smoking Services: current practice, potential effectiveness and cost-effectiveness

2 Planned investigation

2.1 Existing research

2.1.1 Introduction: Smoking remains a major, international cause of morbidity and mortality and reducing smoking should be a priority for health systems like the UK National Health Service (NHS).[1] Although behavioural support, bupropion and nicotine replacement therapy (NRT) are effective treatments provided by the NHS,[2] many smokers who stop after using these subsequently relapse to smoking ('relapsers'). The proportion of relapsers increases with time elapsed after any initial cessation attempt, diminishing the impact of effective therapies on eventual cessation. Interventions that aim to decrease the proportion of relapsers are termed 'relapse prevention' interventions (RPIs). This project proposes an investigation into the potential effectiveness and cost-effectiveness of such interventions within the context of UK clinical practice and an assessment of which RPIs are most feasible for trialling within NHS Stop Smoking Services.

2.1.2 Effectiveness of relapse prevention interventions: A Cochrane review, updated in October 2004,[3] (and summary journal article with searching until August 2005[4]) found no evidence for the effectiveness of any specific type of relapse prevention intervention (RPI), but also noted that there was only a small evidence base from which this conclusion was drawn. Most included trials tested interventions which taught smokers the skills to identify situations that may increase their risk of relapsing and provided them with cognitive and behavioural strategies for coping with these. More intensive RPIs were usually delivered face to face and less intensive ones, involved briefer, minimal contact or self-help versions of these 'skills-equipping' interventions. As included trials involved a variety of RPIs delivered to smokers with varied characteristics both before and after quit attempts, a pooled estimate for the general effectiveness of RPIs is not available and instead review authors pooled analyses for trials in subgroups where comparisons were valid. Trials which recruited smokers who had completed smoking cessation programmes, perhaps provide data which are most relevant to the UK context (see below).[3,4] Among these, five studies found no evidence that RPIs could reduce relapse rates ($n = 1121$; OR, 1.00; 95% CI, 0.80–1.25), whereas two trials found some evidence for the effectiveness of NRT ($n = 2261$; OR, 1.30; 95% CI, 1.06–1.61) and two found no evidence for use of bupropion in relapse prevention ($n = 605$; OR, 1.25; 95% CI, 0.86–1.81). It is possible that further trials have either concluded or been published since the above review searches were conducted.[3,4] This is particularly likely for investigations of newer drug treatments being used for RP, as trials of a new therapeutic agent, varenicline, have reported in this period and in at least one of these studies, this drug was used effectively for relapse prevention.[5]

2.1.3 Clinical practice of smoking cessation in NHS Stop Smoking Services: In 2000, the NHS introduced Stop Smoking Services (SSS) in England after piloting these in a small number of areas[2] and similar services were set up in other UK countries. Between April 2003 and March 2006, 1.5 million smokers set quit dates with English SSS and 832,900 successfully stopped for at least 4 weeks.[6] Around 15% of smokers attending English SSS stop smoking for at least one year[7] at an average cost per life year saved of £438, after allowance for future health care savings.[8] Unfortunately, relapse rates within SSS are high and 75% of smokers who are abstinent 4 weeks after their quit date relapse to smoking by 12 months.[7] Clearly, compared to other health-care interventions SSS are already very cost-effective but this could be further increased by the addition of any effective relapse prevention intervention (RPI) to current, routine SSS smoking cessation treatment.

2.1.4 Provision or trialling of relapse prevention interventions within SSS: There is no current evidence to support the routine provision of RPIs by SSS but because large numbers of motivated smokers access these services, they could provide an ideal environment for conducting RCTs to investigate RPIs' effectiveness. Additionally, if any

RPIs were proven to be effective then delivering these via NHS SSS would ensure that the maximum number of abstinent smokers received these. Consequently, it is important to consider how the ways in which *current standard* drug and behavioural treatments offered by SSS are provided might affect the feasibility of conducting trials for *additional* RPIs or introducing these into routine clinical practice.

All SSS are required to monitor the numbers of smokers who (i) access services and set a quit date and (ii) are abstinent from smoking for at least 4 weeks,[9] but there are no other criteria governing how services should be structured and there is a paucity of contemporary data about this. Shortly after SSS were introduced, most offered 6 (for individuals) or 7 (for groups) session programmes of behavioural support to smokers.[10] However, there are no up to date information available about what constitutes 'treatment' for smoking cessation in UK NHS Stop Smoking services such as the numbers and nature of sessions offered, their length and timing and who delivers these. Additionally, we have no idea about smokers' actual uptake of treatment sessions that they are offered by SSS. However, the length and timing of treatment programmes offered by SSS and the completeness of smokers' attendance at these are determinants of how RPIs could be delivered in addition to SSS current treatment programmes and the likely costs of this to the NHS. For example, if most abstinent smokers actually attend most SSS treatment sessions offered soon after their quit dates, then trialling or providing additional RPIs early in quit attempts would not necessarily involve extra contacts with SSS staff and increased NHS costs. Alternatively, if few abstinent smokers attend treatment sessions after their smoking status is ascertained at 4 weeks, introducing additional RPIs after this time would involve increased costs to the NHS (extra patient contact). Also persuading abstinent smokers to attend SSS for any RPIs being trialled at this time point might be difficult. Finally, if drug treatments were to be trialled or provided for RP in addition to standard smoking cessation, knowing exactly how SSS currently use or recommend nicotine addiction therapies is necessary. Other service provision issues also have the potential to impact on the feasibility to trial the effectiveness of RPIs within NHS Stop Smoking Services and current information on both the nature of treatments provided by SSS and the structure of service provision will help decide priorities for relapse prevention research.

