



**Health  
Information  
and Quality  
Authority**

An tÚdarás Um Fhaisnéis  
agus Cáilíocht Sláinte

# **Health technology assessment (HTA) of smoking cessation interventions**

**22 March 2017**



## About the Health Information and Quality Authority

The Health Information and Quality Authority (HIQA) is an independent authority established to drive high quality and safe care for people using our **health and social care services in Ireland**. HIQA's role is to develop standards, inspect and review health and social care services and support informed decisions on how services are delivered.

HIQA aims to safeguard people and improve the safety and quality of health and social care services across its full range of functions.

HIQA's mandate to date extends across a specified range of public, private and voluntary sector services. Reporting to the Minister for Health and engaging with the Minister for Children and Youth Affairs, HIQA has statutory responsibility for:

- **Setting Standards for Health and Social Services** – Developing person-centred standards, based on evidence and best international practice, for health and social care services in Ireland.
- **Regulation** – Registering and inspecting designated centres.
- **Monitoring Children's Services** – Monitoring and inspecting children's social services.
- **Monitoring Healthcare Safety and Quality** – Monitoring the safety and quality of health services and investigating as necessary serious concerns about the health and welfare of people who use these services.
- **Health Technology Assessment** – Providing advice that enables the best outcome for people who use our health service and the best use of resources by evaluating the clinical effectiveness and cost-effectiveness of drugs, equipment, diagnostic techniques and health promotion and protection activities.
- **Health Information** – Advising on the efficient and secure collection and sharing of health information, setting standards, evaluating information resources and publishing information about the delivery and performance of Ireland's health and social care service.

## Foreword

Given the higher risk of disease and death in smokers, the economic cost of smoking in Ireland is substantial. In 2013, the estimated cost to the **healthcare system was over €460 million, the cost of lost productivity was over €1 billion, and the cost of loss of welfare was over €9 billion.** Smoking cessation substantially reduces the risk of developing most smoking-related diseases and also reduces the risk of death. A diverse range of smoking cessation interventions and services are currently funded by the public health system in Ireland. To consolidate activity in this area and to maximise the clinical benefits, an evidence-based analysis of the clinical and cost-effectiveness of the existing smoking cessation treatments was deemed necessary.

The National Tobacco Control Advisor to the Department of Health requested that the Health Information and Quality Authority (HIQA) undertake a health technology assessment (HTA) of the clinical and cost-effectiveness of pharmaceutical and non-pharmaceutical smoking cessation products and services. This request followed a recommendation in the national strategy **‘Tobacco Free Ireland’** to examine the national and international evidence on the effects of the use of nicotine replacement therapy and other interventions that support smokers to quit smoking. This HTA will provide the evidence to underpin a planned national clinical guideline on smoking cessation interventions and will inform policy decisions about potential improvements to the provision of smoking cessation services in the public health service.

Work on the assessment was undertaken by an Evaluation Team from the HTA Directorate in HIQA. A multidisciplinary Expert Advisory Group was convened to advise HIQA during the course of the assessment. A public consultation was carried out to get feedback from interested parties before finalising the report.

HIQA would like to thank its Evaluation Team, the members of the Expert Advisory Group and all who contributed to the public consultation and the preparation of this report.



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The ethical and legal analysis was written by Prof Deirdre Madden, Faculty of Law, University College Cork.

### **Conflicts of Interest**

None reported.

## List of abbreviations used in this report

<b>COPD</b>	chronic obstructive pulmonary disease
<b>EAG</b>	Expert Advisory Group
<b>EMA</b>	European Medicines Agency
<b>ENDS</b>	electronic nicotine delivery system
<b>ENNDS</b>	electronic non-nicotine delivery system
<b>FDA</b>	Food and Drugs Authority
<b>HIQA</b>	Health Information and Quality Authority
<b>HPRA</b>	Health Products Regulatory Authority
<b>HR</b>	hazard ratio
<b>HSE</b>	Health Service Executive
<b>HTA</b>	health technology assessment
<b>ICER</b>	incremental cost-effectiveness ratio
<b>NICE</b>	National Institute for Health and Care Excellence
<b>NRPA</b>	nicotine receptor partial agonist
<b>NRT</b>	nicotine replacement therapy
<b>OR</b>	odds ratio
<b>PCRS</b>	Primary Care Reimbursement Service
<b>QALY</b>	quality-adjusted life year
<b>RCT</b>	randomised controlled trial
<b>RR</b>	relative risk
<b>UK</b>	United Kingdom
<b>WHO</b>	World Health Organization

## **Advice to the Minister for Health**

The Health Information and Quality Authority (HIQA) carried out a health technology assessment (HTA) of smoking cessation interventions in Ireland to examine the clinical effectiveness, safety and cost-effectiveness of smoking cessation interventions, as well as the organisational, societal and ethical implications of potential changes to the mix of treatments that people use to help them stop smoking.

**The key findings of the HTA that precede and inform HIQA's advice are as follows:**

- Smoking continues to be a major public health problem in Ireland, and is associated with a considerable burden on the public health system. The prevalence of smoking in Ireland is 22.7% in people aged 15 years and over. The prevalence is higher in men (24.3%) than in women (21.2%), and highest in people aged 25 to 29 years (33.4%). Smoking prevalence follows a socio-economic gradient, whereby the prevalence is highest in those of the lowest socio-economic group.
- A diverse range of pharmacological and behavioural smoking cessation interventions are currently funded by the HSE, including both prescription and non-prescription medications, as well as brief intervention training for healthcare professionals who come in contact with smokers. The total annual expenditure on smoking cessation activity in Ireland is estimated to be over **€40 million**.
- HSE has prioritised that brief interventions in the form of brief advice or written materials are to be promoted as part of the routine delivery of care, and have been assumed to form the standard of care in Ireland.
- Approximately half of smokers in Ireland report making at least one quit attempt every year. The most popular cessation method is unassisted quitting (50%), followed by quit attempts involving e-cigarettes (29%) and nicotine replacement therapy (NRT, 12%). Less than 4% report using prescription-only interventions such as varenicline or bupropion.
- The average quit rate for an unassisted quit attempt after 12 months from the attempt is 7.8%.
- All pharmacological interventions included in this analysis were found to be effective. Varenicline was the most effective single therapy, more than two and half times as effective as the control. Varenicline used in combination with NRT was the most effective dual therapy, more than three and a half times as effective as the control. Using NRT products in combination was more effective than a single form of NRT alone.

- Based on two small clinical trials of first-generation devices, e-cigarettes were twice as effective as the control. Six ongoing trials, due to complete between 2017 and 2022, should provide further evidence for e-cigarettes as a smoking cessation intervention in a general population of unselected adults.
- In addition to the uncertainty about the effectiveness of e-cigarettes as a smoking cessation aid, there are also concerns that the social normalisation of e-cigarettes may lead to new use by people who have never smoked, later migration to tobacco cigarettes, long-term nicotine dependency, and other potential and as yet unknown harms.
- E-cigarettes are not currently advocated by the HSE as a means of quitting due to lack of long-term data on their safety. However, behavioural support is provided by HSE smoking cessation services to smokers who choose to use e-cigarettes in their quit attempt.
- All behavioural interventions included in the analysis were found to be effective compared to no treatment. Group behaviour therapy was the most effective behavioural intervention, almost twice as effective as an active control, defined as brief advice or written materials. Individual counselling, intensive advice and telephone support were all found to be more effective than the active control. The effectiveness of pharmacological interventions is improved by an average of 18% by providing any type of adjunct behavioural therapy.
- The volume of evidence for smoking cessation interventions in pregnant women and those attending specialist secondary mental health services was considerably lower than that available for the general population of unselected adults.
- Pregnant women who smoke should be offered a psychosocial intervention in the first instance. The psychosocial intervention with the largest body of evidence to support its effectiveness is counselling.
- Smoking prevalence is particularly high among people with a mental illness. High-intensity interventions combining pharmacotherapy and behavioural support have been shown to improve quit outcomes in people attending secondary mental health services (defined as inpatient, residential and long-term care for serious mental illness in hospitals, psychiatric and specialist units and secure hospitals and patients who are within the care of specialist community-based multidisciplinary mental health teams).
- A review of the safety profile of smoking cessation interventions found that pharmacological therapies are generally safe and well-tolerated in those for whom these treatments are medically indicated for use. The safety of e-cigarettes is an evolving area of research; while potentially safer than smoking, evidence on long-term safety has yet to be established.

- A cost-effectiveness analysis found that all cessation interventions included in the analysis would be considered cost-effective when compared with unassisted quitting. E-cigarettes and using varenicline, alone or in combination with NRT, were found to be the most cost-effective strategies when individual therapies are compared with each other.
- The cost-effectiveness of e-cigarettes is extremely sensitive to changes in the estimated cost and effects of this intervention. This is of particular significance given the high degree of uncertainty that exists in relation to both of these parameters.
- A comparison of alternatives to the current mix of smoking cessation interventions used in Ireland found that maximising the uptake of combination varenicline and NRT is the most cost-effective strategy.
- A budget impact analysis found that maximising the use of combination varenicline and NRT would be associated with an average increase of **approximately €7 million** in the annual cost of providing pharmacological smoking cessation interventions in Ireland.
- However, an examination of the evidence on the effect of different policy initiatives on influencing population level smoking cessation preferences was outside the scope of this analysis, so it is unclear to what extent the uptake of the most effective and efficient treatments can be increased among smokers making a quit attempt in Ireland.
- Increasing the smoking cessation budget to promote the use of varenicline-based regimens, and combination NRT therapy for those for whom varenicline is not suitable, would be a cost-effective use of resources.
- To facilitate this, potential barriers to increased uptake of smoking cessation interventions should be examined by the HSE and the Department of Health. This should include a review of dispensing rules for NRT on the General Medical Services (GMS), current exclusion of NRT from Drugs Payment Scheme (DPS) reimbursement, as well as the very limited number of nurse prescribers within smoking cessation services in Ireland.
- From an ethical perspective, any smoking cessation intervention must be made available in a way that promotes individual choice. This can be achieved by providing information concerning the risks and benefits associated with a particular intervention.
- From an organisational perspective, efforts to increase the use of combination varenicline and NRT will place additional demands on general practitioner (GP) or nurse prescriber services. In the event that use of this intervention reaches plausible maximum levels, the number of prescriptions required could increase by over 50%.

As economic models incorporate a number of assumptions and depend on the quality of available data, the results are subject to a degree of uncertainty. Bearing the assumptions used in this analysis in mind and considering the above findings, **HIQA's advice to the Minister for Health is as follows:**

- Smoking cessation services should, in the first instance, seek to increase the uptake of varenicline (alone or in combination with NRT) among smokers wishing to use some type of pharmacological support in their attempt to quit.
- Although the currently available results for e-cigarettes are promising, there is insufficient evidence at present to reliably demonstrate their effectiveness as an aid to smoking cessation. It would be appropriate to await the results of ongoing trials before deciding whether e-cigarettes should be recommended for those for whom varenicline is not suitable. Should additional evidence confirm the effectiveness of e-cigarettes as a smoking cessation aid, a decision to advocate their use should also take into consideration any additional information on the long-term safety of e-cigarettes use, as well as any emerging data in relation to concerns about the social normalisation of e-cigarettes leading to increased uptake among people who have never smoked, or later migration to tobacco cigarettes.
- In the absence of additional evidence confirming the effectiveness of e-cigarettes, HSE smoking cessation services should seek to promote the uptake of combination NRT treatment among those for whom varenicline is not suitable.
- Providing behavioural support, either alone or in combination with pharmacological interventions, increases the chances of long-term smoking cessation and should continue to be provided to all smokers who would like to avail of this option to help them quit.
- Pregnant women who smoke should be offered a psychosocial intervention in the first instance. The psychosocial intervention with the largest body of evidence to support its effectiveness is counselling.
- While the evidence for smoking cessation interventions among those attending specialist secondary mental health services is very limited, high-intensity interventions combining pharmacotherapy and behavioural support have been shown to improve quit outcomes. However, further research on the effectiveness of smoking cessation interventions in this population is needed.

## **Executive Summary**

### **Background and Terms of Reference**

The Health Information and Quality Authority (HIQA) agreed to undertake a health technology assessment (HTA) of smoking cessation interventions in Ireland following a formal request from the Department of Health's National Tobacco Control Advisor. An evidence-based analysis of the clinical effectiveness and cost-effectiveness of treatments that help people stop smoking was carried out to ensure that the benefits achieved from the current level of funding available are maximised. This HTA also provides evidence to support development of a national clinical guideline on smoking cessation. National Clinical Guidelines are quality assured by the National Clinical Effectiveness Committee (NCEC) and mandated by the Minister for Health to provide guidance and standards for improving the quality, safety and cost-effectiveness of healthcare in Ireland.

This HTA assessed the clinical and cost-effectiveness of pharmacological and non-pharmacological interventions that aid smoking cessation, in order to inform policies aimed at helping individual smokers in their attempt to quit smoking. The Terms of Reference agreed between HIQA and the Department of Health were to:

- Describe the range of smoking cessation therapies available.
- Describe the epidemiology of smoking and smoking-related illness in Ireland.
- Review the effectiveness and safety of the available smoking cessation interventions and their impact on long-term quit rates.
- Compare the cost-effectiveness of interventions that are associated with improved rates of smoking cessation and estimate the costs associated with these interventions within the public health system in Ireland.
- Examine any other relevant issues associated with a decision to change the provision of smoking cessation services by the Health Service Executive (HSE) that may affect patients, staff or the organisation of existing services.
- Based on this assessment, advise on the optimal use of smoking cessation interventions in Ireland.

### **Methods**

This research was carried out in accordance with HIQA's guidelines for the conduct of health technology assessments. In summary, the following took place:

- The Terms of Reference of the HTA were agreed between HIQA and the Department of Health.

- An Expert Advisory Group was convened, with representation from health policy decision-makers, clinicians, patient advocates, professional bodies and experts in health services research and economic evaluation. An Evaluation Team was appointed comprising HIQA staff.
- The Expert Advisory Group reviewed and endorsed a protocol defining the approach to be adopted in the evaluation. Long-term smoking cessation was the agreed primary outcome of interest, consistent with the broader population-based initiatives that aim for a tobacco-free Ireland. The primary population of interest was the general population of adult smokers. Specific subgroups of smokers were identified on the basis of important differences in either the clinical effectiveness or costs associated with their care.
- The burden of smoking and smoking-related diseases in Ireland was assessed.
- Smoking cessation interventions that are routinely available and used in Ireland were identified and described. A comprehensive review of the safety of these interventions was undertaken.
- A systematic review and network meta-analysis was carried out to summarise the available evidence on the clinical effectiveness of smoking cessation interventions among a general population of adult smokers, users of secondary mental health services (defined as inpatient, residential and long-term care for serious mental illness in hospitals, psychiatric and specialist units and secure hospitals and patients who are within the care of specialist community-based multidisciplinary mental health teams), and pregnant women.
- An original economic evaluation was performed to estimate the cost-effectiveness and budget impact of prospective changes in the mix of interventions used among the general population of adult smokers to help them quit.
- Clinical outcomes examined in this HTA included the number of successful quit attempts, as well as longer term clinical outcomes in relation to smoking-related mortality and morbidity.
- The major costs examined in this HTA included the cost of pharmacological and behavioural smoking cessation interventions, and the costs of treating smoking-related illnesses in Ireland.
- The primary analysis compared the cost-effectiveness of current practice in Ireland with alternative mixes of smoking cessation interventions. The choice of comparator was informed by the results of the clinical effectiveness analysis and international data on uptake rates of smoking cessation interventions in other countries.



- The analysis was carried out from a quasi-societal perspective that included costs to the publicly funded health and social care system in Ireland, along with the costs of smoking cessation interventions that fall on individual smokers. The time horizon over which the costs and benefits of screening was calculated was 20 years and both costs and benefits were discounted at 5%.
- A budget impact analysis reporting the incremental costs associated with changes to the provision of smoking cessation services over a five-year time horizon was performed from the perspective of the public health system only.
- An analysis of the ethical, legal and organisational implications of changes to the provision of smoking cessation services was carried out to identify broader considerations that may influence decision-making.
- The complete draft report was reviewed by the Expert Advisory Group, before being made available for public consultation, to give interested parties an opportunity to comment on the draft report before it was finalised.

## Technology description

Currently, the Health Service Executive (HSE) policy is that every person who engages with front-line staff should be asked about their smoking status and the response should be documented. Every smoker should be advised to quit and offered support by HSE staff — this is known as **'brief advice'** and should be provided at every opportunity. The HSE currently funds training in brief advice in the form of **'Brief Interventions for Smoking Cessation'**. Training is aimed at a wide range of healthcare professionals in both the acute and community care settings. This support differs from intensive cessation support services that are provided by trained cessation specialists working in community or hospital settings, or with the national telephone-based intervention QUITline. Brief advice also raises awareness of the harms of smoking in order to discourage people from starting and to motivate more smokers to make a quit attempt.

A diverse range of smoking cessation interventions is currently provided by the HSE to individual smokers in addition to the brief advice targeted at all smokers as outlined above. Based on the analysis conducted in this HTA, total annual expenditure on smoking cessation activity in Ireland is estimated to be over **€40** million. This figure includes the cost to the HSE of providing smoking cessation support through the HSE Tobacco Control Programme, the costs of GP services and pharmacological treatment to those with a medical card, as well as out-of-pocket expenditure by smokers on various smoking cessation products.