2.1.5 Natural history of relapse to smoking in NHS stop smoking service users: Any trials of RPI conducted within SSS would need to demonstrate improvement in relapse to smoking rates compared to those already experienced by smokers trying to quit with SSS support. Additionally, the timing of relapse after quit attempts begin is important because, for RPIs to have maximum effect, these need to be delivered when most quitters are still abstinent. Consequently, 'relapse curves' which plot abstinence from smoking against time (t) [where $t = 0$ at the initiation of a quit attempt] would assist decisions about the optimal time for delivery of RPIs in any trial. Relapse curves would also provide information for health economic modelling aimed at determining the treatment effects that any RPIs delivered by SSS might need in order to be cost-effective.

Unfortunately, SSS do not routinely record data on smoking behaviour at sufficient time points to provide data from which relapse curves could be constructed.[9] However, more detailed, individual-level data collected from SSS users during an earlier evaluation of English SSS and which includes biochemically-validated smoking status data at 4 and 52 weeks after quitting and self report data of when relapse occurred, is available to the research team.[7] These data are the most relevant available on SSS users, but to derive relapse curves, smoking status information from more time points is required, so we propose using these data in conjunction with data from clinical trials to derive 'best estimate' relapse curves for SSS users. Smokers who use SSS are motivated to quit and all receive an intensive behavioural intervention with most also receiving NRT or bupropion.[7] Trial participants who are also treated with intensive behavioural support and NRT or bupropion with might, therefore, be expected to have similar relapse trajectories as SSS users, but the relapse rates from clinical trials may differ from those obtained by SSS. Consequently, this proposal includes a methodology for combining data from participants in these trials with SSS-user data to estimate accurate relapse curves for SSS users.

Overall, this project will reassess the evidence for the effectiveness of relapse prevention interventions from a UK perspective and produce baseline information on the pattern and scale of relapse prevention practice that currently occurs within UK SSS. The feasibility of trialling RPIs within SSS and estimates for the potential cost-effectiveness of RPIs will be provided. Together,

this information will be essential for funding bodies to determine relapse prevention research priorities and for researchers planning UK trials for relapse prevention interventions.

2.2 Research objectives

1. To update estimates of effectiveness in the Cochrane review on interventions for preventing relapse to smoking
2. To assess which studies included in 1 above, provide findings that are generalisable to NHS Stop Smoking Services and which test interventions that might be acceptable to introduce within the UK.
3. To derive 'relapse to smoking' curves for smoking cessation attempts made with NHS Stop Smoking Services using (i) prolonged and (ii) point abstinence from smoking as outcome measures.
4. To survey NHS stop smoking services in order to:
   i. describe and categorise relapse prevention interventions which are currently used in UK NHS Stop Smoking Services
   ii. describe the current treatment provided by UK NHS stop smoking services for smokers who are trying to stop
   iii. describe how treatment in (ii) above is provided (e.g. number and nature of staff involved)
   iv. to ascertain barriers to the trialling or introduction of relapse prevention interventions within current clinical practice.
5. To determine the potential cost-effectiveness of relapse prevention interventions, delivered to smokers using NHS Stop Smoking Services.
6. To identify deficiencies in the evidence base concerning the use of relapse prevention interventions for smoking cessation and to identify priorities for future research.

3 Research methods

The proposed project is divided into four distinct phases and initials here refer to research team members named in a later section:

1. Systematic review to update previous Cochrane review.
2. Systematic review to derive relapse curves for NHS Stop Smoking Service users.
3. Survey of UK NHS Stop Smoking Services.
4. Economic analysis.

3.1 Systematic review to update and augment Cochrane review of RPI effectiveness

Specific objectives are to:

(a) Update estimates of effectiveness from the Cochrane review on effectiveness of interventions for preventing relapse to smoking.
(b) For studies included in (a), assess which provide findings that are generalisable to NHS Stop Smoking Services interventions and which interventions might be acceptable to introduce within the UK.

3.1.1 Search strategy: We will obtain copies of all papers included in the Cochrane review of RPI[11] and use the search strategy from this to identify papers published since the final Cochrane review searches were undertaken (Oct 2004). We aim to find all new, relevant trials including those of new drug therapies (e.g. varenicline).[5] To ensure that we do not miss any relevant studies since October 2004 that are either concluded or ongoing, we will add to the Cochrane review search strategy[11] by (i) conducting a 'review of reviews', looking for similar studies in all of the relevant reviews that have been produced recently (e.g. rapid reviews for NICE guidance), (ii) searching the NRR and trial registers (e.g. Controlled Clinical Trials) and where necessary contacting triallists to ascertain whether results can be provided, (iii) contacting, for information, members of the Society for Research on Nicotine and Tobacco e-mail discussion list, (iv) hand searching abstracts of relevant conferences that are not included in specialist registers of the Cochrane Tobacco Addiction Review Group, (v) searching the reference lists of relevant papers (vi) contacting pharmaceutical companies that produce pharmacotherapies and enquiring about relevant studies. JLB will supervise a research assistant (RA) to conduct searches and will liaise with LS, an author of the original Cochrane review, to ensure that this and other aspects of updating the Cochrane review are properly-conducted.

3.1.2 Updating Cochrane estimates: We will follow the same plan for extracting data, categorising interventions, and data synthesis as in the original review,[11] which defined relapse very broadly and permitted RPIs to be delivered to smokers who had been abstinent for as little as 24 hours. This also allowed inclusion of studies with self-reported smoking cessation as an outcome and required that follow up occurred for 6 months after the RPI intervention was delivered. Updated analyses

of the effectiveness of RP interventions will be performed, as necessary but, given that 38 out of 40 trials in the 2004 review yielded negative findings, it is unlikely that different conclusions will be reached unless significant new data are available. At the conclusion of this process, we will provide data and analyses to LS and other Cochrane review authors for them to include in their biannual review update.

3.1.3 Additional analyses: In addition to updating Cochrane estimates, we will also undertake the following analyses. The Cochrane review used a fixed effects method to pool estimates for the effectiveness of RPIs in sub groups. However, if after considering interventions employed in the sub groups of trials that the Cochrane analysis employed, we consider that heterogeneity between studies is likely (e.g. where treatments of differing intensities are delivered at different times during abstinence after smoking cessation has begun), we will conduct an analysis using a random effects model. We will use I^2 to estimate variability between trials[12] and if I^2 is >85%, this will be taken to be excessive heterogeneity and we will not perform a meta-analysis of sub groups but will restrict our report to individual trial estimates rather than pooled sub group estimates. Where pooling is permissible, we will attempt (data permitting) to conduct analyses to determine effects of RPIs on relapse rates at the following times after provision of relapse prevention interventions: around 1 month (short term), around 6 months (medium term) and 1 year and over (longer term), reporting pooled effectiveness of interventions as odds ratios with 95% confidence intervals. Additionally, we will attempt to report the impact of RPIs on time taken to relapse, using hazard ratios with 95% CIs assessed at 1 year and over.

If updated estimates suggest that RPI are effective in any one context (e.g. for pregnant women or with smokers who have completed treatment programmes), we will investigate data further to determine whether differential effectiveness is observed in sub-groups of trial subjects (e.g. ethnic group or different socioeconomic groups)(Note: the research brief suggests that such analyses should be undertaken, if appropriate). However, we will not pursue these analyses if the overall estimates for effectiveness of RPI remain negative because, in this instance, these would not be scientifically justified.

3.1.4 Generalisability and acceptability of review RPIs to NHS SSS: For all studies included in our updated review, we will extract data describing interventions as per the initial review, taking particular care to ensure that we note:

1. Length of quit attempt prior to delivery of RPI.
2. Whether or not RPI interventions are delivered to abstainers who have attended smoking cessation programmes.

These data will be used in conjunction with survey findings (section, 3.3) to assess relevance of study interventions to the UK and judge the feasibility of trialling or introducing these into SSS.

Generalisability of trial findings: The Cochrane review used a broad definition of relapse which included, for example, failed quit attempts of 24 hours[13] or more and patients who had stopped smoking during hospital admissions.[14] This and other factors could mean that some trials in the review may have findings that are not generalisable to all smokers who engage in quit attempts whilst using NHS SSS. In tandem with the process above, the study team will inspect trial details to determine how generalisable findings are to the NHS SSS and will provide an assessment of this in the final study report. For example, the timing of RPI delivery in relation to period of abstinence from smoking important may be an important determinant of the potential external validity of trial findings.

Acceptability of intervention: This will be assessed in the context of current NHS SSS 'standard treatment and practice' for smoking cessation as revealed in the survey (3.3) and using a research-based model for assessing the feasibility of introducing complex interventions into routine clinical care.[15] Acceptability (or the likelihood that any intervention can become 'normalised'[15] within routine care will be judged against the four constructs of this model: interactional workability; relational integration; skill set workability and contextual integration.[15] The exact criteria for judging feasibility will depend upon survey findings and be derived after discussion of survey findings by the research team but before the assessment process begins. Explicit written criteria for judgements will be produced and these criteria will facilitate judgements in the context of the May criteria.[15] For example, the level of difficulty that introducing RPIs would entail in terms of providing extra resources for SSS delivery (e.g. human or financial resources) or necessitating changes in current clinical practice will be important considerations. Judgements

about feasibility will be made by independently by the RA, TC and AMcN and disagreements will be resolved by a group meeting to achieve consensus. Where possible, studies will be grouped into different categories, based on the feasibility of implementing interventions described and the final study report will contain an assessment of the pros and cons of introducing different RPIs into SSS.

3.2 Deriving relapse curves for NHS Stop Smoking Service users

Objective: To derive relapse to smoking curves for smoking cessation attempts made with NHS Stop Smoking Services using (i) prolonged and (ii) point abstinence from smoking as outcome measures.

Technical note: A relapse curve (survival curve) uses data on smoking status, collected from the time that smokers start quit attempts and subtracts the number of 'relapsers' from the total number of smokers enrolled into a study to derive the number still abstinent as time elapses.[16]

3.2.1 Systematic search for trial data: This literature search will aim to find trials which include at least one treatment group that includes smokers who receive intensive behavioural support, plus a drug treatment for nicotine addiction (e.g. varenicline, NRT or bupropion). Additionally, we will look for any observational studies in which smokers' abstinence over time is monitored, but we will exclude studies reporting analyses of the data contained in the databases that are proposed for use in conjunction with trial data to produce relapse curves[7]). JLB will determine the exact search criteria in conjunction with LS and the RA will conduct searches. LS is Cochrane Tobacco Addiction Group Review Group co-ordinator and has substantial experience of conducting systematic reviews for smoking cessation interventions.

3.2.2 Selecting trials for inclusion in analysis: Two members of the research team will independently inspect the titles and abstracts of all selected studies to determine whether or not these should be included in the review at this stage and any disagreements will be resolved by a third researcher. The full text of all included and potentially relevant studies will be obtained and two researchers will independently assess, using criteria below, whether or not these should be included in the review with the third researcher participating as necessary to ensure that disagreements are resolved by consensus.

We will assess the quality of included studies using accepted criteria[17] including:

(a) method for generating randomisation sequence
(b) method of allocation concealment – considered 'adequate' if the assignment could not be foreseen
(c) who was blinded/not blinded (participants, clinicians, outcome assessors) if this is appropriate
(d) how many participants were lost to follow up in each arm, and whether reasons for losses were adequately reported
(e) whether all participants were analysed in the groups to which they were originally randomised.

We will assume that any trial participants who withdraw from trials have relapsed to smoking.