Pharmacological interventions include nicotine replacement therapy (NRT), antidepressants (specifically bupropion) and nicotine receptor partial agonists (specifically varenicline). Nicotine replacement therapy (NRT), varenicline and

bupropion are currently reimbursed when prescribed through the Primary Care Reimbursement Service (PCRS), although reimbursement of NRT is limited to Medical Card holders only. Behavioural interventions funded and provided free-of-charge by the HSE to all Irish residents include Internet-based support ([www.quit.ie](http://www.quit.ie)), telephone-based support (QUITline), and HSE smoking cessation clinics which offer individual and group behavioural support in some locations. Electronic cigarettes, also known as e-cigarettes, are not currently advocated by the HSE as a means of quitting due to lack of long-term data on their safety. However, HSE smoking cessation services provide support to smokers who choose to use e-cigarettes in their quit attempt through the provision of information and additional behavioural interventions as appropriate to the individual smoker.

### **Epidemiology of smoking and smoking-related illness**

Over one in five (22.7%) people aged 15 years and over smoke in Ireland. Smoking prevalence is higher in men (24.3%) than women (21.2%). Nineteen percent of adults are daily smokers while 4% are occasional smokers. Data from the HSE tracker survey between 2002 and 2012 shows that the prevalence of smoking in Ireland and the number of cigarettes smoked is in decline since 2008. There has been a general trend of reducing prevalence since the 1970s.

A number of legislative or policy interventions have been made in Ireland to reduce exposure to smoke and smoking. These include the bans on advertising, sales to minors, workplace smoking, and smoking in cars carrying minors. These policies are likely to have impacted on smoking either by reducing uptake, encouraging quit attempts or by reducing the quantity of cigarettes smoked. Population-level interventions support a move to a tobacco-free country. The interventions considered in this report support successful smoking cessation in individuals. As such, the individual-level factors that impact on successful quitting were considered, as well as how cessation services might be provided and organised in order to maximise successful cessation.

It is difficult to determine the extent to which smoking decline will continue without changes being made to the quitting services provided to smokers. As smoking in Ireland declines, it is possible that the remaining group of smokers are those with high nicotine dependence and, or those who face barriers to accessing effective services.

It is clear that there are inequalities in smoking cessation. Smoking prevalence is highest and successful quit attempts are lowest for smokers in the lowest socio-economic groups. As the overall prevalence of smoking and the rate of new smokers declines, the demography of current smokers will change. This may require different

approaches to how quitting services are delivered and which interventions are provided.

Cigarette smoking has major negative implications for the health of current smokers, former smokers, and those exposed to second-hand smoke. Cigarette smoking results in significant morbidity and mortality, with further effects on quality of life and use of health service resources. Quitting smoking substantially reduces the risk of disease and can, over time, result in risks similar to that of people who have never smoked for a range of conditions.

More than 5,400 deaths in Ireland each year are due to smoking. When deaths due to second-hand smoke are included, approximately one in five (20.5%) deaths each year are due to tobacco smoke. Using estimates of the proportion of disease that can be attributed to smoking, approximately 28,000 inpatient discharges and 11,000 day cases are due to smoking each year in Ireland.

Smoking during pregnancy is harmful. It is associated with an increased risk of congenital anomalies, preterm birth, intrauterine fetal growth restriction, placental abruption, stillbirth, sudden infant death syndrome, respiratory infection, adverse cognitive and behavioural outcomes in infancy, and the development of chronic disease in adulthood.

Evidence shows that smokers with mental health disorders smoke more heavily, are more nicotine dependent, and have smoked for longer than smokers who do not have an underlying mental health disorder. The factors linking mental health conditions and cigarette smoking are varied and complex. Recent evidence suggests that quitting smoking may improve symptoms of mental illness.

Irish data on the prevalence of smoking in pregnancy and in people with mental health disorders are limited. Evidence from the 'Growing Up in Ireland' (GUI) study reported that the prevalence of smoking in pregnant women in Ireland fell from 28% in 1998 to 18% in 2008. International data show that smoking prevalence is correlated with the severity of mental illness, with prevalence rates of 33% to 70% reported for people with bipolar disorder and 45% to 88% for people with schizophrenia.

Most smokers attempt to quit, and most do so more than once a year. Over time, smokers will typically make many attempts to quit before succeeding. It should be noted that smokers self-select what interventions they will use when attempting to quit. Data from the Healthy Ireland survey 2015 provide information on smoking behaviour and quit attempts in the Irish population. Half of those attempting to quit smoking in Ireland do so without help. A further 29% of smokers trying to quit use e-cigarettes as an aid (alone or in combination with another intervention).

Approximately 16% of quit attempts are made using some form of pharmacotherapy (for example, NRT). However, reporting a quit attempt without support may not capture the interventions people have used on previous quit attempts. Those who make attempts without support may have used behavioural support previously and are therefore not necessarily without knowledge or understanding of what is involved. It is also possible that some smokers may consider receiving brief advice as 'no support', **although there is no evidence to confirm or refute this.**

## **Clinical effectiveness**

A review of clinical effectiveness considered studies evaluating smoking cessation interventions in three distinct population groups:

1. general unselected\* adult population;
2. people attending secondary mental health services (defined as inpatient, residential and long-term care for serious mental illness in hospitals, psychiatric and specialist units and secure hospitals and patients who are within the care of specialist community-based multidisciplinary mental health teams);
3. pregnant women.

The primary outcome of interest was long-term (six months or more) smoking cessation, and abstinence in late pregnancy in pregnant women.

### **General adult population**

An updated systematic review identified 313 studies that met the inclusion criteria for the general adult population, half of which were published after January 2000. Sixty two percent of the studies had follow-up at 12 months or longer to estimate long-term abstinence. A quarter of the studies were considered at low risk of bias. Sixty five percent of the studies used biochemical verification of quitting, and 58% measured continuous abstinence as distinct from point prevalence, that is to say abstinence at a point in time.

Interventions could be broadly classified as pharmacotherapy or behavioural interventions. While the definitions of pharmacotherapy interventions were clear, definitions of behavioural interventions were not standardised. The absence of standard definitions for behavioural interventions, including the choice of treatment, provider and the duration, number and frequency of sessions added complexity to their classification. In addition, there could be overlap between behavioural interventions offered. Often, more than one support was provided at a time, and they could be provided with or without adjunct pharmacotherapy. In addition, many

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\* Not selected on the basis of predefined conditions.

pharmacotherapy trials provided supportive care in the form of a behavioural intervention to both the control and intervention arm participants.

Separate network meta-analyses of pharmacological and behavioural therapies were carried out. The effectiveness of each of the behavioural interventions was presented in relation to an active control, such as brief advice or written smoking cessation materials.

All pharmacological interventions were found to be more effective than the control. Varenicline was the most effective single therapy, more than two and half times as effective as control. Varenicline with NRT was the most effective dual therapy, more than three and a half times as effective as control. Combination NRT was more effective than a single form of NRT alone. E-cigarettes were twice as effective as control; however, this estimate was based on only two trials including a relatively small number of participants.

All behavioural **therapies were more effective than an alternative of 'do nothing'.**

Brief intervention in the form of brief advice or written materials are one and a half times more likely to result in a successful quit attempt than quitting with no form of support. The HSE is committed to promoting smoking cessation at all patient contacts through brief intervention and written materials. As such, brief advice and written materials may be considered the standard of care in Ireland for those making a quit attempt. Group behaviour therapy was the most effective behavioural intervention, almost twice as effective as an active control, defined as brief advice or written materials. Individual counselling, intensive advice and telephone support were all found to be more effective than the active control. The substantial variation in how behavioural interventions were defined and delivered often resulted in differing treatment effects. Variability was seen in the frequency and intensity of interventions, with no evidence of a dose-response relationship. The effectiveness of pharmacological interventions was improved by an average of 18% by providing adjunct behavioural therapy.

### **Pregnant women**

In total, 73 studies evaluating either pharmacological or behavioural interventions in pregnant women were included in this review. The studies broadly support the view that smoking cessation interventions are effective in pregnancy. Due to the fact that bupropion and varenicline are not recommended in pregnancy, NRT is the only pharmacotherapy licensed for use in pregnant smokers who wish to quit, and its efficacy appears to be lower in pregnant smokers than in non-pregnant smokers. Eight trials investigated NRT use as a smoking cessation aid in pregnancy, and they were deemed of high quality. Some evidence of a beneficial effect was found for

NRT in this group with a 41% increase in cessation rates, but this did not reach statistical significance.

The review identified 64 studies evaluating psychosocial interventions for smoking cessation in pregnancy; however, these were rated as being of low quality. There was evidence to suggest that counselling, health education and financial incentives increase cessation rates in pregnant smokers.

Due to the limited effectiveness of interventions in pregnancy, smokers should be encouraged to quit prior to conception when more treatment options are available and therapy is more likely to succeed. As many smokers quit of their own accord in the early stages of pregnancy, it is possible that interventions in pregnancy (particularly in later pregnancy) are focused on more heavily dependent women and those with greater barriers to successful cessation. This may explain the lower efficacy compared with non-pregnant populations. The modest impact of NRT may be due to inadequate dosing in pregnancy.

#### [People attending secondary mental health services](#)

Ten studies examining smoking cessation interventions in people attending secondary mental health services were included in this review. In the mental health population group, efficacy data for cessation interventions were only retrieved for patients with schizophrenia, schizoaffective disorder and bipolar disorder. The only statistically significant evidence of a beneficial treatment effect was for bupropion when used as an adjunct to behavioural therapy plus NRT in a population with schizophrenia or schizoaffective disorder, where it was almost four times as effective as behavioural therapy plus NRT alone.

The lack of evidence for effectiveness in the mental health population is due to the fact that few studies, in particular large-scale, high-quality studies, have been conducted to date. Recruitment of patients to randomised controlled trials (RCTs) from mental health populations is reported to be problematic, and many trials focused on the adverse event profile rather than efficacy of the intervention. Studies excluded from this review include those that report shorter cessation outcomes and a smoking reduction rate. Researchers have speculated that reducing the risks of smoking, rather than cessation, may be a better initial focus for the mental health population due to the higher nicotine dependence and greater burden of disease compared with the general population. Absolute quit rates in the control arms tended to be low relative to those observed for the general population. Motivation to quit is important in this group; in two trials comparing bupropion to placebo, only one in three (33%) were motivated to quit smoking, lowering the likelihood of successful cessation.

It is important to note that this review excluded the EAGLES 2016 trial - the largest trial conducted to date in patients with a current or previous mental health condition comparing varenicline, bupropion, NRT and placebo. This trial did not meet the inclusion criteria of this clinical effectiveness review for participants to be attending secondary mental health services. However the safety data from the EAGLES trial were considered below.

The studies included in this review were intended to be representative of the three populations of interest. In terms of age, gender, and level of dependency, the study populations would appear to be broadly applicable to the Irish setting. The mental health subgroup identified in this assessment relates to those attending secondary mental health services, and therefore may be considered to include those with more severe and enduring mental illnesses. The HSE Mental Health Division reports that over 90% of mental health needs can be successfully treated within the primary care setting. While the general adult population considered in this report would include those with mental health issues exclusively treated in primary care, the efficacy of smoking cessation interventions for this cohort was not specifically assessed.

## **Safety**

A review of the safety profile of smoking cessation interventions found that pharmacological therapies are generally safe and well-tolerated in those for whom these treatments are medically indicated for use. Behavioural interventions were found to be safe. However, there are limited options available for certain patient groups, including pregnant women and certain mental health populations, due to contraindications<sup>†</sup> and relative contraindications to the use of selected pharmacological interventions.

Most adverse events associated with nicotine replacement therapy (NRT) are mild and temporary in nature. Commonly reported side effects include mild skin sensitivity (patch), hiccoughs and gastrointestinal disturbance (gum), local irritation of mouth, nose and throat (inhaler, spray and sublingual tablets). Chest pain and heart palpitations are the only potentially clinically significant serious adverse events to emerge from clinical trials. NRT does not appear to be associated with an increase in serious cardiovascular adverse events, in those with or without pre-existing cardiac disease.

Nausea is the most commonly reported adverse event associated with using varenicline. Other common adverse events include insomnia, abnormal dreams and headache. There is conflicting evidence regarding cardiac adverse events associated

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<sup>†</sup> A contraindication may be defined as a condition which makes a particular treatment potentially inadvisable.



with varenicline. A systematic review and meta-analysis from 2016 did not find evidence of an association in people with or without cardiovascular illness. Warnings about the use of varenicline in patients with pre-existing psychiatric conditions were lifted in May 2016 following the publication of safety and efficacy data from the EAGLES trial.

The most common adverse events associated with the use of bupropion are insomnia, dry mouth and nausea. Allergic reactions requiring medical treatment are rare. Bupropion increases the risk for seizures; a seizure rate of one in 1,000 is given in the product safety data. Bupropion is not recommended for use in patients with an increased risk of seizures, or in patients with a history of bipolar disorder as it may precipitate a manic episode.

Nicotine crosses the placenta from mother to baby. The long-term fetal and neonatal effects of NRT are unclear; however, it is safer than continued smoking. No major congenital malformations associated with NRT use have been observed in randomised controlled trials and observational studies. NRT is recommended during pregnancy, particularly when behavioural therapy fails. However, the use of bupropion and varenicline is not recommended during pregnancy or breastfeeding.

Safety data on e-cigarettes are limited to two small short-term clinical trials. Mild, temporary adverse drug reactions were found, such as throat and respiratory irritation and dry cough. Toxicological studies have demonstrated that while toxic chemicals may be present in e-cigarette vapour, they are at a lower concentration than in cigarette smoke. E-cigarettes have only been in use for a short time, and so data on long-term toxicity are not yet available. While the clinical effect of long-term e-cigarette use is unknown, the risk to bystanders from **'passive vaping'** appears to be very low. The safety of e-cigarettes is an evolving area of research; while believed to be safer than smoking, evidence on long-term safety has yet to be established.

## **Economic evaluation**

A cost-effectiveness analysis found that all cessation interventions included in the analysis would be considered cost-effective when compared with unassisted quitting. E-cigarettes and using varenicline, either alone or in combination with NRT, were found to be the most cost-effective strategies when individual therapies are compared with each other. The cost-effectiveness of e-cigarettes is extremely sensitive to any new evidence that could change the estimated cost and effects of this intervention. This is of particular significance given the high degree of uncertainty that exists in relation to both its costs and effects.



A comparison of alternatives to the current mix of smoking cessation interventions used in Ireland was carried out using international data as an indicator of plausible changes in the usage of the most cost-effective cessation interventions. This included a scenario where combination varenicline and NRT use was maximised, and a scenario where e-cigarette uptake reached levels recently reported in England. This analysis found that maximising the uptake of varenicline and NRT in combination is the most cost-effective strategy.

It is unclear to what extent policy initiatives can influence overall smoking cessation preferences, particularly in light of the high use of e-cigarettes in Ireland in the absence of any explicit endorsement by quit services. Based on the results of two studies, an increase in the uptake of e-cigarettes to peak rates currently reported in England (45%) may improve the cost-effectiveness of the overall mix of cessation interventions in Ireland, by increasing the average number of successful quit attempts at an acceptable cost. However, these results are sensitive to changes in the estimate of the effectiveness of e-cigarettes, which is currently associated with a high degree of uncertainty due to the limited numbers of high quality studies involving this intervention currently available.

A budget impact analysis on the incremental cost associated with changes to the existing standard of care found that maximising the use of combination varenicline and NRT would be associated with an average increase of approximately €7 million in the annual cost of providing pharmacological smoking cessation interventions in Ireland. A scenario analysis was carried out in which the uptake of e-cigarettes was increased to rates currently observed in England (while still not being reimbursed through the Primary Care Reimbursement Service). This analysis showed that increased uptake of e-cigarettes from 29% to 45% would result in a decrease in expenditure on pharmacological smoking cessation interventions of approximately **€2.6 million per year**. Alternatively, if e-cigarettes were funded to the same extent as NRT, **the additional cost to the health service would be approximately €6 million per annum at current use rates, or €7.5 million** if usage rose to rates currently reported in England.

## **Wider implications**

From an ethical perspective, smoking is not generally considered to be morally wrong and therefore is a matter of individual choice for the consumer. Any smoking cessation intervention must be made available in a way that promotes individual choice. This can be achieved by providing information concerning the risks and benefits associated with a particular intervention. In balancing ethical considerations of benefit versus harm, cessation aids have been shown to increase the chances of long-term quitting among those who are motivated to stop smoking. However, there

are concerns about the social normalisation of some cessation aids, such as e-cigarettes. If e-cigarette use becomes socially acceptable, it could lead to new use of nicotine by people who have never smoked before, later migration to tobacco cigarettes, long-term nicotine dependency, and other potential as yet unknown harms. When scientific data are contradictory or quantitatively scarce, it may be necessary to make temporary decisions that can be changed as new facts become known. In the absence of clear evidence in relation to potential long-term risks associated with some smoking cessation interventions, such as e-cigarettes, such an approach would involve continuing to advise smokers who wish to quit of all the cessation interventions while providing as much information as possible in relation to safety and efficacy.

Marketing and advertising are important in public perception of smoking cessation interventions. The government has an ethical duty to ensure that the media portrayal of the product is appropriately aligned with its known degree of risk. This is the dealt with in the recent EU Tobacco Products Directive, which aims at harmonising the quality and safety requirements of tobacco products and e-cigarettes for the benefit of consumers. Although negative health effects from the use of e-cigarettes are currently unknown, there is concern that potential legal liability may be possible if future research finds that negative effects do result from their use. Provided appropriate warnings and information leaflets containing accurate information are included with the sale of any such product, it is difficult to see how a legal action might successfully be taken if this were to occur.