The following inclusion criteria have been informed by a previous review which attempted to construct relapse curves for smokers who were attempting to stop smoking without any form of treatment or support.[18] Study subjects will need to (i) be followed prospectively, (ii) be adult daily smokers [> 18], (iii) have received behavioural support *plus* one or more drug treatment for smoking cessation (iv) have reported a clearly defined quit date and subsequent follow-ups associated with this (v) have follow up data recorded for at least 12 months and on at least three occasions in the first month after their quit date. This final criterion is important because previous work suggests that most relapse occurs early in quit attempts.[16]

3.2.3 Data extraction: For all included studies, the RA will extract the following data to derive survival curves for relapse to smoking amongst trial participants:

- where survival curves are reported, these will be converted into daily abstinence rates from these using 'DIGIMATIC™' software (scans graphical plots and converts into numerical data)
- proportion of trial participants reporting prolonged abstinence[19] from smoking at all time points when this data collected between quit date and final follow up
- proportion of trial participants reporting point abstinence[19] from smoking at all time points when this data collected between quit date and final follow up

- number enrolled into trial at randomisation
- number of smokers followed up at each point (for studies where survival curve not reported)
- demographic characteristics of trial sample (i.e. age, sex, ethnicity and socioeconomic characteristics)
- trial setting
- proportions of trial participants in different demographic groups (i.e. age, sex, ethnicity and socioeconomic characteristics) reporting prolonged abstinence[19] or point abstinence[19] from smoking at all time points when this data collected between quit date. (Note: we anticipate that very few trials will publish detailed data on smoking cessation in different demographic groups.)

Extracted data will be double checked by AMcN and consensus will be achieved about disagreements by referring to TC, as appropriate.

3.2.4 Derivation of relapse curves using trial data: A previous study which tried to derive relapse curves for smokers who stop without any sort of support found that few trials in this group of smokers published sufficient data from which relapse curves could be constructed.[18] Consequently, although reported prolonged abstinence from smoking is the most relevant outcome for our purposes, we also propose deriving relapse curves using reported point prevalence (i.e. short periods of smoking cessation) at time points after quit date.

For both outcomes, the proportion of trial subjects reported to be abstinent (point or prolonged) at different time points will be combined, taking into account the size of individual trials and a pooled value for abstinence at different time points after quit date will be determined. We will use the same approach towards testing for heterogeneity as outlined in 3.1.3. and if there is too much heterogeneity or insufficient data to allow pooled relapse curves to be drawn, relapse curves from individual trials will be presented together.

If individual curves are presented, we will explore whether variability in relapse curves shapes is affected by the final effectiveness of smoking cessation interventions in individual trials by replotting curves so that the final point on each is zero. Additionally, we will group together trials of different interventions (e.g. NRT vs bupropion) to determine whether or not these have similar relapse curve shapes.

It is possible that there will be insufficient data to determine the characteristics of relapse curves in the first month after quitting, which is the time period during which the majority of relapse is thought to occur. In this is eventuality, we will access and investigate the use of data from the publicly-available GlaxoSmithKline (GSK) Clinical Trial Register which is available at: http://ctr.glaxowellcome.co.uk/Summary/bupropion/studylist.asp. This contains summaries of all GSK trials investigating the drug bupropion (a.k.a. Wellbutrin) and includes over 20 trials with smoking cessation as an outcome. Some of these trials have not been published in conventional medical journals and contain potentially-useful data. However, if such data were to be used then these trials would need an identical (i.e. to published data) assessment of methodological quality and the origin and quality of the data used for deriving different sections of relapse curves would be made explicit. Additionally, if these data are used, the study team will need to ensure that these data compliment that which is available in published reports and there is no 'double-counting' of trial register report data which is also contained in papers identified by literature searching.

If, after the above procedure has been followed, it is still not possible to derive complete relapse curves, we will attempt to obtain further data from pharmaceutical companies that produce NRT and/or varenicline. Obtaining NRT trial data might be problematic because most NRT trials were conducted some time ago and there have been many pharmaceutical company mergers since then. It is more likely that Pfizer would be able to provide data from unpublished varenicline trials, but the trial team do not believe that it is appropriate to approach Pfizer with such a request at this point for the following reasons:

(i) There may be enough published literature in peer review journals from which relapse curves can be drawn.

(ii) Any request for data would be best made when the research team's exact data needs are clearly defined [i.e. which part(s) of the relapse curve require further data]. This would enable focused question(s) to be asked of Pfizer rather than a broad request for data from trials of a new product which could be considered 'sensitive'.

3.2.5 Derivation of relapse curves for special populations of smokers: If possible, we will repeat the

analyses conducted in 3.2.4 for sub-groups smokers defined by demographic characteristics. However, it is very likely that trial reports will not contain enough data to permit this and the next section indicates how we can produce estimates for the shape of relapse curves within these groups.

3.2.6 Combining trial and routine data on patients attending NHS Stop Smoking Services: Although the participants in trials used to derive relapse curves above are similar to SSS users, we cannot assume that relapse curves for both groups will be identical because participants in trials often differ from the wider patient community. Consequently, we propose comparing individual-level data on relapse that has been obtained from SSS users attending two English[7] and a number of Scottish SSSs[20] with trial data to obtain 'best-estimate' relapse curves for SSS attenders. We propose that the analysis above (3.2.4/5) should determine the *shape* of relapse curves in this group and that data collected from SSS users will indicate the *likely abstinence rates* for patients form different demographic groups at one and 12 months.