From an organisational perspective, efforts to increase the use of combination varenicline and NRT will place additional demands on general practitioner (GP) or nurse prescriber services. In the event that use of this intervention reaches plausible maximum levels, the number of prescriptions required could increase by over 50%. However, it is recognised that many smoking cessation interventions are opportunistic, with healthcare providers availing of opportunities to encourage cessation as part of consultations primarily directed at other areas of care.

Alternatively, if e-cigarette use in Ireland (26%) rose to maximum levels currently reported in England (45%), and smokers choose this option without seeking medical advice, the number of prescriptions required could fall by nearly 40%. E-cigarettes are unusual as they are the only intervention in this analysis that is not advocated by HSE QUIT services or funded through the public health system. If the results reported so far are confirmed in subsequent trials and e-cigarette use continues to rise, there is a risk that an ever greater number of people will attempt to quit smoking without involving any trained smoking cessation staff and the potential benefit of providing this treatment in conjunction with behavioural support interventions may be lost. Given the increasing use of e-cigarettes, it is of vital

importance that their potential benefit and harms continue to be discussed with smokers to ensure informed decision-making in relation to their use. As new evidence emerges, there is likely to be ongoing resource implications for the health service to educate providers on this topic and to ensure that consistent advice is provided. In the long term, decreased smoking prevalence will result in a lower prevalence of smoking-related diseases and decreased demands on services providing treatment for these conditions. However, these changes are unlikely to be seen for many years.

Best practice guidelines for smoking cessation have been developed to support mental health service providers. However, in the absence of reliable data, the extent to which smoking cessation interventions are consistently being offered to or availed of by smokers in secondary mental health services in Ireland is unknown. There is limited evidence for smoking cessation interventions in the mental health population due to difficulties in recruiting and conducting randomised controlled trials (RCTs) in this population. As a result, it is difficult to make specific recommendations in terms of resource impact. Bupropion as an adjunct to behavioural therapy and NRT was found to have a beneficial effect in a population with schizophrenia or schizoaffective disorder. In the absence of evidence to say otherwise, it is assumed that interventions which are effective in the general population are also beneficial in mental health populations. International data suggest that smoking prevalence among the mental health population has changed little over the past 20 years. Specialist inpatient and community mental health services are particularly suited to the provision of tailored support by experienced mental health staff. However, the resource implications for providing interventions and staff training may be significant given the recognised staffing constraints that exist in mental health settings.

Based on the available evidence, pregnant women who smoke should be offered a psychosocial intervention in the first instance. The psychosocial intervention with the largest body of evidence to support its effectiveness is counselling. Maternity services should ensure that all front-line staff are trained in some form of counselling intervention. The most significant resource implication for the implementation of counselling is time, both in antenatal clinics and training time. Evidence for the effectiveness of NRT for smoking cessation in pregnancy is unclear. Other smoking cessation interventions that are effective in pregnancy will have varying levels of resource implications. Health education interventions may require fewer resources, while incentives and feedback interventions may require more intensive resources in terms of time, training and finances.

## Discussion

This assessment shows that smoking cessation interventions are cost-effective when compared with unassisted quitting. E-cigarettes and use of varenicline, alone or in combination with NRT, provide the best value for money based on currently available information. However, the effect estimate for e-cigarettes is based on pooling two trials. Neither trial found a statistically significant benefit, and both had absolute quit rates in the control and intervention arms that were low compared with average absolute quit rates among trials of other interventions with comparable relative effect sizes. Given the limited number of randomised controlled trials (RCTs) and the rapidly evolving range of e-cigarette products, there is a high level of uncertainty surrounding both the clinical and cost-effectiveness of this intervention. The results of the economic analysis of e-cigarettes are extremely sensitive to changes in both these parameters. There is also considerable uncertainty about the long-term health effects of e-cigarette use, along with concerns that their widespread promotion by health professionals could normalise nicotine consumption or act as a gateway to using tobacco for new generations of people who have never previously smoked.

The assessment found that increasing the uptake of varenicline and NRT to plausible maximum levels was the optimal strategy for improving quit rates. This would also be associated with significant additional drugs costs, as well as increases in demand for GP and nurse prescribing services. However, there is considerable uncertainty about the extent to which health policy can influence uptake rates of different interventions among smokers, particularly given the existing low uptake rates of the most effective interventions observed in Ireland and elsewhere. While it is beyond the scope of this analysis to identify the specific policy measures that are likely to have the most impact on improving smoking cessation preferences at a population level, the HTA does address the first objective of identifying policy goals that smoking cessation services could work towards, and has considered the desirability or otherwise of expected changes that are likely to occur given current trends in the uptake of smoking cessation interventions.

International data suggest that e-cigarette use will continue to grow in popularity as an aid to smoking cessation. Based on the limited available evidence, this would also be expected to improve average quit outcomes compared with current practice, though less than that of maximising combination varenicline and NRT use. These results are again likely to change when further research becomes available.

Increased e-cigarette use would also likely result in lower expenditure by the public health system on other prescription drugs due to a decline in their uptake, assuming the current funding model remains unchanged. For those choosing to make a quit attempt without the aid of pharmacotherapy or e-cigarettes, there is good evidence to show that behavioural support increases quit rates compared with receiving no

support. There is insufficient evidence to reliably differentiate between the effectiveness of different types of behavioural support when used in combination with pharmacotherapy. However, based on existing studies the addition of any type of behavioural support is associated with a beneficial effect on quitting outcomes. Rather than considering other potential benefits of behavioural support and educational interventions (for example, harm reduction by reducing the number of cigarettes smoked per day, reducing the risk of relapse for those who successfully quit smoking), this analysis focuses solely on quit outcomes and may underestimate the clinical effectiveness and cost-effectiveness of some of the interventions evaluated.

The evidence for smoking cessation treatments among specific subgroups of the population is more limited. Although there is a lack of data on the relative effectiveness of different smoking cessation interventions for people attending secondary mental health services, high-intensity programmes combining pharmacotherapy and behavioural support have been shown to improve quit outcomes in this group. Among pregnant women, behavioural support interventions such as counselling, health education and the use of financial incentives can significantly improve quit outcomes during pregnancy.

## **Conclusion**

Smoking cessation services should seek to increase the uptake of the use of varenicline, alone or in combination with NRT, among smokers wishing to use some type of pharmacological support in their attempt to quit. Although the available results for e-cigarettes are promising, there is insufficient evidence to demonstrate their effectiveness as an aid to smoking cessation at present. The evidence base for e-cigarettes will evolve as further trials are completed, and their effectiveness for smoking cessation should be re-evaluated as new evidence becomes available. It would be appropriate to await the results of ongoing trials before deciding whether e-cigarettes should be recommended for those for whom varenicline is contraindicated, not tolerated or non-preferred. Should additional evidence confirm the effectiveness of e-cigarettes as a smoking cessation aid, a decision to advocate their use should also take into consideration any additional information on the long-term safety of e-cigarettes use, as well as any emerging data in relation to concerns about the social normalisation of e-cigarettes leading to increased uptake among people who have never smoked, or later migration to tobacco cigarettes.

Providing behavioural support, either alone or in combination with pharmacological interventions, increases the chances of long-term smoking cessation and should continue to be provided to all smokers who would like to avail of this option to help them quit.

Pregnant women who smoke should be offered a psychosocial intervention in the first instance. The psychosocial intervention with the largest body of evidence to support its effectiveness is counselling. While the evidence for smoking cessation interventions among those attending secondary mental health services is very limited, high-intensity interventions combining pharmacotherapy and behavioural support have been shown to improve quit outcomes. However, further research on the effectiveness of smoking cessation interventions in this population is needed.

## Plain language summary

The Health Information and Quality Authority (HIQA) agreed to undertake a Health Technology Assessment (HTA) of smoking cessation interventions in Ireland **following a request from the Department of Health's National Tobacco Control** Advisor. This HTA included drug therapies, e-cigarettes and behavioural interventions that help people to stop smoking. The aim of the assessment was to determine how well the interventions work (effectiveness) and which ones provide the most benefit for the least cost (cost-effectiveness).

### Key messages:

More than one in five (22.7%) people aged 15 years and over smoke in Ireland. Half of these smokers report making an attempt to quit smoking in the last year. In half of these attempts to quit, smokers reported using no help (unassisted quitting), almost one in three (29%) used e-cigarettes, around 16% used drug interventions (for example, nicotine replacement therapy [NRT]) and a small number reported using behavioural interventions (for example, counselling).

### Do these interventions work?

All the drug treatments were found to be effective compared to no treatment. When looking at each drug on its own, a prescription-only drug called varenicline was the most effective. However, using a combination of varenicline and NRT together was found to be the most effective drug intervention. People using this combination were more than three and a half times more likely to quit than those who did not receive this treatment.

Based on two clinical trials, e-cigarettes were found to double the chances of successfully quitting. However, more evidence is needed to draw conclusions about the safety and benefits of using e-cigarettes as an aid to stop smoking.

Group behavioural therapy, individual counselling, intensive advice and telephone support were all found to be effective interventions. Group therapy was found to be the most effective of these behavioural supports. Adding behavioural support to a drug therapy improved the effectiveness by about 18%.

Smoking during pregnancy is known to be harmful. Also, many of the drug therapies are not recommended for women to use during pregnancy. This HTA found that pregnant women who smoke should be offered behavioural support such as counselling to help them quit smoking.

Smokers with mental health disorders tend to smoke more heavily and find it harder to quit. This HTA found that interventions that combine drug therapy and

behavioural support improve quit rates in people with mental health disorders attending secondary mental health services (such as community and outpatient mental health clinics).

### **Are they good value for money?**

All of the interventions this HTA examined were found to be cost-effective when compared to quitting without help. Based on the available information, e-cigarettes and using varenicline, alone or in combination with NRT, were found to be the best value for money. For those who cannot or choose not to use varenicline, combination NRT is the best option, given the limited evidence that is currently available for e-cigarettes as a smoking cessation treatment.

### **Conclusion**

Services to help people quit smoking should try to increase the use of varenicline, alone or in combination with NRT, for smokers who want to use drug therapy as part of their quit attempt. Although the results for e-cigarettes are promising, there is not enough evidence to recommend their use. Without additional evidence to confirm the effectiveness of e-cigarettes, HSE services to help people quit smoking should try to increase the use of combination NRT treatment among those for whom varenicline is not suitable.

Behavioural support such as counselling, either alone or in combination with drug therapy, increases the chances of quitting smoking in the long term. It should be provided to all smokers willing to use this option to help them quit.

Pregnant women who smoke should be offered a behavioural intervention, such as counselling, to help them quit smoking.

There is not a lot of evidence for smoking cessation interventions for people attending secondary mental health services. However, treatments that combine smoking cessation drug therapy with behavioural support have been shown to improve the chance of quitting. More research on the effectiveness of smoking cessation interventions in this population is needed to determine what the best treatment is.



# 1 Introduction

## 1.1 Background to the request

The Health Information and Quality Authority (HIQA) agreed to undertake a health technology assessment (HTA) of smoking cessation interventions in Ireland following receipt of a formal request for a HTA from the National Tobacco Control Advisor to the Department of Health. HIQA had previously been notified of a general motion carried at an annual general meeting of the Irish Medical Organisation calling on HIQA to carry out HTAs on both pharmaceutical and non-pharmaceutical smoking cessation products and services in order to properly inform smokers, health service managers, health professionals and politicians on the merits or otherwise of providing smoking cessation services to the smoking population.

Reducing the numbers of smokers in Ireland is a long-established priority within the public health system. The mortality rate in smokers is two to three times higher than in those who have never smoked.<sup>(1)</sup> Twelve percent of mortality globally can be attributed to tobacco smoking, including second-hand smoke.<sup>(2)</sup> In 2015, 22.7% of persons aged 15 years and over in Ireland were smokers, and 18% of all deaths each year are attributable to tobacco smoke. When deaths due to second-hand smoke are included, approximately one in five (20.5%) deaths each year are due to tobacco smoke (see Chapter 3).

The economic cost of smoking in Ireland is substantial. In 2013, the estimated cost **to the healthcare system was over €460 million, the cost of lost productivity was over €1 billion, and the cost of loss of welfare was over €9 billion.**<sup>(3)</sup>

**In October 2013, the Department of Health published its policy document 'Tobacco Free Ireland'. This outlined the multi-faceted approach, targets and action plan for achieving a population smoking prevalence of less than 5% by 2025.**<sup>(4)</sup> The policy and rationale of the report was based on the World Health Organization's (WHO) MPOWER model.<sup>(5)</sup> This model was developed to enable countries to implement the Framework Convention on Tobacco Control measures. Six effective and evidence-based tobacco control policies are identified by this framework:

- **M**onitoring of tobacco use and prevention policies
- **P**rotecting people from second-hand smoke
- **O**ffering to help people who want to quit
- **W**arning of the dangers of tobacco
- **E**nforcing bans on advertising, promotion and sponsorship
- **R**aising taxes on tobacco.

**‘Tobacco Free Ireland’** also includes themes such as protecting children, denormalisation of tobacco use, building and maintaining compliance with tobacco legislation and regulating the tobacco retail environment. Interventions provided to promote smoking cessation in current smokers who wish to quit may also impact on other policy areas, for example, the use of behavioural interventions to raise awareness of the dangers of tobacco and to motivate and encourage more smokers to make an attempt to quit. While the remit of this assessment is limited to smoking cessation, some of the interventions detailed may have an impact beyond what is considered in this report.

A diverse range of smoking cessation interventions is currently funded by the public health system in Ireland. Pharmaceutical interventions that are currently reimbursed through the Primary Care Reimbursement Service (PCRS) include nicotine replacement therapy (NRT), varenicline and bupropion. The Health Service Executive (HSE) also provides and promotes a wide range of behavioural interventions, ranging from the Internet-based intervention [www.quit.ie](http://www.quit.ie), the telephone-based intervention QUITline, and a range of HSE QUIT clinics and courses, including individual and group behavioural support in some areas.<sup>(6)</sup>

An evidence-based analysis of the clinical and cost-effectiveness of the existing mix of smoking cessation treatments was deemed necessary to consolidate activity by the HSE in this area and to ensure that the clinical benefits that can be obtained from the existing allocation of funding are maximised. This HTA also provides the evidence to underpin development of a planned national clinical guideline on smoking cessation. National Clinical Guidelines are quality assured by the National Clinical Effectiveness Committee (NCEC) and mandated by the Minister for Health to provide guidance and standards for improving the quality, safety and cost-effectiveness of healthcare in Ireland.

## **1.2 Terms of Reference**

The Terms of Reference agreed between HIQA and the Department of Health were to:

- Describe the range of smoking cessation therapies available.
- Describe the epidemiology of smoking and smoking-related illness in Ireland.
- Review the effectiveness and safety of the available smoking cessation interventions and their impact on long-term quit rates.
- Compare the cost-effectiveness of interventions that are associated with improved rates of smoking cessation and to estimate the costs associated with these interventions within the public health system in Ireland.
- Examine any other relevant issues associated with a decision to change the

provision of smoking cessation services by the HSE that may affect patients, staff or the organisation of existing services.

- Based on this assessment, to advise on the optimal use of smoking cessation interventions in Ireland.

The 'Tobacco Free Ireland' report outlines a range of initiatives, including population-based initiatives that aim to reduce the prevalence of smoking in Ireland to less than five percent by 2025.<sup>(4)</sup> The remit of this HTA was to assess the clinical and cost-effectiveness of pharmaceutical and non-pharmaceutical interventions that aid smoking cessation to inform policies aimed at helping individual smokers in their quit attempt. Harm reduction interventions designed to reduce the number of cigarettes smoked per day and interventions to reduce the risk of relapse for those who successfully quit smoking were outside the scope of this assessment. By excluding harm reduction outcomes, the HTA may underestimate the clinical effectiveness and cost-effectiveness of some of the interventions evaluated. The HTA examined other relevant issues in relation to the provision of smoking cessation services in order to advise on the optimal mix of treatment to help smokers quit. As noted, the HTA will also form the basis of a national clinical guideline on smoking cessation.

### 1.3 Overall approach

HIQA convened an Expert Advisory Group (EAG) comprising representation from relevant stakeholders. The role of the EAG was to inform and guide the process, provide expert advice and information and to provide access to data where appropriate. A full list of the membership of the EAG is available in the acknowledgements section of this report. The Terms of Reference of the EAG were to:

- contribute to the provision of high quality and considered advice by the Authority to the HSE
- contribute fully to the work, debate and decision-making processes of the group by providing expert guidance, as appropriate
- be prepared to provide expert advice on relevant issues outside of group meetings, as requested
- provide advice to the Authority regarding the scope of the analysis
- support the Evaluation Team led by the Authority during the assessment process by providing access to pertinent data, as appropriate
- review the project plan outline and advise on priorities, as required
- review the draft report from the Evaluation Team and recommend amendments, as appropriate

- **contribute to the Authority's development of its approach to HTA by** participating in an evaluation of the process on the conclusion of the assessment.

HIQA appointed an Evaluation Team comprising internal staff from the Health Technology Assessment directorate to carry out the assessment.

The Evaluation Team circulated a protocol to the EAG outlining the proposed approach to synthesising the available evidence in order to estimate the clinical effectiveness, cost-effectiveness and budget impact of smoking cessation interventions in Ireland. Consistent with the broader population-based initiatives that aim for a tobacco-free Ireland, the agreed primary outcome of interest was long-term smoking cessation. Feedback was sought from the EAG on the specific subgroups of smokers that would be examined separately on the basis of important differences in either the clinical effectiveness or costs associated with their care. Given the additional time and resources needed to conduct separate assessments, it was noted that the number of subgroups must be limited to those of the highest priority in terms of policy making. Two distinct subgroups were identified and endorsed by the EAG: pregnant women, and people with serious mental illness. It was recommended that the latter subgroup should be defined on the basis of the setting and services within which care is provided rather than on the basis of their underlying illness with a view to maximising the usefulness of this analysis to inform future national guidelines and policy making. The mental health subgroup was therefore defined as those accessing secondary mental health services [inpatient, residential and long-term care for serious mental illness in hospitals, psychiatric and specialist units and secure hospitals] and patients who are within the care of specialist community-based multidisciplinary mental health teams.

The Terms of Reference of the HTA were reviewed by the EAG at the initial meeting of the group. Interim findings from the assessment as well as other issues including the results for the cost-effectiveness model were discussed at a subsequent meeting. A draft report was made available for public consultation prior to being finalised. Amendments were made, as appropriate, and the draft was reviewed again by the EAG before its submission for approval by the HIQA Board. The completed assessment will be submitted as advice to the Minister for Health and the HSE and published on the HIQA website.

## **1.4 Public consultation**

The draft HTA was launched for a period of public consultation between 5 January 2017 and 3 February 2017, to provide all interested parties an opportunity to comment on the report before it was finalised. HIQA received feedback from 48

separate individuals or organisations as part of this process. All feedback was considered in detail as the final report was prepared. Details of the submissions received, along with our responses and any changes made to the draft report because of these submissions are provided in the consultation summary document published alongside this report on the HIQA website.

## **2 Description of the technology**

The interventions evaluated in this health technology assessment (HTA) were limited to those that can be provided to smokers at an individual level to help them increase their chances of quitting for good. This could include pharmacotherapy, behavioural support, or a combination of the two. Excluded from this analysis were interventions that are enacted at a societal level to reduce the number of people who start smoking in the first place or that work as a disincentive to continued tobacco use. This included measures such as packaging and advertising regulations, increased taxation, and limiting the locations where smoking is permitted.

Furthermore, given the vast array of interventions that could potentially be provided to individual smokers, it was necessary to prioritise those that are most relevant to policy makers, patients and the Irish health system, as an exhaustive review of the clinical effectiveness and safety of all possible treatment options was not feasible. Identification of interventions for inclusion in this HTA was performed by combining recently published overviews of cessation interventions with data on the most commonly used treatments in Ireland, and advice from the Expert Advisory Group (EAG).

It is also important to note that each of the included interventions was of interest only insofar as they helped increase the chances of long-term smoking cessation. This HTA did not examine the impact of the interventions in terms of any potential harm reduction associated with their use, such as helping people to reduce the number of cigarettes smoked per day, reducing exposure to second-hand smoke, or relapse prevention measures. Neither did it extend to examining the relative effectiveness of different patient recruitment strategies that may be employed with various treatment modalities. Issues of access to, and uptake of, smoking cessation treatments in Ireland, and the likely implications of any potential future policy changes, are described in Chapter 7.

### **2.1 Smoking cessation interventions**

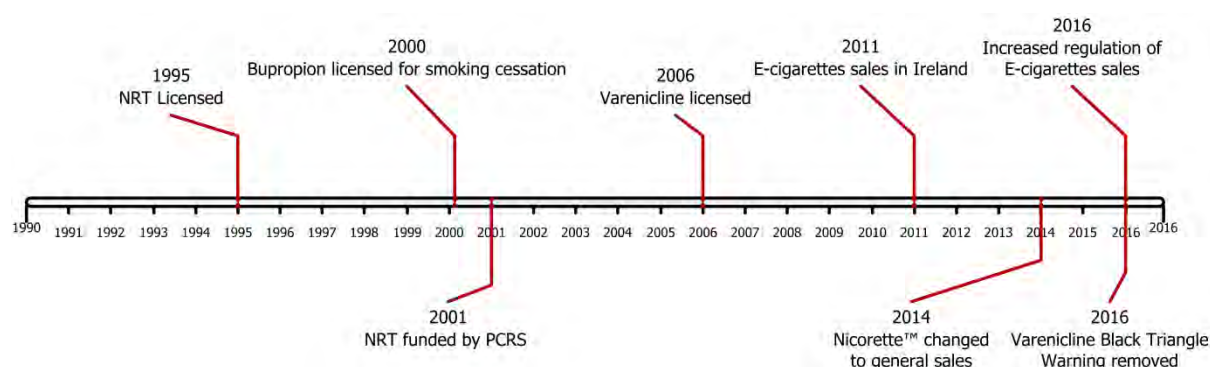
Smoking cessation interventions that were evaluated in this HTA include both pharmacological and non-pharmacological interventions. The pharmacological interventions assessed were: nicotine replacement therapy (NRT), electronic cigarettes (e-cigarettes), antidepressants (specifically bupropion) and nicotine receptor partial agonists (NRPA). The non-pharmacological interventions assessed were: acupuncture, and a range of behavioural interventions including motivational interviewing, brief advice, telephone-based interventions, Internet-based interventions, mobile phone-based interventions, individual behavioural counselling, group behaviour therapy and the Allen Carr method. Financial incentives for

pregnant women to quit were also evaluated. The effectiveness and safety of these interventions is reviewed in detail in Chapters 4 and 5.

## 2.1.1 Pharmacological interventions for smoking cessation

There is a range of pharmacological interventions available for smoking cessation in Ireland. Figure 2.1 provides a timeline of important dates in relation to their availability, licensing status and reimbursement. The individual interventions are discussed in more detail in the sections below.

**Figure 2.1 Sales of pharmacological aides in Ireland – key dates**



### 2.1.1.1 Nicotine Replacement Therapy (NRT)

Nicotine replacement therapy (NRT) aims to reduce the physiological and psychomotor withdrawal symptoms that smokers experience during a quit attempt, by replacing the nicotine from cigarettes by nicotine delivered without the use of tobacco.<sup>(7, 8)</sup> Due to the way in which nicotine is metabolised, oral tablets do not provide an efficient method of achieving adequate levels of the drug in the central nervous system. This has led to the development of NRT products designed for absorption through the oral or nasal mucosa (chewing gum, lozenges, sublingual tablets, inhaler or inhalator, spray) or through the skin (transdermal patches).<sup>(7)</sup> NRT products may be used alone or taken in combination with other NRT products. It is generally recommended that NRT products are taken in conjunction with behavioural support and counselling.

A range of NRT products have been licensed for use in Ireland since 1995. These products are regulated by the Health Products Regulatory Authority (HPRA) (available at [www.hpra.ie](http://www.hpra.ie)). In 2014, the HPRA authorised Nicorette™ as the first NRT product to be sold in general retail and grocery outlets in Ireland, as opposed to being a pharmacy-only product. NRT products have been funded for Medical Card<sup>‡</sup>

<sup>‡</sup> Medical Cards allow people to access Family Doctor or GP services, community health services, dental services, prescription medicine costs, hospital care and a range of other benefits free of charge. Anyone above the age of 16 and ordinarily resident in Ireland may apply for a Medical Card and eligibility is based on assessment of means.

holders through the Primary Care Reimbursement Service (PCRS) since 2001.<sup>(9)</sup> While all NRT products available in Ireland are now available without a prescription, to be reimbursed through the PCRS they must be prescribed by a doctor or nurse prescriber that holds a contractor agreement with the HSE. NRT prescriptions are not currently reimbursed by the PCRS for other categories (for example the Drug Payment Scheme<sup>§</sup>) which may act as a disincentive for its use in these groups. The HSE also provides NRT at a discounted rate to hospital staff in certain locations to promote the health and wellbeing of staff, and as a support to the implementation of the HSE tobacco-free campus policy.<sup>(10)</sup>

Ireland partially funds **(copay of €2.50 per month)** NRT for those patients with medical card eligibility under the GMS scheme.<sup>(11)</sup> In the UK, NRT is fully funded (subject to co-pay for a proportion of the population), while France and Cyprus fund NRT with restrictions; Belgium funds NRT for pregnant women only, and Denmark funds NRT in certain counties.<sup>(12)</sup>

While generally safe, the most serious adverse events reported with NRT administration are heart palpitations and chest pain, but there is no evidence of an increase in heart attacks or death.<sup>(7)</sup> More common and less serious adverse events include gastrointestinal complaints and insomnia. Other adverse events are specific to the mode of administration, including skin irritation via transdermal patch, mouth soreness and ulceration via oral route, and throat irritation and coughing via inhaler or spray. The safety of NRT is assessed in detail in Chapter 5.

NRT is not indicated in children aged less than 12 years; however, it may be administered to adolescents aged 12 to 18 years under the recommendation of a health professional.<sup>(13)</sup>

Different NRT products may be taken in combination. This approach is particularly useful in smokers whose nicotine dependence is resistant to NRT when taken as monotherapy.<sup>(14)</sup> In Ireland, Nicorette® has advised combining its transdermal patch **(INVISIPATCH™) with Nicorette® gum** when monotherapy fails or for those who are heavy smokers.<sup>(13)</sup> Certain forms of NRT are also licensed for periods of temporary abstinence from smoking, such as Nicorette® inhaler and gum. Information on the range of NRT products available in Ireland is summarised in Table 2.1.

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<sup>§</sup> Under the Drugs Payment Scheme, an individual or family in Ireland pays a set amount each month (**€144 in December 2016**) for approved prescribed drugs, medicines and certain appliances for use by that person or his or her family in that month.  
[http://www.hse.ie/eng/services/list/1/schemes/drugspaymentscheme/Your\\_Guide\\_to\\_Drugs\\_Payment\\_Scheme.html](http://www.hse.ie/eng/services/list/1/schemes/drugspaymentscheme/Your_Guide_to_Drugs_Payment_Scheme.html)



**Table 2.1 Nicotine replacement therapy (NRT) products and usual treatment regimens<sup>(15)</sup>**

Type of NRT	Brand Name(s)	Typical Regimen	Behavioural support	Contraindications
<b>Transdermal Patch</b>	Nicorette <sup>®</sup> <b>Invisi Patch™</b> , Nicotinell <sup>®</sup> TTS, NiQuitin <sup>®</sup> Patch	Regimen for Nicorette <sup>®</sup> <b>Invisi Patch™</b> : Heavy smokers (>20 CPD): 25mg for 8 weeks, then 15mg for 2 weeks, then 10mg for 2 weeks Light smokers (<20 CPD): 15mg for 8 weeks then 10mg for 4 weeks	Concurrent behavioural support is recommended	Use in non-smokers Patients with hypersensitivity to nicotine or any of the components of the patch Patients with acute unstable coronary conditions, recent cerebrovascular accident Diseases of the skin at patch site Children under 12 (for those aged 12 to 18 years, use is indicated only under the recommendation of healthcare professional)
<b>Gum</b>	Nicorette <sup>®</sup> Gum, Nicotinell <sup>®</sup> Gum	Regimen for Nicorette <sup>®</sup> Gum: Heavy smokers (>20 CPD): 4mg for 12 weeks (when there is an urge to smoke, max 15 per day)  Light smokers (<20 CPD): 2mg for 12 weeks (when there is an urge to smoke, max 15 per day)	Patient counselling and support normally improve the success rate	Use in non-smokers Patients with hypersensitivity to nicotine or any of the other ingredients in the gum
<b>Lozenge</b>	Nicorette <sup>®</sup> Lozenge, Nicotinell <sup>®</sup> Lozenge, NiQuitin <sup>®</sup> Lozenge	Regimen for Nicorette <sup>®</sup> Lozenge: Heavy smokers (>20 CPD): 4mg for 6 weeks, to a maximum of 9 months, (when there is an urge to smoke, max 15 per day) Light smokers (<20 CPD): 2mg for 6 weeks, to a maximum of 9 months, (when there is an urge to smoke, max 15 per day, and discontinued when dose is reduced to 1-2 per day)	Should preferably be used in conjunction with a behavioural support programme	Use in non-smokers or children under 12 Patients with hypersensitivity to nicotine or any of the ingredients of the lozenge. People with hypersensitivity to peanut or soya (NiQuitin <sup>®</sup> Lozenge)

Type of NRT	Brand Name(s)	Typical Regimen	Behavioural support	Contraindications
<b>Inhaler</b>	Nicorette <sup>®</sup> Inhaler	Nicorette <sup>®</sup> Inhaler should be used whenever the urge to smoke is felt, up to a maximum usage of six 15mg cartridges per day, for a maximum of three months	Counselling and support from family, friends and health professionals can improve the chances of abstinence	Use in non-smokers or children under 12 Patients with hypersensitivity to nicotine or any of the excipients of the inhaler
<b>Spray</b>	Nicorette <sup>®</sup> QuickMist Spray	One spray delivers 1 mg nicotine in 0.07 ml solution Weeks 1-6: Use 1 or 2 sprays when cigarettes normally would have been smoked or if cravings emerge Weeks 7-12: Start reducing the number of sprays per day. When subjects have reduced to 2-4 sprays per day, oromucosal spray use should be discontinued	Should preferably be used in conjunction with a behavioural support programme	Use in non-smokers or children under 12 Patients with hypersensitivity to nicotine or any of the excipients of the spray
<b>Oro-dispersible Film</b>	NiQuitin <sup>®</sup> Strip	Each orodispersible film contains 2.5 mg nicotine. Weeks 1 to 6: 1 nicotine film every 1 to 2 hours Weeks 7 to 9: 1 nicotine film every 2 to 4 hours Weeks 10 to 12: 1 nicotine film every 4 to 8 hours	Should preferably be used in conjunction with a behavioural support programme	Use in non-smokers or children under 12 Patients with hypersensitivity to nicotine or any of the excipients of the film

Key: NRT – nicotine replacement therapy; CPD – cigarettes per day; TTS – transdermal therapeutic system

### 2.1.1.2 Electronic cigarettes (e-cigarettes)

E-cigarettes, also known as electronic nicotine delivery systems (ENDS), are electronic devices that heat a liquid to produce an aerosol (commonly referred to as vapour) which is then inhaled by the user. The liquid is contained in a reservoir within the device and generally consists of propylene glycol and glycerol, with or without nicotine and flavourings.<sup>(16)</sup> E-cigarettes do not contain tobacco, but provide sensations that are similar to cigarette smoking. This may help smokers achieve long-term abstinence by alleviating some of the sensory and behavioural challenges associated with smoking cessation, as well as helping to reduce nicotine withdrawal symptoms (in cases where the liquid also contains nicotine).

Since their invention in 2003, there has been constant innovation and development of more efficient and appealing e-cigarette products. Currently, there are mainly three types of devices available.<sup>(17)</sup> First-generation devices generally mimic the size and look of regular cigarettes and consist of small lithium batteries and liquid-filled cartridges. Batteries may be disposable (to be used once only) or rechargeable. Second-generation devices consist mainly of higher-capacity lithium batteries and atomizers, with the ability to refill them with liquid (sold in separate bottles). Third-generation devices consist of very large-capacity lithium batteries with integrated circuits that allow users to change the voltage or power (wattage) delivered to the atomizer. Studies to date have mostly analysed first-generation devices in terms of efficacy and safety.<sup>(17)</sup>

Chemical and toxicological studies indicate that the use of e-cigarettes may be less harmful than smoking.<sup>(17)</sup> There is no tobacco and no combustion involved in e-cigarettes use; therefore, regular users may avoid several harmful toxic chemicals that are typically present in the smoke of tobacco cigarettes. However, studies have demonstrated that trace amounts of potentially harmful chemicals may be released, such as formaldehyde and acetaldehyde, and tobacco-specific nitrosamines (TSNAs).<sup>(18)</sup> It is worth noting, however, that levels of these compounds are substantially lower than that found in tobacco smoke, and in some cases (such as nitrosamines), are comparable to the amounts found in pharmaceutical nicotine products.<sup>(19)</sup>

Passive inhalation of e-cigarette emissions has not yet been shown to be harmful; however, more studies are required in this area.<sup>(17, 20)</sup> For those who switch to using e-cigarettes containing nicotine, there is also concern around the health effects of sustained nicotine addiction. Direct confirmation from clinical studies that long-term e-cigarette use is safe and leads to reductions in smoking-related diseases is not available, and it will take a few decades before a beneficial effect relative to continued smoking can be established. Nonetheless, it is feasible to detect early

changes in airway function and respiratory symptoms in smokers switching to e-cigarettes. Initial findings from long-term studies support a beneficial effect of e-cigarette use in relation to respiratory outcomes when compared to continued smoking.<sup>(21)</sup> The safety of e-cigarettes is discussed in detail in Chapter 5.

In Ireland, e-cigarettes are generally sold over the counter in retail premises; no product currently has a licensed indication for smoking cessation. In the UK, one e-cigarette product has been licensed, however as of December 2016 it has not yet been marketed.<sup>(22)</sup> In May 2016, the regulations transposing the European Union (Manufacture, Presentation and Sale of Tobacco and Related Products) Directive into Irish law were signed. This provided for greater regulation in relation to the safety and quality requirements for e-cigarettes and refill containers, as well as stricter rules on advertising and sponsorship, and registration requirements for cross-border distance sales.<sup>(23)</sup>

Since e-cigarettes first became available in 2006, there has been a significant increase in the prevalence of e-cigarette use. One large-scale study of e-cigarette use across the EU reported an increase in ever use (defined as current use or any past use or attempted use) from 7.2% in 2012 to 11.6% in 2014.<sup>(24)</sup> The majority of respondents to this survey were current or ex-smokers, with desire to quit reported as a major reason for their use.