The English SSS database contains data from 6959 SSS attenders, who set quit dates between May and November 2002[7] and the Scottish database, similar data collected between October 2004 and February 2005.[20] The English database includes data from three time points (enrolment, four weeks and one year) and the Scottish from two (enrolment and four weeks), so relapse curves could not be constructed from these data alone. Nevertheless, these databases contain individual-level data on a wide range of variables for SSS attenders (e.g. age, gender, ethnic group, socioeconomic status, motivation to stop smoking) and to the authors' knowledge, these are the main sources of data from which relapse rates of different SSS client groups could be determined. It should be noted that this research team has unrestricted access to databases needed for these analyses. In addition, the research team are aware that a small number of SSS have recently begun to collect data on smoking status at more time points after their quit attempts than they are required to do for monitoring purposes (personal communication, A McEwen). A research collaborator, Dr Andy McEwen, who manages the Smoking Cessation Service Research Network (SCSRN) will investigate the feasibility of using these data too.

LB will provide the two databases which will be combined and from these data we will calculate the proportions of SSS users who set quit dates and were subsequently recorded as not smoking (with biochemical verification) at 4 and 52 weeks after this. Next, we will recalculate these rates by age, gender, ethnic group, level of nicotine addiction, level of initial motivation to stop and socioeconomic status. Using these data and imputing data for other time points based on the overall shape of relapse curves derived in 3.2.4/5 above, we will draw estimated relapse curves for SSS users from with these different characteristics.

3.3 Survey of UK NHS Stop Smoking Services

Specific objectives are to:

(i) describe and categorise relapse prevention interventions which are currently used by UK NHS Stop Smoking Services

(ii) describe the current treatment provided by UK NHS stop smoking services to smokers who are trying to stop

(iii) describe <u>how</u> treatment in (ii) above is provided (e.g. number and nature of staff involved)

(iv) to ascertain barriers to the trialling or introduction of relapse prevention interventions within current clinical practice.

The feasibility of trialling or introducing RPIs into clinical practice and also their potential cost-effectiveness will vary with current UK SSS clinical practice. Consequently, we will conduct a postal survey of English and Scottish NHS stop smoking services to determine current practice and provision of relapse prevention interventions in these services and make an estimate of the costs associated with delivering these. To ensure that the survey asks valid questions, we will first undertake qualitative interviews with a selection of NHS stop smoking service staff.

3.3.1 Qualitative pilot work: NHS SSS staff will be recruited at the Third UK National Smoking Cessation Conference (UKNSCC) which is to be held in June 2007 in London and is organised by AMcE, a study collaborator. This large conference is held for health professionals working in NHS SSS and is well attended by representatives from many such services throughout the UK. The lead applicant successfully recruited smoking cessation advisors for research in a similar way during the 2006 conference. If, for any reason recruitment is not possible at this conference, we will seek health professionals for interview from contributors

to the Smoking Cessation Service Research Network (network of NHS SSS that are interested in research and run by AMcE). Both proposed methods of recruiting health professionals for interview avoid the need to obtain research governance approval from R&D departments.

The research team will offer to run or contribute to a workshop on relapse prevention at this conference and during this will inform workshop attenders about the proposed survey and invite them to be interviewed to assist with the development of the survey questionnaire. We will recruit, for individual interviews (face to face or telephone), twenty health professionals who work for SSS as smoking cessation advisors or managers. Where possible, interviews will be held during or soon after the conference with the aim of all being completed within one month. Interviews will be semi-structured,[21] conducted by a research assistant, audio taped and transcribed. Interviewees' perceptions of what relapse prevention entails will be explored. As there is no universally accepted definition of relapse prevention, interviewees' perceptions will be used to ensure that the subsequent survey uses a definition of RP that is clearly understandable to SSS staff. Interviews will explore experiences of delivering RPIs within stop smoking service (if indeed this is happening) including interventions' content and timing in relation to other aspects of SSS treatment for smokers. Health professionals who have first hand experience of delivering relapse prevention support will be asked about the challenges experienced (e.g. lack of patient motivation). With all interviewees we will ascertain their opinion on the factors which could hinder or help the introduction of relapse prevention support within their service. Additionally if, in our review (3.1), we identify interventions we believe are feasible for introduction within the UK, we will ascertain interviewees' opinions about these. Interviews will be analysed by at least two researchers who will read and reread transcripts in an iterative process to identify key themes arising from data and also categories within themes. Interpretation of findings from interviews will be cross checked between researchers conducting the analysis and a systematic approach will be taken to reintegrating coded data.[22,23] At the end of this process, key themes arising from interview data and categories within these will be summarised.

3.3.2 Postal survey: The survey will be administered by the Nottingham-based research assistant and the questionnaire used will be designed after input from Ann McNeill, Tim Coleman, John Britton, Paul Trueman, Linda Bauld (all co-applicants) and Andrew McEwen (collaborator). Bauld, Coleman and Mc Neill have previously conducted surveys of smoking cessation services and will use this experience to ensure that the proposed survey has the highest possible response rate.

Our aim is for all managers of PCT-run (CHP-run in Scotland) smoking cessation services to receive and potentially complete one questionnaire. Generally, in England and Scotland, each PCT/CHP runs one NHS Stop Smoking Service (SSS), though in some areas these may share one manager and associated administrative services. Primary care health service administration is currently being reorganised and consequently NHS SSS in some areas are being either combined or disaggregated depending upon the re-configuration of the PCTs in which they are located. For example, in Nottingham City before reconfiguration one smoking cessation service served four PCTs, but this is set to increase to two services working within the same area. Care will, therefore, be required in deriving a sampling frame for the survey and our procedure for doing this is described below. One cannot be certain of the exact sample size for the survey, though this should not exceed the combined number of PCTs and CHPs in England and Scotland and the unit of analysis for the questionnaire will be the smoking cessation service. The survey will commence approximately 9 months after the start of the project (around Dec 07 if the project commences in April 07).