There is general agreement that compared with tobacco smoking, e-cigarette use **reduces users' exposure** to toxic substances and, in the UK, support appears to be growing within the public health system for their use.<sup>(25, 26)</sup> However, many health organisations have been reluctant to support the use of e-cigarettes, citing a lack of long-term data on the effect of their use on users and those exposed to the exhaled vapour, concerns about the quality controls used in their manufacture, and fears that these devices will act as a gateway to tobacco use or to the renormalisation of smoking in society.<sup>(27)</sup> While the HSE smoking cessation services do not currently recommend their use as a means of quitting, they do provide support to individuals who choose to use e-cigarettes during a quit attempt.<sup>(6)</sup>

### 2.1.1.3 Bupropion

A number of different medications designed to treat depression have been studied as potential smoking cessation interventions. The exact mechanism by which these agents contribute to smoking cessation has not been definitively established.<sup>(28)</sup> The two drugs that have been studied most frequently in this context are bupropion and nortriptyline, and of these, only bupropion is currently licensed in Ireland for smoking cessation, under the brand name Zyban™. Due to the fact that it is not currently available in Ireland, nortriptyline was not included among the treatments examined in this HTA.

The most commonly reported adverse events associated with bupropion include insomnia, nausea or vomiting, and dizziness.<sup>(29)</sup> Bupropion is also associated with an increased risk of seizures (occurring at a rate of one in 1,000 users, as per the product safety data).<sup>(30)</sup> Concurrent use of medications that lower seizure threshold must be avoided, such as antidepressants, antipsychotics, systemic corticosteroids, theophylline and tramadol. Patients who abuse alcohol or have sustained a head injury are also at risk of bupropion-induced seizure, as are patients who suffer from anorexia or bulimia nervosa.<sup>(31)</sup> Bupropion is contraindicated in patients with bipolar affective disorder, as this antidepressant can precipitate a manic, mixed, or hypomanic episode.<sup>(32)</sup>

Concerns have been raised about the safety of bupropion (and varenicline, see section 2.1.1.4), particularly with regard to neuropsychiatric adverse events such as suicidality and aggression.<sup>(33)</sup> These concerns led to the EAGLES trial (Evaluating Adverse Events in a Global Smoking Cessation Study, published in April 2016), which sought to evaluate the neuropsychiatric safety of bupropion, varenicline and nicotine patch in smokers with and without psychiatric disorders. Relative to nicotine patch or placebo, the study did not show a significant increase in neuropsychiatric adverse events attributable to varenicline or bupropion in patients with or without pre-existing psychiatric disorders.<sup>(34)</sup> It is important to note, however, the limitation of randomised controlled trials (such as the EAGLES trial) in capturing rare adverse events. The safety of included smoking cessation interventions is assessed in detail in Chapter 5.

Use of bupropion is contraindicated in pregnant women in Ireland.<sup>(35)</sup> While studies are inconsistent, one epidemiological study of a registry of pregnancies found a higher frequency of cardiac malformations in pregnancies exposed to bupropion.<sup>(36)</sup> Conversely, another prospective safety study did not find a higher rate of major malformations; however, significantly more spontaneous abortions were observed.<sup>(37)</sup> The safety of bupropion is discussed in more detail in Chapter 5.

Bupropion was licensed in Ireland in June 2000 as a prescription-only medication, and it is reimbursed on the Primary Care Reimbursement Service (PCRS). Details on dosage, duration of treatment and contraindications for the use of bupropion are provided in Table 2.2.<sup>(15)</sup>

**Table 2.2 Summary of usual treatment regimen and contraindications for bupropion for smoking cessation<sup>(15)</sup>**

Parameter	Details
Brand name & dose	Zyban™ 150 mg prolonged release tablets.
Behavioural support	Indicated as an aid to smoking cessation in combination with motivational support in nicotine-dependent patients.
Usual treatment regimen	It is recommended that treatment is started while the patient is still smoking, and a target stop date is set within the first two weeks of treatment, preferably in the second week. The initial dose is 150 mg to be taken daily for six days, increasing on day seven to 150 mg twice daily. There should be an interval of at least eight hours between successive doses. The maximum single dose must not exceed 150 mg and the maximum total daily dose must not exceed 300 mg. Patients should be treated for seven to nine weeks. If at seven weeks no effect is seen, treatment should be discontinued.
Contraindications	Patients with hypersensitivity to bupropion or any of the medication's excipients; those with a current seizure disorder or any history of seizures; those with a known central nervous system (CNS) tumour; those who are undergoing abrupt withdrawal from alcohol or any medicinal product known to be associated with risk of seizures on withdrawal; those with a current or previous diagnosis of bulimia or anorexia nervosa; those with severe hepatic cirrhosis; those taking monoamine oxidase inhibitors (MAOIs); those with a history of bipolar disorder; those being treated with any other medicinal product containing bupropion; pregnant women.

#### 2.1.1.4 Nicotine Receptor Partial Agonists

Nicotine receptor partial agonists may help people to stop smoking by both reducing withdrawal symptoms (acting as an agonist) and reducing smoking satisfaction (acting as an antagonist).<sup>(38)</sup> Three different agents in this class have been developed to date, however only one is currently licensed in Ireland. Varenicline (trade name Champix®) was licensed in Ireland in September 2006 as a prescription-

only medication, and it is reimbursed on the Primary Care Reimbursement Service (PCRS).

Cytisine, sold under the trade name Tabex™, has been available in a number of eastern and central European countries since the 1960s, but is not licensed or distributed in Ireland or other western European countries.<sup>(39, 40)</sup> However, there has been renewed interest in this drug due to recent positive trial data and its relatively low cost.<sup>(41)</sup>

Varenicline is generally well-tolerated, with the most commonly reported adverse events consisting of nausea, abnormal dreams, insomnia, taste perversion, flatulence, dyspepsia, constipation, and headache.<sup>(42)</sup> Varenicline is not recommended during pregnancy, as the currently available studies of varenicline use in pregnancy are insufficient to provide evidence for safety.<sup>(43)</sup>

Due to an initial concern of clinically significant neuropsychiatric events associated with varenicline administration, the European Medicines Agency issued a warning for its use in patients with pre-existing psychiatric conditions. However, this black triangle warning was subsequently removed in May 2016.<sup>(44)</sup> This emerged following publication of safety and efficacy data from the EAGLES (Evaluating Adverse Events in a Global Smoking Cessation Study) trial in April 2016 which found no increased incidence of adverse neuropsychiatric effects in patients with or without pre-existing psychiatric disorders.<sup>(34)</sup>

Details on dosage, duration of treatment and contraindications for the use of varenicline are provided in Table 2.3.<sup>(15)</sup>

Both varenicline and cytisine were assessed in this HTA. Although cytisine is not currently available in Ireland, there is a possibility that it may be licensed for use in the future, so an analysis of the clinical and cost-effectiveness of this treatment may be relevant in the medium to long term. However, all analyses were also carried out with cytisine excluded to reflect the range of treatments currently available in Ireland.

**Table 2.3 Summary of usual treatment regimen and contraindication for varenicline for smoking cessation<sup>(15)</sup>**

Parameter	Details
Brand name & dose	Champix <sup>®</sup> 0.5mg and 1mg film-coated tablets.
Behavioural support	Smoking cessation therapies are more likely to succeed for patients who are motivated to stop smoking and who are provided with additional advice and support.
Usual treatment regimen	Dosing should usually start at one to two weeks before the target stop smoking date and treatment should continue for 12 weeks. For patients who have successfully stopped smoking at the end of 12 weeks, an additional course of 12 weeks treatment at 1mg twice daily may be considered for the maintenance of abstinence. The recommended dose is 1mg twice daily following a one week titration as follows: Days 1-3 – 0.5mg once daily Days 4-7 – 0.5mg twice daily Days 8 – End of treatment – 1mg twice daily.
Contraindications	Patients with hypersensitivity to varenicline or any of the medication's excipients; pregnant women.

## 2.1.2 Non-pharmacological interventions for smoking cessation

### 2.1.2.1 Acupuncture

Acupuncture is a form of complementary medicine that involves the insertion of fine needles into your skin at strategic points on your body, with the aim of reducing withdrawal symptoms associated with smoking cessation. There are mainly two acupuncture techniques used for this type of treatment, one involves needles being inserted for the duration of the treatment only (usually 15-20 minutes), while the other involves the use of indwelling needles that are left in place for a number of days, with patients being advised to press these needles when they experience withdrawal symptoms.<sup>(45)</sup> This HTA reviewed the evidence supporting the use of acupuncture involving either of these techniques for long-term smoking cessation.

While acupuncture is not currently reimbursed through the public health system, a number of private health insurance providers in Ireland do provide cover when the acupuncturists are registered with professional bodies, such as the Acupuncture Council of Ireland and the Acupuncture Foundation Professional Association.



Adverse reactions to acupuncture are limited to mild, short-lasting effects such as pain at site of insertion, bleeding and worsening of pre-existing symptoms. Serious complications are exceedingly rare.<sup>(46)</sup>

There are a range of related therapies that have previously been examined in the context of smoking cessation. These include acupressure (using pressure alone to stimulate various sites, rather than needles), laser therapy (stimulating areas of the skin using a low level laser beam), or electrical stimulation using surface electrodes or through the application of an electrical current between pairs of acupuncture needles. However, due to insufficient evidence of efficacy, these were not included in this HTA.

### 2.1.2.2 Behavioural interventions

There is a diverse range of behavioural support interventions designed to help smokers quit (see Chapter 4, Figure 4.6 for those considered in this HTA). These interventions can be used alone, or in conjunction with pharmacotherapy or other forms of behavioural support, and they may be delivered in a number of different settings. Behavioural interventions may also be designed to achieve additional outcomes, including raising awareness and warning about the dangers of tobacco, promoting a tobacco-free environment, and motivating individual smokers to make a quit attempt. These additional outcomes were not considered as part of this HTA which specifically examined the evidence supporting behavioural interventions in the context of smoking cessation. The following outlines the interventions that were considered. The population of interest was an unselected group of adult smokers in a community setting. Interventions targeting pregnant women and patients with a psychiatric comorbidity were assessed separately.

#### 2.1.2.2.1 Motivational interviewing

Motivational interviewing is a behavioural support intervention designed to help smokers overcome any lack of motivation or resistance to change that may be hindering their attempt to quit. It was first described by Miller in 1983 in the context of alcohol abuse, where it was defined as 'a directive, client-centred counselling style for eliciting behaviour change by helping clients to explore and resolve ambivalence'.<sup>(47)</sup>

The four general principles underpinning the technique are:

- expressing empathy
- developing discrepancy
- rolling with resistance
- supporting self efficacy.<sup>(48)</sup>

Motivational interviewing can range from single appointments to multiple sessions provided over an extended period of time. Sessions or appointments can be conducted face-to-face, by telephone or within groups.<sup>(49)</sup>

Training in motivational interviewing is currently funded by the HSE, for example through dedicated training courses at nurse education centres and training courses aimed at other treatment providers (such as occupational therapists and speech and language therapists). Motivational interviewing is also provided free of charge in various antenatal clinics to support smoking cessation, again funded by the HSE.<sup>(6)</sup> It is worth noting that training in motivational interviewing is often generic, however, and that this intervention may also be applied to a wide range of other risk factors targeting behavioural changes in relation to diet, exercise and alcohol consumption.

#### *2.1.2.2 Brief Advice*

Brief Advice interventions are designed to increase smoking cessation rates by encouraging healthcare professionals to enquire about the smoking status of patients and offer guidance and encouragement to smokers on quitting. These interventions may combine verbal advice with the provision of materials on smoking cessation, as well as one or more follow-up visits. The rationale for this type of intervention originated in trials carried out in the 1980s. These trials suggested that physician advice could help improve cessation rates.<sup>(50-52)</sup>

**The HSE currently funds training in brief advice in the form of 'Brief Interventions for Smoking Cessation'. This training is aimed at a wide range of personnel in both the acute and community care settings. Its framework is based on the '5 A's':**

- **Ask:** systematically identify all smokers at every visit. Record smoking status, number of cigarettes smoked per day/week and year started smoking.
- **Advise:** urge all smokers to quit. Advice should be clear and personalised.
- **Assess:** determine willingness and confidence to make a quit attempt.
- **Assist:** aid the smoker in quitting. Provide behavioural support. Recommend/prescribe pharmacological aids. If not ready to quit promote motivation for future attempt.
- **Arrange:** follow-up appointment within one week or if appropriate refer to specialist cessation service for intensive support. Document the intervention.

A pharmacy-led smoking cessation service is also offered by the Irish Pharmacy Union, similarly following the '5 A's' of Brief Advice for Smoking Cessation.

### *2.1.2.2.3 Telephone interventions*

Telephone interventions designed to improve smoking cessation rates can involve telephone contact with minimal support (for example, the provision of printed self-help material), or telephone calls in combination with pharmacotherapy or more intensive behavioural support interventions (for example, face-to-face counselling).<sup>(53)</sup> There are significant differences in the populations targeted by these types of interventions. Some of these interventions include smokers who have decided they want to make a quit attempt and initiate contact with a smoking cessation helpline (such as the **HSE's QUITline**) **in order to receive support and** information about quitting. Other interventions have involved smokers who may, or may not, want to quit smoking and are contacted and provided with information, support and encouragement to increase their likelihood of making a quit attempt and succeeding.

This assessment focussed on the effect of additional telephone calls from counsellors for those who contact smoking cessation services, rather than the effect of offering counselling to smokers who had not contacted these services or expressed a desire to quit.

In Ireland, the QUITline telephone service is funded by the HSE. Initially provided by the Irish Cancer Society, since 2014 its service has been outsourced (by open tender process) to provide an integrated service. In addition to a telephone support service, QUITline now incorporates SMS messaging, live chat, an online quit plan with targeted daily supportive emails, a quit app and a Facebook page.

Following initial contact with the telephone service, a trained advisor explains the programme, and the client is asked to set a quit date and to sign up to a service of supportive phone calls over a 12-month period. The advisor calls the client on their target quit date, then once a week for the first four weeks, and again at three months and 12 months. In addition, advisors may be contacted at any time between phone calls (by text, email, live chat or phone).<sup>(6)</sup>

### *2.1.2.2.4 Mobile phone-based interventions*

Text message-based interventions that use mobile phone technology to communicate with smokers in an effort to increase long-term abstinence rates have been used in Ireland and internationally.<sup>(6, 54)</sup> These can provide encouragement and support to smokers wishing to quit and are tailored to the stage of quitting the individual is at. Mobile phone-based interventions may be provided in conjunction with other types of behavioural or pharmacological interventions. The HSE-funded QUITline incorporates SMS messaging in its smoking cessation service.

#### *2.1.2.2.5 Internet-based interventions*

Given the increasing level of access, relatively low cost, and ability to deliver an interactive experience that is tailored to the needs of individual smokers, the Internet would appear to be a potentially effective medium with which to provide behavioural change interventions. This assessment examined the evidence supporting the use of Internet-based interventions for those wishing to quit, either as a stand-alone programme or as an addition to pharmacotherapy.<sup>(55)</sup> Different forms of Internet-based interventions were evaluated, including interventions of higher intensity (interactive sessions, tailored to the patient) and those of lower intensity (static websites, generic advice). The HSE provides the Internet-based intervention QUIT ([www.quit.ie](http://www.quit.ie)), offering a range of services for smoking cessation. They include interactive e-mail and instant messaging by trained counsellors, along with online information on smoking cessation.<sup>(6)</sup>

#### *2.1.2.2.6 Individual behavioural counselling*

One-to-one counselling for the purpose of helping smokers to quit is a behavioural support intervention that can be provided alone, or in conjunction with other behavioural supports or pharmacotherapy. A 2005 Cochrane review highlighted the difficulties extricating the effect of counselling for patients who present solely on the basis of a desire to quit smoking from counselling that is delivered to smokers who attend medical services during the course of their clinical care.<sup>(56)</sup> Given this issue, the approach adopted in this HTA was to examine studies where counselling was delivered on a one-to-one basis by counsellors trained in smoking cessation. Counselling delivered as part of routine clinical care in a given setting (and which may target multiple risk factors in addition to smoking) was considered under Brief Advice (Section 2.1.2.2.2). Individual behavioural counselling interventions that followed the principles of motivational interviewing were not included, as these were evaluated separately in the section on motivational interviewing (Section 2.1.2.2.1).

#### *2.1.2.2.7 Group behaviour therapy*

Group behaviour therapy has been reported to confer a number of benefits to smokers wishing to quit. These include generating emotional experiences, imparting information and teaching new skills.<sup>(57, 58)</sup> Group behaviour therapy can differ considerably in relation to the number and duration of meetings, and may be facilitated by health professionals or by former group members.<sup>(59)</sup> This HTA examined the effectiveness of group behaviour therapy involving multiple face-to-face meetings where smokers receive behaviour support such as information, advice and encouragement to achieve long-term abstinence.

#### *2.1.2.2.8 Allen Carr method*

The Allen Carr method of smoking cessation is a self-help approach to smoking cessation, **described in his 1985 book 'Allen Carr's Easy Way to Stop Smoking'**. This book has since sold over 13 million copies worldwide.<sup>(60)</sup>

The approach involves changing the way smokers think about their addiction, and the withdrawal symptoms associated with quitting, in a way that reduces their desire to smoke and makes it easier for them to achieve long-term abstinence. In addition to the book, the Allen Carr method is taught in seminars held in a host of countries, including Ireland.

#### *2.1.2.2.9 Financial incentives for pregnant women*

Smoking cessation programmes sometimes provide rewards in the form of money or vouchers to incentivise smokers to quit. These rewards can be given for attending the programme, or for having achieved milestones, such as having remained abstinent for a given period of time. This HTA examined the effectiveness of incentivised programmes to help pregnant women achieve abstinence, either for the duration of the pregnancy only, or for a longer period of time. It did not include interventions aimed at other types of smokers, or interventions where the healthcare professionals providing the service receive financial incentives based on the performance of the programme.