Interview data and relevant systematic review findings will be combined to design a postal questionnaire, which will be piloted on interviewees before distribution to all SSS managers in England and Scotland. For this survey to be successful, it is vital that addressees are appropriate and their contact details correct. There is currently no up to date list of SSS managers in the UK, so initially the RA will contact the English DH/Scottish Office to determine which Primary Care Trusts (Community Health Partnerships in Scotland) return statistics for NHS Stop Smoking Services. Then the RA will telephone and/or e-mail these PCTs/CAPs to obtain postal and e-mail contact details for SSS managers and hence a sampling frame for the survey, so that both contact modalities can be used for an initial mailing. Research team members have previously conducted similar surveys of SSS and have found this approach results in questionnaires reaching

the relevant professionals.[10,24] One postal/e-mail and one telephone reminder will be used to secure healthy response rates.

Items for the survey questionnaire will, to an extent, be determined by the outcome of qualitative pilot work (Section 3.3.1). However, we will aim to ask about the delivery of relapse prevention interventions by SSS in terms that respondents are familiar with and understand, but which also facilitate comparison with other research on relapse prevention interventions. The survey will investigate the feasibility of introducing effective but unused relapse prevention interventions (identified in the earlier review) into routine care by SSS. It will also be important for the survey to produce information for estimation of costs involved in the delivery of interventions. Consequently, respondents will be asked to indicate the nature of interventions that SSS deliver to smokers, the time involved and any other potential costs. Questions on cost will be designed in conjunction with Paul Trueman and based upon those used in a previous survey of Stop Smoking Services and which contributed to an analysis of their cost-effectiveness.

The brief survey instrument will ask about size and location of SSS, current provision of both smoking cessation and relapse prevention interventions, who delivers these and an estimate of the time involved and other potential costs (e.g. prescription or advisor travel costs). Questions concerning costs of interventions will be informed by relevant items from a similar survey that contributed to an assessment of the cost-effectiveness of SSS which was conducted by study team members.[10] Additionally, respondents will be asked their perceptions of organisational factors (relevant to their particular SSS) which could influence the introduction of any new relapse prevention interventions into their services.

3.3.3 Survey analysis: As the survey is predominantly descriptive, data analysis will reflect this and quantitative data will be presented as summary statistics with measures of spread. No hypotheses generating analyses are planned. We expect that the survey will provide (i) clear descriptions, with quantification, of RPIs (if any) that SSS currently employ, (ii) a clear summary of *how* current treatments for smoking cessation by SSS are provided (i.e. length of treatment courses, group or individual sessions etc.), (iii) likely costs of providing RPIs, (iv) the structure and organisation of SSS (i.e. how many staff, staff salaries etc.) and (v) organisational factors within SSS that may hinder trialling of RPIs or their introduction into routine clinical practice. Consequently, survey findings will provide a clear snapshot of current practice in relapse prevention, with data to help assess the feasibility of how RPIs might be trialled or even introduced into clinical practice.

3.4 Health economic analysis

Objective: To determine the potential cost-effectiveness of relapse prevention interventions, delivered to smokers using NHS Stop Smoking Services.

Input to this exercise will be dependent upon project outcomes prior to this point. If RPIs have been found to be effective with some patient sub-groups or relapse rates have been found to differ between sub groups of SSS attenders, then modelling will also investigate the potential for different RPIs to be more or less cost-effective with different SSS client groups. It is envisaged that the following inputs would be used in a modelling exercise:

1. Description of RPIs derived from review (3.1) and survey (3.3).
2. Estimated costs of delivering RPIs within UK NHS SSS.
3. Potential treatment effects for RPIs described in 1 & 2.
4. Relapse curves derived in 3.2 – Potential cost-effectiveness of RPIs will vary with timing of their delivery after quit attempts have started, as the numbers of smokers who are abstinent from smoking (and in whom relapse can be prevented) will decrease with time elapsed after quit attempts began.

3.4.1: Data analysis: The description of RPIs will come from categorisation of interventions in the review (3.1). In addition to describing RPIs, we will indicate the feasibility of introducing each into clinical practice based on our assessment made in section 3.1 in conjunction with survey data from 3.3. The estimated costs of delivering RPIs will be dependant on configurations of SSS revealed in our survey and we will use a similar approach to costing delivery of RPIs as was used in our analysis of the cost-effectiveness of English smoking cessation services.[8] Costs are dependant on, for example, whether or not (i) interventions are delivered to groups or individuals, (ii) the salaries of those delivering them and (iii) whether or not drug treatments are provided.

Current systematic review evidence suggests that no interventions reduce relapse to smoking at 6 months of follow up, so economic modelling will involve sensitivity analyses using imputation of potential treatment effects, based on the most likely values as per systematic review findings. If, however, our updated review indicates that any type of RPI is/are effective, then modelling for these will be based around newly derived treatment effects. We will also investigate the potential impact on cost-effectiveness of delivering RPIs at different times after smokers become abstinent and hence to different proportions of smokers who have not yet relapsed to smoking.

The economics of the RPIs will be analysed using economic modelling techniques to extrapolate data on the short-term impact of the interventions to longer-term outcomes. The model is expected to build on previously completed models for smoking cessation, which may be adapted to review relapse prevention. The research team at the University of York are currently in the process of developing an economic model of smoking cessation interventions to inform the development of the NICE guideline on smoking cessation. It is hoped that it will be possible to adapt this model to help determine the cost-effectiveness of smoking relapse interventions.

The data on the effectiveness of the RPIs will be derived from the systematic review conducted at the earlier stage of this research. The resources involved in the provision of the RPIs under review are expected to be drawn from the survey of current practice. Unit costs will be applied to these resources in order to estimate the costs of providing the interventions. Unit costs will be drawn from widely used sources (e.g. Unit Costs of Health & Social Care, PSSRU).

In order to determine the cost-effectiveness of the interventions under consideration, it will be necessary to extrapolate the short-term outcomes of RPIs over a longer-term, possibly the lifetime of an individual. The extrapolation of findings will be based on biologically plausible models which, wherever possible, will be drawn from published research identified as part of the systematic review. However, where such models are unavailable in the published evidence, it may be necessary to draw on clinical expertise both within and outside of the research team, for assumptions on the longer-term impact of RPIs. Any assumptions used to inform the modelling exercise will be clearly reported and subject to sensitivity analysis. Sensitivity analysis will also be conducted on other key parameters identified from the systematic review, if there is cause to believe that there is uncertainty around the reported estimates. Univariate and multi-variate sensitivity analysis will be conducted as part of the research. It may also be appropriate to consider undertaking probabilistic sensitivity analysis, in order to report the cost-effectiveness acceptability curves.

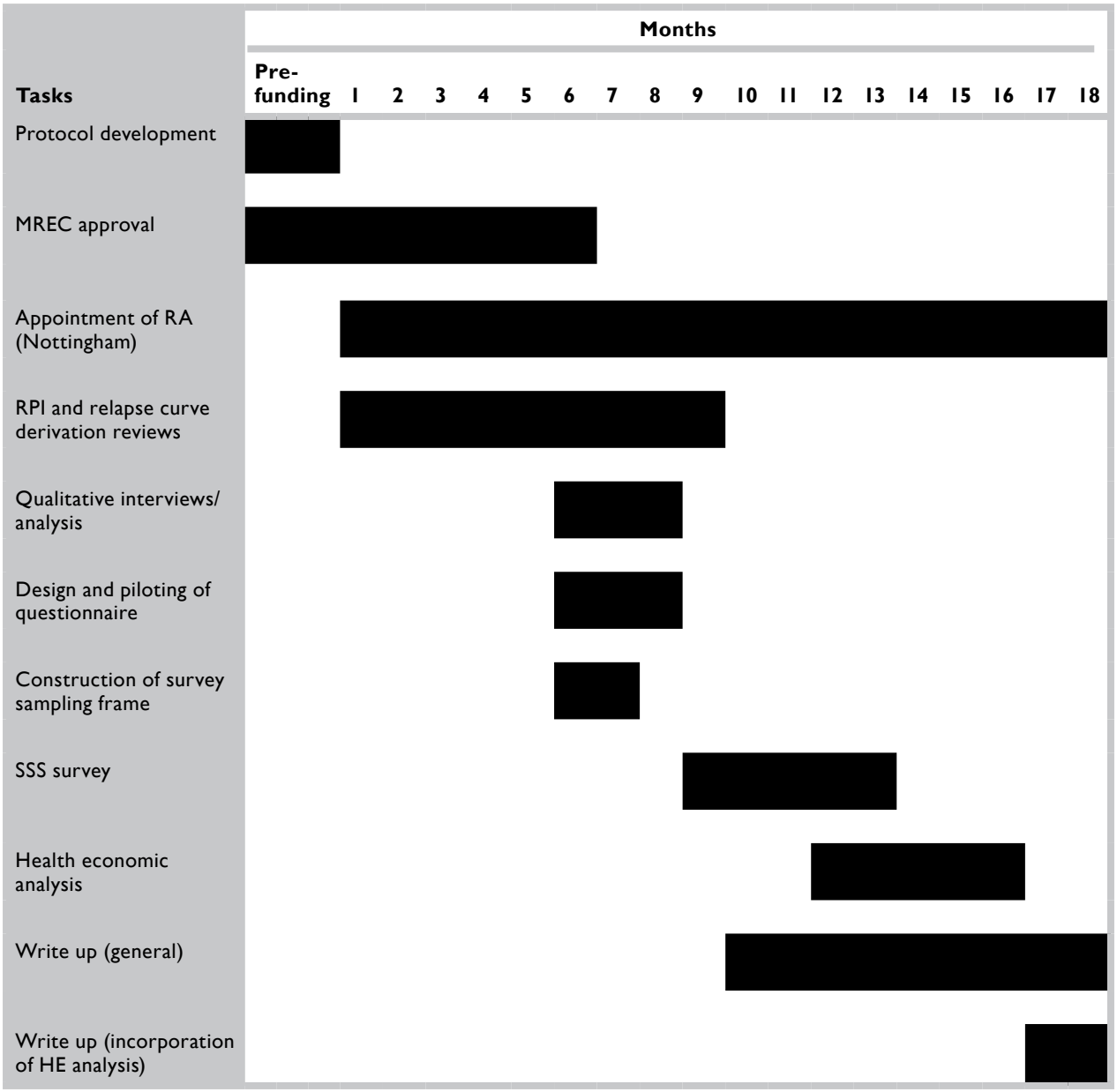
Outcomes of the model will be presented as cost per life year saved and cost per quality adjusted life year saved. Disaggregated findings, such as number of attendees remaining abstinent at a particular time, may also be reported.

The approach to modelling will adhere to best practice principles, such as those set out by Drummond[25] and the NICE reference case.

4 Ethical issues

Any delays encountered in obtaining necessary ethical permissions are unlikely to delay the project as systematic reviews will be conducted before the SSS survey. Ethical approval will be required to conduct qualitative interviews with SSS professionals but, as these are not recruited via NHS organisations, formal R&D approval will not be required. Patient information from the English and Scottish databases will be provided to the research team in an anonymous format and all patients enrolled into these databases have previously consented for these data to be used for research. Consequently, obtaining ethical approval to use these data for the proposed analyses is not likely to be problematic. If data from other NHS SSS has been obtained using similar consent procedures and these data can be provided anonymously to the research team, then ethical permission to use such data should not be problematic and accessing the data will be within the resources of the proposed project. If, however, this is not the case, then we will not use these data for our analyses. As part of our ethical approval application, we will highlight, drawing attention to COREC definitions of audit and research, our belief that the proposed survey of NHS stop smoking services is an audit of service provision, rather than original research. This will ensure that research governance approval is not needed. If this argument is not accepted by the REC, however, and the research team need to obtain R&D approval from the many PCTs in which SSS are located, then completion of this project within the timescale below will be less feasible.