### **2.1.3 Excluded interventions**

As described earlier, the sheer number of potential smoking cessation therapies meant that it was not feasible to include every type of intervention that can be provided to individuals attempting to give up smoking. As a result, it was necessary to prioritise therapies that are currently provided to or used by smokers in Ireland, and for which there was a prospect that sufficient evidence would be available to reliably estimate their clinical and cost-effectiveness.

Some of the interventions that were not examined in this HTA include hypnotherapy, silver acetate, nicotine vaccines, cannabinoid type 1 receptor antagonists or anxiolytics. As noted previously, this HTA was confined to interventions that help smokers achieve long-term abstinence and so did not include studies aimed at preventing relapse or increasing the recruitment of smokers into cessation programmes.

## **2.2 Discussion**

Almost half (48%) of all smokers who attempted to quit in 2014 in Ireland did not seek any help or use any quitting aid, choosing instead to rely on willpower alone.<sup>(61)</sup>

The pharmacological and behavioural interventions described in this HTA, therefore, aim to increase the likelihood of cessation beyond what can be achieved by willpower alone.

The interventions evaluated were not an exhaustive list of smoking cessation interventions. The prioritisation process took into consideration interventions that were most relevant to smokers and policy makers, and only interventions that were applicable to the Irish health system were included. It is worth noting, however, that these interventions are used in Ireland to differing degrees. Uptake is further examined in Chapter 3.

The types of interventions evaluated were limited to those that can be provided to smokers at an individual level to encourage long-term cessation. This HTA did not examine the impact of treatments in terms of any potential harm reduction associated with their use, such as helping people to reduce the number of cigarettes smoked per day, nor did it examine interventions enacted at a societal level to reduce smoking initiation.

A range of behavioural interventions were included in this HTA. Evaluation of these interventions was complicated however due to an absence of standard definitions for these interventions, including the choice of treatment provider and the intensity of the intervention (influenced by duration, number and frequency of sessions). In addition, there could be substantial overlap between the interventions. Often, more than one intervention was provided simultaneously, and they could be provided with or without adjunct pharmacological aides, adding further complexity to their analysis.

The target population in this assessment was unselected adult smokers in a community setting. Pharmacological interventions are contraindicated for certain patient groups. Both bupropion and varenicline administration are contraindicated in pregnancy. In addition, bupropion is contraindicated in a range of conditions, including that of bipolar affective disorder. Due to these contraindications, the additional risk to the fetus (in the case of pregnant women) and the higher prevalence of smoking in psychiatric patients, the safety and efficacy of the various smoking cessation interventions in these subgroups were analysed separately.

Currently, prescribed pharmacological agents (nicotine replacement therapy (NRT), bupropion and varenicline) are reimbursed through the Primary Care Reimbursement Service (PCRS), although reimbursement of NRT is limited to Medical Card holders only. Behavioural interventions funded and provided by the HSE free-of-charge to all Irish residents include Internet-based support ([www.quit.ie](http://www.quit.ie)), telephone-based support (QUITline), and HSE smoking cessation clinics (offering individual and group

behavioural support in some locations). The cost-effectiveness and budget impact of the cessation interventions considered in this report are examined in Chapter 6.

## **2.3 Key points**

- Reducing the prevalence of smoking is a key priority within the public health system.
- A diverse range of smoking cessation interventions is available in Ireland.
- Pharmacological interventions include nicotine replacement therapy (NRT), electronic cigarettes, antidepressants (specifically bupropion) and nicotine receptor partial agonists (varenicline and cytisine).
- Prescribed nicotine replacement therapy (NRT), varenicline and bupropion are currently reimbursed through the Primary Care Reimbursement Service (PCRS), although reimbursement of NRT is limited to Medical Card holders only.
- Neither varenicline nor bupropion are indicated for use in pregnant women in Ireland.
- Bupropion is contraindicated in certain patient groups, including those at increased risk of seizures and those with bipolar affective disorder.
- Warnings cautioning the use of varenicline in patients with pre-existing psychiatric conditions were lifted in May 2016 following publication of safety and efficacy data from the EAGLES trial. The study did not show a significant increase in neuropsychiatric adverse events that could be attributed to varenicline or bupropion relative to nicotine patch or placebo in patients with or without pre-existing psychiatric disorders.
- Electronic cigarettes, also known as e-cigarettes, are not currently advocated by the HSE as a means of quitting due to lack of long-term data on their safety. However, support is provided by HSE smoking cessation services to smokers who choose to use e-cigarettes in their quit attempt.
- Non-pharmacological interventions include acupuncture, motivational interviewing, brief advice, telephone-based interventions, Internet-based interventions, mobile phone-based interventions, individual behavioural counselling, group behaviour therapy and the Allen Carr method.
- The absence of standard definitions for behavioural interventions, including the choice of treatment provider and the intensity of the intervention (influenced by duration, number and frequency of sessions), adds complexity to their analysis. In addition, there may be substantial overlap between these interventions. Often more than one intervention is simultaneously provided, and they may be provided with or without adjunct pharmacological therapy.



## 3 Epidemiology

Since the 1950s, evidence has shown the link between tobacco smoking and morbidity. Initially, evidence focused on lung cancer in men, but subsequent research has shown causal links to a wide range of conditions. The purpose of this chapter is to provide an overview of current knowledge in relation to tobacco smoking and ill health. This chapter also reviews data on the prevalence of smoking and smoking cessation in Ireland.

### 3.1 Effects of smoking

Since the early 1960s there has been a wealth of research on the effects of smoking, demonstrating causal links between smoking and a range of diseases. A 1962 analysis combined data from the Framingham men with the Albany, New York, male cohort, and found cigarette smoking predicted myocardial infarction, coronary heart disease mortality, and all-cause mortality.<sup>(62)</sup> In 1964, the US Surgeon General published a **report, 'Smoking and Health', which concluded that there was a causal link between cigarette smoking and lung cancer in men.**<sup>(63)</sup> The report reviewed over 2,000 documents and highlighted a dose-response relationship, stating that the risk of lung cancer is reduced by stopping smoking. It noted that from the year 1900, the prevalence of cigarette smoking in US adults increased steadily, reaching 42% of the **adult population by 1964. The publication of the Surgeon General's report that year** marked the start of a decline in smoking prevalence; by 2012, 18% of US adults smoked.

Almost all (98%) smokers in Ireland use manufactured or hand-rolled cigarettes.<sup>(64)</sup> This section therefore focuses primarily on the impact of cigarette smoking, as distinct from pipe, cigar or other forms of tobacco smoking.

#### 3.1.1 Physical impact of smoking

Cigarette smoke contains more than 5,000 chemical compounds, including more than 70 established carcinogens.<sup>(65-67)</sup> These chemical components are held in a mixture of gas phase and particulate matter. There are a range of complex biological and behavioural mechanisms through which the inhalation of cigarette smoke leads to disease.<sup>(65)</sup> The quantity of toxic particles and gases inhaled from a cigarette depends on the nature of the tobacco, the volume and number of puffs of smoke drawn from the cigarette, the amount of air drawn in through ventilation holes as the smoke is inhaled, and the local characteristics **of the smoker's lungs.**<sup>(65)</sup> Toxins in cigarette smoke are deposited and absorbed by the body as the inhaled smoke moves from the mouth, through the airways and into the alveoli in the lungs.



Cigarette smoke is classified as a Group 1 carcinogen (carcinogenic to humans) by the International Agency for Research in Cancer (IARC), causing a range of cancers, including cancers of the lung, oral cavity, oesophagus, stomach, and colorectum. It includes over 70 carcinogens evaluated by the IARC as having sufficient evidence for carcinogenicity, of which 16 are identified as Group 1 carcinogens. The IARC also now considers that there is sufficient evidence for the carcinogenicity of parental smoking, specifically for hepatoblastoma in children with a positive association also for childhood leukaemia.<sup>(67)</sup>

Clinical and experimental studies indicate that cigarette smoking contributes significantly to cardiovascular morbidity and mortality due to a combination of atherosclerosis, thrombosis and vascular dysfunction. Clinical atherosclerosis syndromes (such as, angina, acute coronary syndrome, and stroke,) start and progress due to the pro-inflammatory effect of cigarette smoke as well as its adverse effect on blood lipid profiles and its impairment of vasomotor function. Cigarette smoking is also associated with an increased incidence of myocardial infarction. This is thought to be due to its alteration of platelet function, fibrinolysis, and antithrombotic and prothrombotic factors leading to initiation and, or progression of thrombus (clot) formation and impaired clot dissolution. While nicotine contributes to smoking-related increases in cardiac output, heart rate and blood pressure, its impact on disease formation including atherosclerosis and thrombosis is more controversial. Instead, it is thought that these effects of cigarette smoking are due to free radical-mediated oxidative stress, including a loss of the protective effect of nitric oxide.<sup>(68)</sup>

### **3.1.2 Attributable disease**

Exposure to tobacco smoke may cause disease through a variety of complex mechanisms. Genetic predisposition also impacts on how toxic components in tobacco smoke may cause disease. Furthermore, tobacco smoke may act in combination with environmental factors such as radon exposure. As such, the extent to which tobacco smoke will cause disease in a given individual depends on a wide range of factors.

Numerous studies have sought to estimate the impact of smoking on morbidity, often through the use of health and lifestyle surveys that include disease status as well as smoking behaviour and other known risk factors, such as age and sex. Disease status is measured in relation to a set of diseases for which a causal relationship with smoking has been demonstrated.

The risk of attributable disease is typically estimated separately for males and females, and also for current and former smokers. Smokers that quit continue to have an elevated risk for many diseases when compared with those who have never

smoked. The risk ratios are presented for all adults over a certain age, and are not provided by smoking history in terms of the quantity of cigarettes smoked. Given the difficulties in retrospectively determining smoking history, it is pragmatic to use a classification of current, former and never smokers. Current smokers can be further divided into regular and occasional smokers. Regular smokers are generally defined as those that smoke at least one cigarette per day, whereas occasional smokers do not smoke every day.

Based on UK data, the risk ratios for 26 conditions show the differing impacts of smoking on current and former smokers (Table 3.1).<sup>(69)</sup> In all cases, the risk ratios are relative to the risk in the cohort of people who have never smoked. For most conditions, the risk ratio is substantially reduced for former smokers, with the notable exception of chronic obstructive lung disease and chronic airway obstruction. Risk ratios associated with cancers of the trachea, lung and bronchus, cancer of the larynx, and chronic airway obstruction are all in excess of four for both current and former smokers.

### **3.1.3 Burden on healthcare utilisation**

Given the higher risk of disease in current and former smokers when compared with those who have never smoked, it is anticipated that smoking status may predict healthcare utilisation. A US study using survey data on 15,332 respondents showed that hospital utilisation was higher among current and former smokers than in people who had never smoked.<sup>(70)</sup>

The number of inpatient and day case discharges in the Irish public healthcare system that can be attributed to smoking from 2013 to 2015 was estimated using the relative risks of disease related to smoking status (Table 3.2). The largest smoking-related contributor to inpatient discharges was chronic airway obstruction (32,548 discharges), followed by ischaemic heart disease (11,998 discharges). Regarding day cases, the largest contributors were cancer of the trachea, lung and bronchus (5,183 day cases), ischaemic heart disease (4,888 day cases) and colorectal cancer (2,957 day cases). In total, smoking-related illness is estimated to generate 29,010 inpatient discharges and 10,613 day cases each year.

Hospital utilisation figures must be considered in the context of 1,872,182 inpatient discharges and 2,918,499 day cases in the same three-year period. Although the cases that can be attributed to smoking present only a small proportion of all hospital cases, these data does not take into account length of stay or the diagnosis related groups, which give an indication of the complexity of the cases. The figures are also a conservative estimate, as they do not include cases related to second-hand smoke exposure.

**Table 3.1 Risk ratios for diseases in current and former smokers relative to never smokers<sup>(69)</sup>**

Condition	ICD10 code	Age	Females		Males	
			Current smokers	Former smokers	Current smokers	Former smokers
Cancers						
Trachea, lung, bronchus	C33-C34	35+	12.69	4.53	23.26	8.70
Upper respiratory sites	C00-C14	35+	5.08	2.29	10.89	3.40
Oesophagus	C15	35+	7.75	2.79	6.76	4.46
Larynx	C32	35+	13.02	5.16	14.60	6.34
Cervical	C53	35+	1.59	1.14	N/A	N/A
Bladder	C67	35+	2.22	1.89	3.27	2.09
Kidney and renal pelvis	C64-C66, C68	35+	1.40	1.10	2.50	1.70
Stomach	C16	35+	1.36	1.32	1.96	1.47
Pancreas	C25	35+	2.25	1.55	2.31	1.15
Unspecified site	C80	35+	2.20	1.30	4.40	2.50
Myeloid leukaemia	C92	35+	1.20	1.30	1.80	1.40
Colorectal	C18-C20	35+	2.14	1.47	2.14	1.47
Liver	C22	35+	1.70	1.40	1.70	1.40
Respiratory diseases						
Chronic obstructive lung disease	J40-J43	35+	12.04	11.77	17.10	15.64
Chronic airway obstruction	J44	35+	13.08	6.78	10.58	6.80
Pneumonia, influenza	J10-J18	35-64	4.30	1.10	2.50	1.40
	J10-J18	65+	2.20	1.10	2.00	1.40
Tuberculosis	A15-A19	35+	2.30	1.00	2.30	1.00
Circulatory diseases						
Other heart disease	I00-I09, I26-I51	35+	1.49	1.14	1.78	1.22
Ischaemic heart disease	I20-I25	35-54	5.30	2.60	4.20	2.00
	I20-I25	55-64	2.80	1.10	2.50	1.60
	I20-I25	65-74	2.10	1.20	1.80	1.30
	I20-I25	75+	1.40	1.20	1.40	1.10
	I72-I78	35+	2.17	1.12	2.07	1.01
Cerebrovascular disease	I60-I69	35-54	5.40	1.30	4.40	1.10
	I60-I69	55-64	3.70	1.30	3.10	1.10
	I60-I69	65-74	2.60	1.30	2.20	1.10
	I60-I69	75+	1.30	1.00	1.60	1.10
	I71	35+	7.07	2.07	6.21	3.07
Atherosclerosis	I70	35+	1.83	1.00	2.44	1.33
Diabetes Mellitus	E11	35+	1.37	1.14	1.37	1.14
Digestive system						
Stomach/duodenal ulcer	K25-K27	35+	5.50	1.40	5.40	1.80
Crohns disease	K50	35+	2.10	1.00	2.10	1.00
Periodontal disease/periodontitis	K05	35+	3.97	1.68	3.97	1.68

**Table 3.1 continued (Risk ratios for diseases in current and former smokers relative to never smokers<sup>(69)</sup>)**

Condition	ICD10 code	Age	Females		Males	
			Current smokers	Former smokers	Current smokers	Former smokers
Other diseases						
Age-related cataract	H25	45+	1.54	1.11	1.54	1.11
Hip fracture	S72.0-S72.2	55-64	1.17	1.02	1.17	1.02
	S72.0-S72.2	65-74	1.41	1.08	1.41	1.08
	S72.0-S72.2	75+	1.85	1.22	1.76	1.14
Spontaneous abortion	O03	35+	1.28	1.00	N/A	N/A

Although cancers are almost exclusively treated in a secondary care setting, many of the other conditions which may be attributable to smoking will include management in a primary care setting. In the absence of detailed Irish primary care data, it was not possible to estimate the impact of smoking on the use of primary care services in Ireland. However, a US study estimated that smoking status was a statistically significant positive predictor of specialty care visits and hospitalisations, but not of primary care visits (adjusting for health status, age, sex, education, income, obesity and alcohol abuse).<sup>(71)</sup> Lower use of primary care by smokers has been found in other studies,<sup>(72, 73)</sup> suggesting that smokers use primary care services less frequently than former smokers and those who have never smoked. Jorm et al. concluded that smokers may have a lower propensity to seek healthcare, thereby missing out on access to preventive services.<sup>(73)</sup>

### 3.1.4 Smoking in pregnancy

Smoking during pregnancy can harm both mother and fetus. Maternal smoking is associated with an increased risk of a range of congenital anomalies, preterm birth, intrauterine fetal growth restriction, placental abruption and stillbirth.<sup>(74-77)</sup> Cigarette smoke contains chemicals which can contribute to poor infant outcomes.<sup>(78)</sup> Carbon monoxide displaces oxygen and impairs the release of oxygen from haemoglobin, reducing oxygen availability to the fetus. Nicotine reduces placental blood flow. Both carbon monoxide and nicotine adversely affect fetal growth. Intrauterine fetal growth restriction is the most common cause of antepartum stillbirth in normally formed fetuses.<sup>(79)</sup>

A systematic review, which included 96 population-based studies conducted in five high-income countries (Australia, Canada, US, UK and the Netherlands), was published as part of the 2011 Lancet series on stillbirth prevention.<sup>(80)</sup> Maternal smoking was one of the seven most important risk factors for stillbirth in high-income countries, and one of two risk factors which can be altered. Raising awareness and

the implementation of effective interventions for smoking in pregnancy is a priority. In high-income countries, a woman living under adverse socioeconomic circumstances has twice the risk of having a stillborn baby compared to a woman living without such disadvantage.<sup>(81)</sup> Improved access to appropriate antenatal care and programmes that increase the smoking cessation rate in pregnancy will help to reduce these health inequalities.