5 Project timetable and milestones



6 Expertise of research team

Co-applicants

Linda Bauld Linda Bauld has substantial experience of research involving NHS stop smoking services. She was a member of a DH team which evaluated English SSS, has completed a similar project for Scotland and is an author of the recent NICE rapid review of the effectiveness of NHS Stop Smoking Services. Dr Bauld has access to data for use in 3.2. *John Britton* is an epidemiologist and triallist with an interest in smoking cessation and currently works with a local NHS SSS to execute a clinical trial investigating the effectiveness of Varenicline for smoking cessation. He Chairs the Royal College of Physician's Tobacco Advisory Group, has a broad interested in smoking cessation trials and will provide strategic level input. *Tim Coleman* also worked on the English SSS evaluation and currently is chief investigator for a trial of NRT in pregnancy that involves close liaison with a number of NHS stop smoking services. *Jo Leonardi-Bee* is a medical statistician with experience of systematic review methodology and provides valuable relevant expertise in both areas. *Ann McNeill* is a recent (September 2006) appointment to The University of Nottingham. She is an internationally-renowned expert on smoking cessation and tobacco control and has completed numerous projects in this area, including being a key member of the English

evaluation of smoking cessation services mentioned above. More recently, Prof McNeill produced an exhaustive NICE rapid review into the effectiveness of brief interventions. Although she is a new appointment to Nottingham, Professor McNeill has a strong history of collaboration with other members of the research team. *Paul Trueman* is the Director of the York Health Economics Consortium at the University of York. Paul is an experienced health economist who specialises in the conduct of economic evaluations using modelling techniques as well as analysis alongside clinical trials. Paul is currently leading a research team at the University of York in undertaking a rapid review and economic model of smoking cessation services for input to the NICE guideline on this topic. Paul will be supported by *Matthew Taylor* (*not a named applicant*) who has expertise in economic modelling techniques and has worked on models in a wide range of diseases including, coronary heart disease, rheumatology and nephrology. Matthew has a particular interest in the application of probabilistic sensitivity analysis.

Collaborators

Christine Godfrey is a Health Economist with a particular interest in smoking cessation. She has lead on the health economic components of the DH-funded English evaluation of the English smoking cessation services, the Thorax smoking cessation guidelines and, more recently, a NICE rapid review of the cost-effectiveness of brief interventions for smoking cessation. *Lindsay Stead* is an information scientist who is expert in systematic review and has worked within the Cochrane Collaboration Review Group for many years, producing a wide range of reviews on smoking-related topics, including the initial relapse prevention review.[3] *Andy McEwen* is a Senior Research Nurse at the CRUK Health Behaviour Unit with strong research and clinical links with NHS SSS; he is also Programme Director of the UKNSCC and is developing the Smoking Cessation Service Research Network (SCSRN) in which a small group of SSS collect comprehensive data on service attenders.

7 Justification of support required

One research assistant (RA) is required for 18 months to ensure that primary data collection is conducted thoroughly and the diverse data retrieved from literature searches is synthesised appropriately into a coherent research report. The RA will conduct literature research and lead on data extraction. (S)he will conduct pilot qualitative interviews with smoking cessation health professionals and conduct the postal survey of NHS stop smoking services. (S)he will lead on and co-ordinate collaboration with the health economic team at York and will co-ordinate writing of the final project report. Contributions for the academic time of all team members are written proposal.

Office costs: The research assistant will require a computer, monitor, printer, 'Digimatic™' and qualitative analysis data software, office consumables and access to a telephone and shared IT systems. Recording and transcription equipment will also be required. *Travel:* Rail travel for meetings (6 individual journeys), travel within Nottingham (as the research team work on different sites) and for the RA to conduct up to half the 20 interviews is required. *Teleconference:* 4 teleconferences are required to ensure that the expertise of all researchers is effectively utilised, and in particular for the model building and testing stage of the HE analysis. *Dissemination:* Travel and conference registration for one international conference is included. *Postage:* is primarily required for the survey of SSS and costs for undertaking 2 literature reviews are included.

The York team conducting the *health economic analysis* are a self-funding unit and are not subject to FEC. Consequently, their costs have been entered onto the application form as a *consumable* which will be supplied on a sub-contract basis to the UoN. The Paul Trueman's and Matthew Taylor's time is costed in at £850 and £750 per day respectively and the time of a third data analyst is also required at a daily rate of £650. The table below indicates days spent on the various activities involved in the HE analysis. Total = £26,200

	Days contributed by staff HE team member		
Activity	**PT**	**MT**	**Data analyst**
Development of model	1	2	
Build model in EXCEL	1	3	3
Populate model		2	5
Run model	0.5	2	
Sensitivity analysis	0.5	5	
Report writing	3	5	
Quality assurance	1	1	
Total	7	20	15

8 Projected outputs

The following outputs are anticipated: (i) HTA monograph, (ii) data for updating Cochrane RPI review provided to authors, (iii) paper describing relapse curves for attenders at smoking cessation services, (iv) paper describing current treatment for smoking cessation provided by NHS SSS, (v) paper describing the potential cost-effectiveness of RPI interventions delivered via NHS Stop Smoking services.

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We look forward to hearing from you.

NETSCC, Health Technology Assessment
Alpha House
University of Southampton Science Park
Southampton SO16 7NS, UK
Email: hta@hta.ac.uk
www.hta.ac.uk

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