Maternal smoking is also associated with an increased risk of sudden infant death syndrome and respiratory infections in infancy.<sup>(76)</sup> Adverse cognitive and behavioural outcomes associated with maternal smoking include conduct disorder, attention-deficit or hyperactivity disorder, poor academic achievement, and cognitive impairment.<sup>(82)</sup>

**The 'Barker hypothesis', also known as the 'developmental origins of adult disease', the 'fetal origins hypothesis' and the 'developmental origins of health and disease',** proposes that many common chronic conditions are the result of poor intrauterine health and poor postnatal health.<sup>(83)</sup> Babies with low birth weight experience rapid catch up growth which can result in obesity and chronic disease such as coronary artery disease, diabetes and hypertension.<sup>(84)</sup> Smoking cessation during pregnancy would not only improve maternal and fetal health, but could also contribute to a reduction in the incidence of chronic disease in adults.<sup>(85)</sup>

**Table 3.2 Hospital utilisation in Ireland attributable to smoking, 2013-2015**

Condition	ICD10 codes	Inpatient	Daycase
<b><i>Cancers</i></b>			
Trachea, lung, bronchus	C33-C34	6,665	5,183
Upper respiratory sites	C00-C14	1,602	867
Oesophagus	C15	1,413	1,392
Larynx	C32	727	515
Cervical	C53	149	145
Bladder	C67	1,453	1,107
Kidney and renal pelvis	C64-C66, C68	575	710
Stomach	C16	535	617
Pancreas	C25	482	447
Unspecified site	C80	178	123
Myeloid leukaemia	C92	248	1,058
Colorectal	C18-C20	2,269	2,957
Liver	C22	327	120
<b><i>Respiratory diseases</i></b>			
Chronic obstructive lung disease	J40-J43	765	597
Chronic airway obstruction	J44	32,548	2,530
Pneumonia, influenza	J10-J18	6,246	78
Tuberculosis	A15-A19	96	38
<b><i>Circulatory diseases</i></b>			
Other heart disease	I00-I09, I26-I51	7,797	1,836
Ischaemic heart disease	I20-I25	11,998	4,888
Other arterial disease	I72-I78	333	519
Cerebrovascular disease	I60-I69	4,541	100
Aortic aneurysm	I71	1,322	90
Atherosclerosis	I70	983	176
Diabetes Mellitus	E11	977	1,856
<b><i>Digestive system</i></b>			
Stomach/duodenal ulcer	K25-K27	1,101	844
Crohns disease	K50	335	1,684
Periodontal disease/periodontitis	K05	12	20
<b><i>Other diseases</i></b>			
Age-related cataract	H25	36	1,264
Hip fracture	S72.0-S72.2	1,034	0
Spontaneous abortion	O03	284	76
<b>Total</b>		<b>87,030</b>	<b>31,838</b>

Note: data uses discharge data from the Hospital Inpatient Enquiry (HIPE) system and smoking prevalence data from the Healthy Ireland survey combined with the relative risk data from Table 3.1.

### **3.1.5 Smoking and mental health**

Smokers with mental health disorders smoke more heavily, are more nicotine dependent, and have smoked for longer than the general population.<sup>(86)</sup> The relationship between mental health and smoking is complex, particularly given that nicotine dependence itself can be considered as a psychiatric disorder. ICD-10 includes mental behavioural disorders due to both dependence on, and withdrawal from nicotine. Nicotine dependence is thus the most prevalent mental disorder, and once established, can persist for decades with rates of permanent remission of less than 3% per annum.<sup>(87)</sup>

The reasons for widespread smoking behaviour in those with severe and enduring mental health conditions such as schizophrenia are not well understood. There is contradictory evidence that smoking may be a risk factor for schizophrenia (precipitating its onset in vulnerable individuals) or that it represents an independent protective factor against its development. Schizophrenia is associated with cognitive deficits, including impairments in learning, memory, executive function and cognitive processing speed, some of which may be transiently improved with nicotine.<sup>(87)</sup> However, evidence also suggests that current cigarette smoking may be associated with worse cognitive and adaptive functioning in those with serious mental illness.<sup>(88)</sup> Tobacco smoking increases the metabolism of some antipsychotic medications, so patients may use tobacco to counteract their side-effects.<sup>(89)</sup>

Evidence suggests that smoking increases the risk of mental health disorders, including depression and anxiety. Recent evidence suggests that these psychiatric symptoms may improve following chronic smoking cessation.<sup>(90)</sup> However, it is also noted that smoking cessation has been associated with a worsening of depressive symptoms in a minority of people with depression. Nicotine has also been suggested as a form of self-medication, alleviating symptoms of depression due to nicotinic acetylcholine receptor desensitisation.<sup>(87, 91)</sup>

### **3.1.6 Second-hand smoke**

Cigarette smoke can be inhaled as mainstream or sidestream smoke. Mainstream smoke is the smoke that is inhaled directly through a burning cigarette. Sidestream smoke is mainly produced by smouldering cigarettes, and is inhaled by the smoker and by those in the vicinity of the cigarette. Sidestream smoke is a major component of second-hand smoke. Although the chemical composition of mainstream and sidestream smoke differ, they are both carcinogenic. Second-hand smoke, also referred to as environmental tobacco smoke, is a mixture of sidestream smoke and mainstream smoke that has been exhaled by a smoker. Passive smoking is the inhalation of second-hand smoke.

A major report by the US Surgeon General concluded that second-hand smoke causes premature mortality and morbidity in children and adults who do not smoke.<sup>(76)</sup> For children, exposure to second-hand smoke increases the risk of sudden infant death syndrome, acute respiratory infections, ear problems and more severe asthma. Furthermore, exposure to second-hand smoke slows lung growth. For adults, exposure to second-hand smoke has immediate adverse effects on the cardiovascular system, and causes lung cancer and coronary heart disease. Importantly, the report concluded that there is no risk-free level of exposure to second-hand smoke.

Non-smokers can be exposed to second-hand smoke in a variety of settings. Since the introduction of the workplace smoking ban in Ireland, the primary source of exposure is within the home. Ireland was the first country to adopt a nationwide ban on smoking in workplaces, recognising the harmful health effects of second-hand smoke.<sup>(92)</sup> A report by the Environmental Protection Agency (EPA) in Ireland estimated that there were 846 cases of chronic bronchitis, 244 cardiopulmonary deaths, and 7.5 cases of lung cancer occurring in non-smoking adults each year due to exposure to second-hand smoke in the home.<sup>(93)</sup> Similarly, in children, the EPA estimated there were 3.9 deaths due to sudden infant death syndrome, 500 hospital discharges for lower respiratory illness, and 690 new cases of asthma each year due to exposure to second-hand smoke in the home.

## **3.2 Health outcomes associated with smoking**

The increased morbidity associated with smoking has a consequent impact on both mortality and quality of life.

### **3.2.1 Mortality**

Mortality in smokers is two to three times that of people who have never smoked.<sup>(94)</sup> Twelve percent of mortality globally can be attributed to tobacco smoking, including second-hand smoke.<sup>(2)</sup>

A US study of 19,705 male physicians found significantly higher mortality rates among current smokers compared with former and never smokers.<sup>(95)</sup> The risk of death in former smokers was significantly reduced within 10 years of quitting smoking. Twenty years after quitting, the risk of death declined to that of people who had never smoked in smokers who quit before the age of 50 years. Studies have estimated the percentage of deaths attributable to smoking range from 21% for males and 17% for females in the US,<sup>(96)</sup> to 19% in England and Wales, 22% in Denmark, and 25% in the Netherlands.<sup>(97)</sup>



The relative risk of mortality due to smoking has increased over time.<sup>(98)</sup> The increased mortality risk may reflect changes in cigarette design that affect the nature of the inhaled smoke and the absorption of toxic components into the body. The increased risk also reflects the expanding body of evidence that demonstrates a causal link between smoking and an increasing numbers of diseases.

The impact of quitting on the risk of mortality is highly significant. The excess risk associated with smoking can be almost eliminated by quitting smoking before the age of 40 years.<sup>(98)</sup> Although the benefits of quitting are greatest if achieved before the age of 40 years, quitting at any age can confer reductions in risk.<sup>(99)</sup> There is also a dose-response relationship between the quantity of cigarettes smoked and the risk of mortality.<sup>(100)</sup> Estimates of attributable mortality are based on smoking status and not the quantity of smoking. As such, the applicability of relative risks across populations is dependent on smokers having similar histories in terms of the quantity of cigarettes smoked.

Most of the increased mortality risk in smokers can be explained by the common diseases listed in Table 3.3. However, evidence suggests that there may be associations between smoking and a range of other causes of death. One US study estimated that 17% of excess mortality in smokers was not explained by cases currently linked to smoking.<sup>(94)</sup> As such, estimates of smoking attributable mortality may represent substantial underestimates.

**Table 3.3 Risk ratios for adult mortality from smoking-related diseases relative to never smokers, adults 35 years of age and older<sup>(101)</sup>**

Disease category	Males		Females	
	Current smoker	Former smoker	Current smoker	Former smoker
<b><i>Malignant neoplasms</i></b>				
Lip, oral cavity, pharynx (C00–C14)	10.89	3.40	5.08	2.29
Esophagus (C15)	6.76	4.46	7.75	2.79
Stomach (C16)	1.96	1.47	1.36	1.32
Colorectal (C18–C20)	2.14	1.47	2.14	1.47
Liver (C22)	1.70	1.40	1.70	1.40
Pancreas (C25)	2.31	1.15	2.25	1.55
Larynx (C32)	14.60	6.34	13.02	5.16
Trachea, lung, bronchus (C33–C34)	23.26	8.70	12.69	4.53
Cervix uteri (C53)			1.59	1.14
Kidney and renal pelvis (C64–C65)	2.72	1.73	1.29	1.05
Urinary bladder (C67)	3.27	2.09	2.22	1.89
Acute myeloid leukemia (C92.0)	1.86	1.33	1.13	1.38
<b><i>Cardiovascular diseases</i></b>				
Coronary heart disease (I20–I25)				
Persons 35–64 years of age	2.80	1.64	3.08	1.32
<b>Persons ≥65 years of age</b>	1.51	1.21	1.60	1.20
Other heart disease (I00–I09, I26–I28, I29–I51)	1.78	1.22	1.49	1.14
Cerebrovascular disease (I60–I69)				
Persons 35–64 years of age	3.27	1.04	4.00	1.30
<b>Persons ≥65 years of age</b>	1.63	1.04	1.49	1.03

**Table 3.3 continued (Risk ratios for adult mortality from smoking-related diseases relative to never smokers, adults 35 years of age and older<sup>(101)</sup>)**

Disease category	Males		Females	
	Current smoker	Former smoker	Current smoker	Former smoker
Atherosclerosis (I70)	2.44	1.33	1.83	1.00
Aortic aneurysm (I71)	6.21	3.07	7.07	2.07
Other arterial disease (I72–I78)	2.07	1.01	2.17	1.12
Diabetes Mellitus (E11)	1.37	1.14	1.37	1.14
<b>Respiratory diseases</b>				
Tuberculosis (A15 – A19)	2.30	1.00	2.30	1.00
Influenza, pneumonia (J10–J11, J12–J18)	1.75	1.36	2.17	1.10
Bronchitis, emphysema (J40–J42, J43)	17.10	15.64	12.04	11.77
Chronic airways obstruction (J44)	10.58	6.80	13.08	6.78

Note: the classification of 'never smokers' is based on those who answered 'no' to the questions: 'Do you smoke tobacco products?' and 'Did you ever smoke tobacco products (in the past)?'.

According to Ireland's Central Statistics Office (CSO), the total number of deaths registered between 2013 to 2015 was 88,560.<sup>(102)</sup> An estimated 16,372, or 18.5%, of those were attributable to smoking. The main contributors to smoking-attributable mortality were lung cancer, chronic obstructive pulmonary disease (COPD) and coronary heart disease. The smoking-attributable burden is equivalent to approximately 5,457 deaths each year. This is a conservative estimate, as it does not include the risks associated with second-hand smoke.

In the Global Burden of Disease study, it was estimated that 90% of tobacco-related deaths could be attributed to smoking, and 10% to second-hand smoke.<sup>(2)</sup> If such a ratio was applicable to Ireland, then the burden of mortality due to smoking including second-hand smoke would be 20.5%. A report on the economic cost of smoking in Ireland commissioned by the Department of Health estimated that there were 5,860 deaths in 2013 caused by smoking, and a further 92 deaths due to second-hand smoke.<sup>(103)</sup> The evidence on smoking-attributable mortality is evolving as new data emerge demonstrating the magnitude of causal relationships between smoking and disease. This analysis focused on the primary contributors to smoking-

attributable disease rather than presenting an exhaustive list. It is evident that smoking-related mortality in Ireland is broadly similar to estimates from the US and Northern European countries.

There are similar implications for people with mental health issues who smoke in terms of increased risk of morbidity and mortality. However, the higher prevalence of smoking in those with mental health issues has consequences for the size of the population at elevated risk.<sup>(104)</sup> Similarly, those with greater levels of psychological distress smoke greater quantities of cigarettes, on average, and extract more nicotine from each cigarette.<sup>(105)</sup> Due to the dose-response relationship between smoking and outcomes, it is probable that the relative risk of morbidity and mortality for the general population underestimates the risk for the population with mental health issues.

Smoking-related morbidity is noted to be high in patients with severe and enduring mental illness, with half of all deaths attributed to smoking. US data from a cohort of individuals hospitalised on at least one occasion with a primary psychiatric diagnosis suggest that 53% of total deaths in schizophrenia, 48% in bipolar disorder and 50% in major depressive disorder are attributable to smoking. Excess mortality is particularly evident for smoking-related cardiovascular and respiratory disease,<sup>(106)</sup> with chronic lung disease and obstructive sleep apnoea noted to be highly prevalent in individuals with serious mental illness.<sup>(107, 108)</sup> Despite persistent high prevalence of other risk factors including obesity, diabetes and hypertension as well as significant post-cessation weight gain, sustained smoking cessation has been documented to reduce 10-year cardiovascular risk in outpatients with a diagnosis of schizophrenia, schizoaffective disorder or bipolar disorder.<sup>(108)</sup>

**Table 3.4 Mortality in Ireland attributable to smoking, 2013-2015**

Disease category	Age range	Deaths (2013-2015)	
		Total	Attributable to smoking
<i>Malignant neoplasms</i>			
Lung cancer	35+	5,510	4,510
Other cancers	35+	10,269	2,241
<i>Cardiovascular diseases</i>			
Coronary heart disease	35+	13,388	3,294
Other cardiovascular diseases	35-64	1,340	337
Other heart disease	65+	5,298	737
Cerebrovascular disease	65+	5,211	476
Other vascular diseases	65+	1,274	535
Diabetes Mellitus	65+	572	32
<i>Respiratory diseases</i>			
Influenza, pneumonia, TB and COPD	35-64	456	312
Influenza, pneumonia and TB	65+	3,064	490
COPD	65+	4,224	3,408
<b>Total</b>			16,372

Note: Data combines population and mortality data from the Central Statistics Office with smoking prevalence data derived from the Healthy Ireland survey. Relative risks derived from Table 3.3 with diseases grouped as per the methodology of the 2014 US Surgeon General's report.<sup>(101)</sup>

### 3.2.2 Quality of life

Smoking is associated with a range of debilitating chronic diseases, and is therefore likely to be associated with reduced quality of life. A systematic review of quality of life and smoking found that: smoking reduces quality of life, the magnitude of the reduction is related to the quantity of cigarettes smoked, second-hand smoke reduces quality of life, and quitting smoking improves quality of life.<sup>(109)</sup> The magnitude of the difference between smokers and non-smokers varies across studies, and may be partly confounded by biological, clinical, lifestyle and socioeconomic factors.<sup>(110)</sup> Reported differences in quality of life scores between smokers and non-smokers are of the order of 0.03 to 0.05.<sup>(110-112)</sup>

## 3.3 Smoking behaviour in Ireland

Two main sources of data on smoking prevalence were used in this report: the monthly Smoking Prevalence Tracker 2002 to 2016, and the Healthy Ireland survey 2015. Smoking prevalence data are also collected as part of the CSO Irish Health

Survey, and formerly through a variety of surveys including SLÁN and Living In Ireland. Although historical prevalence data are considered briefly, this chapter focuses on the data that describe the recent trends and changes in smoking behaviour in Ireland.

The Smoking Prevalence Tracker is carried out by a monthly telephone survey of 1,000 adults and asks questions on smoking status, number of cigarettes smoked, and e-cigarette usage.<sup>(113)</sup> In this survey, a smoker is defined as someone who **smokes at least one cigarette (packaged or 'roll your own') per week.**

The 2015 Healthy Ireland survey was an interviewer-administered survey of 7,539 adults conducted between November 2014 and August 2015.<sup>(64)</sup> The Healthy Ireland survey included questions on smoking status, types of product used, quit attempts and method used in quit attempt. The survey also asked about motivation to quit. A daily smoker was defined as someone who smoked at least once a day, while an occasional smoker smoked at least once a week. A current smoker was defined as those who either smoked daily or occasionally. Smokers included those using **manufactured and 'roll your own' cigarettes, pipes, cigars, and other products.**

For this section, a combination of both data sources was used. The monthly Smoking Prevalence Tracker provides longitudinal data, while Healthy Ireland provides useful data on prevalence and cessation attempts.

### **3.3.1 Prevalence**

The prevalence of current cigarette smoking in Ireland among persons aged 15 years and over in 2015 was 22.7% (Table 3.5); 19% were daily and 4% were occasional smokers. This figure is equivalent to approximately 818,000 smokers aged 15 years and over. The prevalence was higher in males (24.3%) than females (21.2%), and was highest in those aged 25 to 44 years (29.3%). When considered in five-year age bands, the prevalence was highest in those aged 25 to 29 years, with a third of this population smoking (33.4%). The prevalence of smoking followed a socio-economic gradient, such that those of lower socio-economic status had a higher prevalence of smoking. Prevalence was higher in those with Medical Cards (28.3%) than those without (19.2%).

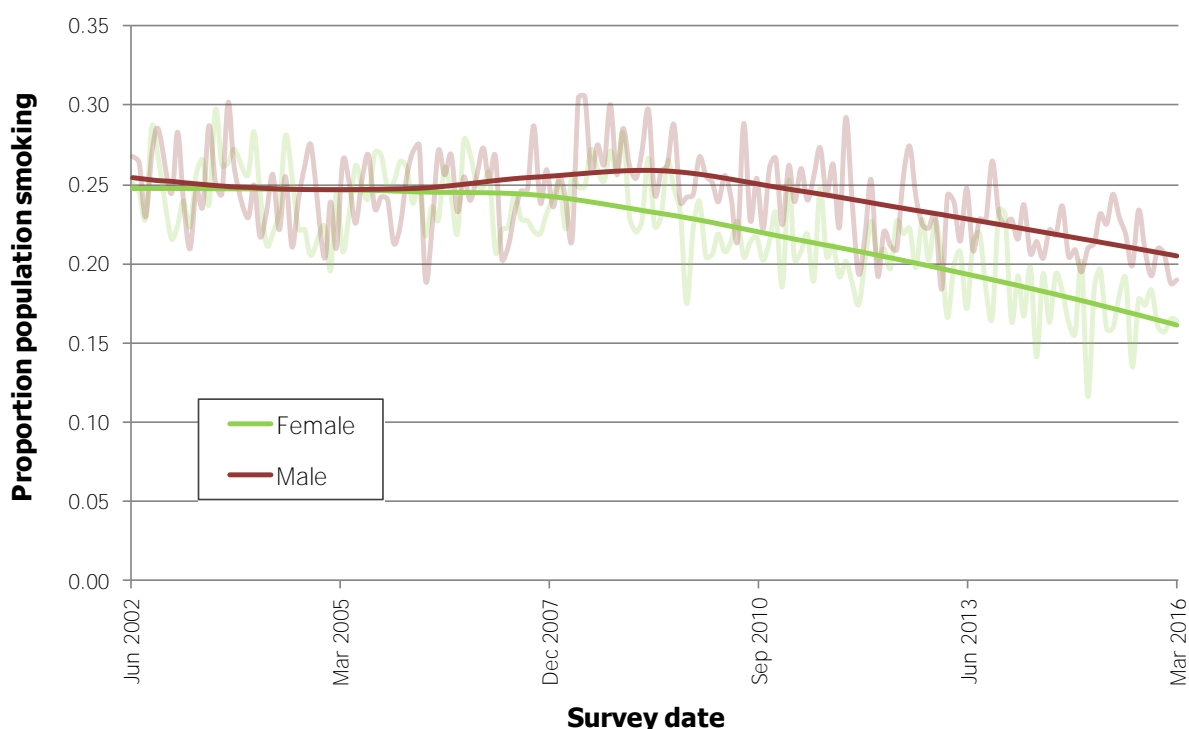
**Table 3.5 Prevalence of smoking in Irish adults, 2015 (Healthy Ireland survey)<sup>(61)</sup>**

Subgroup	Prevalence	Quantity*
All respondents	22.7%	11.6
Sex		
Males	24.3%	12.5
Females	21.2%	10.6
Age group		
15-24	18.9%	7.7
25-44	29.3%	11.0
45-64	21.9%	14.1
65+	12.2%	12.6
Medical Card status		
Medical Card holder	28.3%	13.4
No Medical Card	19.2%	10.0
Socio-economic group		
Higher managerial/professional	16.2%	8.9
Intermediate	15.2%	10.6
Routine/manual	28.7%	12.1
Unspecified	33.7%	14.0

\* Quantity expressed as average number of cigarettes per day combining both regular and occasional smokers.

Based on the Tracker data, the prevalence of smoking was largely static at 25% for males and females from 2002 until 2006 (Figure 3.1). The prevalence of smoking in women began to decline after 2007 to the current figure of 16.7%. The prevalence in men did not begin to decline until late 2009. The absolute number of smokers in Ireland between 2002 and 2016 peaked in 2008, with 932,000 smokers. The absolute number of smokers has been in decline since 2008, and is currently estimated at 682,000 smokers based on these data. As already noted, the Smoking Prevalence Tracker results show a lower estimate of prevalence than the Healthy Ireland survey, and therefore represents an underestimate of the total number of smokers at present and historically. A reducing prevalence of smoking has been observed globally in both developed and developing countries.<sup>(114)</sup> It should be noted that the prevalence of smoking was historically much higher. In the early 1970s, prevalence was in excess of 50% in males and 40% in females, and even this is likely an underestimate of the prevalence of smoking in the 1970s as the definition of a smoker was restricted to those smoking one or more cigarettes per day, and therefore excluded occasional smokers.<sup>(115, 116)</sup> Thus the recent prevalence must be considered in terms of the historical prevalence, and the substantial reductions that have taken place since the early 1970s.

**Figure 3.1 Prevalence and quantity of smoking in Irish adults by month, 2002 to 2016**



Note: HSE Smoking Prevalence Tracker data. Solid lines based on smoothing splines. The prevalence estimates from the HSE Smoking Prevalence Tracker are lower than those of the Healthy Ireland survey.

The Healthy Ireland and Smoking Tracker surveys do not collect information in relation to pregnancy and diagnosed mental health conditions, and therefore do not provide data on those distinct subgroups of the population.

There are a number of studies that provide data on the prevalence of smoking in pregnancy in an Irish population. The 'Growing Up in Ireland Longitudinal Study' collected data on smoking in pregnancy from mothers of a nine month old infant cohort born between December 2007 and June 2008,<sup>(117)</sup> and from mothers of a nine year old child cohort born between November 1997 and October 1998. Women may under-report smoking in pregnancy due to the associated stigma, so reporting bias may have been an issue for both cohort studies. The child cohort study reported that 28% of mothers smoked at some stage during the pregnancy,<sup>(118)</sup> but this rate fell to 18% in the later infant cohort study. The infant cohort study reported that 13% of mothers smoked during all three trimesters. Sixteen percent of women reported smoking in the first trimester of pregnancy, indicating that there was some degree of smoking cessation during the second and third trimesters.

A 2012 study of lifestyle changes in 718 women during pregnancy based at Cork University Maternity Hospital reported smoking prevalence of 23.9% before



pregnancy and 20.9% during pregnancy.<sup>(119)</sup> The study found smoking prevalence to be highest in younger mothers, although this may have been confounded by educational status. A 2011 study of pregnant women attending the Coombe Women and Infants University Hospital in Dublin reported a prevalence of 12.2% at the first antenatal visit.<sup>(120)</sup> The study found that there was little change in smoking behaviour between the first antenatal visit and the third trimester of pregnancy. A recent study published in February 2017 examined annual trends of maternal smoking reported at the first antenatal visit in the Coombe Women and Infants University Hospital over a five-year period.<sup>(121)</sup> The number of women who reported smoking at the first antenatal visit decreased from 14.3% in 2011 to 10.9% in 2015. These women were more likely to be younger, multiparous, unemployed and to have a history of mental health problems than women who did not report smoking at the first antenatal visit. They were also less likely to have planned their pregnancy than women who did not report smoking at the first antenatal visit. Smoking cessation interventions in pregnancy may need to be combined with other interventions because women who continued to smoke at the first antenatal visit reported high levels of alcohol intake and illicit drug use. It is important that women who smoke are identified at the first antenatal visit in order to be given the support they require to optimise not only their birth outcomes, but their long-term health and that of their infants.

Secondary analysis of the Growing Up in Ireland child cohort data, conducted by the Institute of Public Health in Ireland and the Tobacco Free Research Institute Ireland, reported an association between smoking in pregnancy and low birth weight (less than 2.5kg at birth).<sup>(122)</sup> Based on these data, 43.8% of women who reported having a low birth weight baby reported smoking in pregnancy, while 27.2% of women who reported having a normal birth weight baby (greater than or equal to 2.5kg) reported smoking in pregnancy. The median (interquartile range) birthweight of babies born to smoking mothers was 3.3kg (2.99kg to 3.7kg) while it was 3.6kg (3.2kg to 3.9kg) for babies born to non-smoking mothers. However, the observed difference did not reach statistical significance levels. In a separate analysis of the child cohort data, a statistically significant association between maternal smoking in pregnancy and attention deficit hyperactivity disorder (ADHD) in the nine year old child was reported.<sup>(118)</sup>

Data on smoking prevalence in those with mental health issues in Ireland are very limited. The 2015 Healthy Ireland survey recorded smoking status and whether the respondent had a probable mental health problem. The proportion classified as having a probable mental health problem was 6.3% for men and 14.4% for women. The prevalence of smoking was 35.2% in those with a probable mental health problem, in contrast to a prevalence of 21.5% in the rest of the population. The 2007 SLÁN survey collected information on mental health and smoking status,

reporting that smokers were more likely to report mental health problems than former or never smokers.<sup>(123)</sup> Smokers are almost twice as likely to report probable mental health problems, major depressive disorder, and generalised anxiety disorder compared with former and never smokers. The nature of the survey questions did not provide detailed psychiatric information, and hence it does not provide estimates of smoking prevalence in distinct groups such as those with schizophrenia or bipolar disorders.

A joint report by the UK Royal College of Physicians and Royal College of Psychiatrists reviewed the evidence on smoking and mental health.<sup>(124)</sup> Prevalence varied by subgroups, although they reported a prevalence of 37% for those with a longstanding mental health condition. Using data from 1993 to 2010, they reported that, while smoking prevalence was in decline in patients with no longstanding mental health condition, it had remained static in those with a longstanding mental health condition. Data from a 2007 Adult Psychiatric Morbidity Survey were highlighted, which indicated that 34.0% of adults reporting a common mental disorder were smokers. Further confirmation of a high prevalence of smoking in the mental population was suggested by 2009-2010 primary care data indicating a prevalence of 30.3% among adults with diagnosed mental disorders and those taking psychoactive medications. These figures were in the context of a smoking prevalence of 21% in the general population of England.

A review of US surveys found a smoking prevalence of 24.9% among adults with mental illness (operationalised as those reporting severe psychological distress, probable depression, or receiving treatment for mental illness).<sup>(125)</sup> However, smoking prevalence may vary substantially by specific condition and is noted to be correlated with the severity of the mental illness. For example, based on international data smoking prevalence in people with schizophrenia is approximately three times that of the general population.<sup>(91)</sup> A national health interview survey from the US considered specific conditions and found smoking prevalence of 46.4% for bipolar disorder, 59.1% for schizophrenia, 37.2% for hyperactivity, 35.4% for dementia, and 38.1% for serious psychological distress.<sup>(104)</sup> This was relative to a prevalence of 18.3% in people with no specified lifetime mental illness. Elsewhere, prevalence rates of 45% to 88% have been reported among people with schizophrenia, 33% to 70% in those with bipolar disorder, while those with depressive or anxiety disorders are noted to be more than twice as likely to smoke as those without.<sup>(106)</sup>

### **3.3.2 Types of tobacco products**

Based on the 2015 Healthy Ireland survey data, 78% of daily smokers use manufactured cigarettes, 24% use hand-rolled cigarettes, 1.3% use pipes and 0.7%

use cigars. Among daily smokers, 3% reported using two or more tobacco products, 92% of whom used a combination of manufactured and hand-rolled cigarettes.

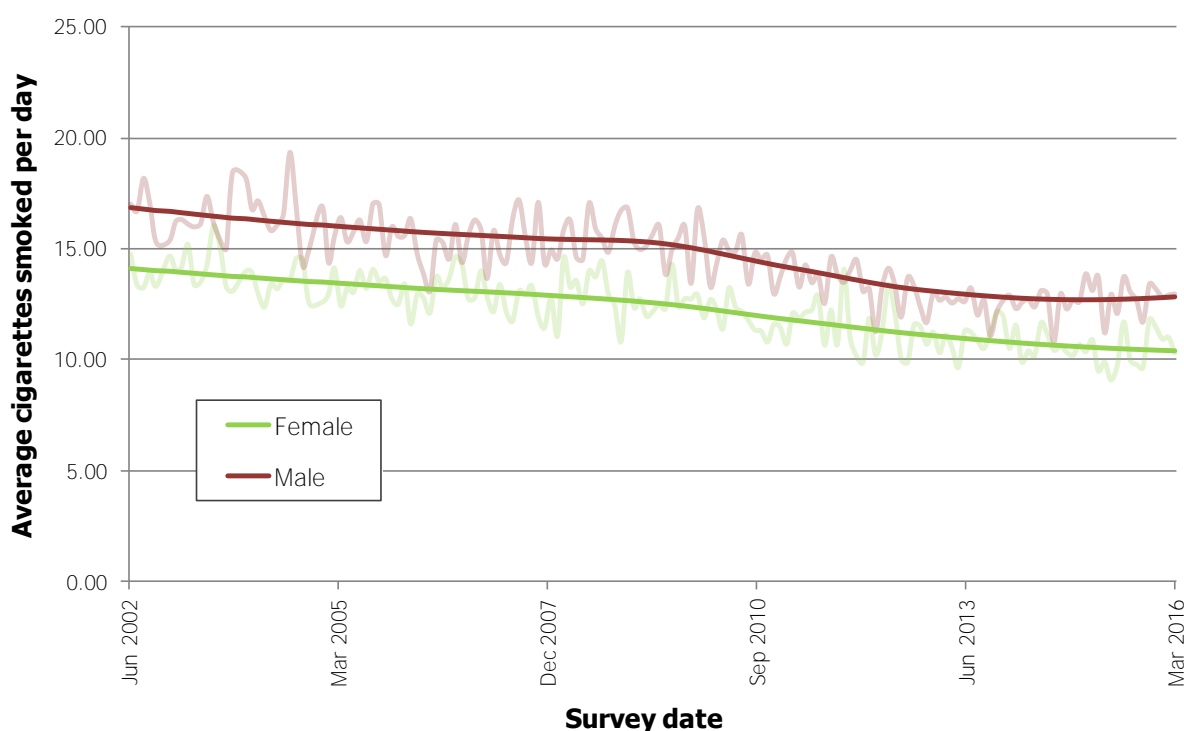
Product usage was similar in occasional smokers, with 82% using manufactured cigarettes, 19% using hand-rolled cigarettes, 0.9% using pipes, and 3.3% using cigars. Four percent of occasional smokers use more than one product, 74% of whom used a combination of manufactured and hand-rolled cigarettes.

### 3.3.3 Quantity of smoking

As there is a demonstrated dose-response relationship between quantity of smoking and attributable risk, it is useful to consider the number of cigarettes smoked in Ireland and how that figure has changed over time.

In 2002, data from the HSE Smoking Prevalence Tracking survey suggest the average number of cigarettes smoked per day in Ireland was 14.1 for females and 16.7 for males. Since then there has been a steady decline, with rates in the twelve months to March 2016 at approximately 10.3 cigarettes per day for females and 12.3 cigarettes per day for males (Figure 3.2). This corresponds with the estimates from the Healthy Ireland survey.

**Figure 3.2 Average number of cigarettes smoked per day by Irish adults, 2002 to 2016**



Note: HSE Smoking Prevalence Tracker survey data. Solid lines based on smoothing splines.

Despite the apparently low average number of cigarettes smoked per week, there is substantial variability in individual consumption. In both the HSE Smoking Prevalence Tracker survey and the Healthy Ireland Survey, some individuals report consumption in excess of 70 cigarettes per day. According to the Healthy Ireland survey data, one third (33%) of regular smokers of manufactured cigarettes consume 20 or more cigarettes per day.

Cigarette consumption is lowest in 15 to 24 year olds (9.7 cigarettes per day) and in upper middle and lower middle class groups (10.2 cigarettes per day) (see Table 3.5).

Cigarette consumption is higher in those using manufactured compared with hand-rolled cigarettes. In daily smokers, the average number of manufactured cigarettes consumed was 11 per day in contrast to 3.2 per day of hand-rolled cigarettes.

The Irish survey data do not give information on quantity of cigarettes consumed in pregnant women or those with mental health issues. Data from the Growing Up in Ireland study suggest that the number of cigarettes smoked per day during pregnancy ranged from seven, for those with the highest education, to 11, for those with the least education.<sup>(117)</sup> These data suggest that the quantity of cigarettes smoked during pregnancy is similar or slightly lower than that for unselected adult women. A US study showed that the number of cigarettes smoked increased with level of psychological distress, meaning those with mental health issues smoked more cigarettes on average than those with no mental health issues.<sup>(105)</sup>

### **3.4 Smoking cessation**

The data on attributable risks and mortality indicate a clear benefit for former smokers relative to current smokers, and therefore a clear benefit from smoking cessation. In 2015, based on data from the Healthy Ireland survey, 32% of daily smokers and 30% of occasional smokers were either trying to quit or actively planning to quit when asked.<sup>(64)</sup> A further 34% of daily smokers and 22% of occasional smokers were thinking about quitting but not planning to. Quitting often occurs with little planning: a substantial proportion of quit attempts by smokers motivated to quit are spur of the moment.<sup>(126)</sup>

An international study of over 21,000 smokers found that 40% of smokers report a quit attempt in a given year, and that there was an average of 2.1 quit attempts in this 40% in a year.<sup>(127)</sup> Another multi-country study including 2,431 smokers reported that 93% of participants had made previous quit attempts, and that the average number of previous quit attempts was 4.1.<sup>(128)</sup> However, the number of previous attempts is likely to be subject to recall bias, and could be substantially higher. A Canadian study estimated that the number of previous attempts was 6.3

based on recall by successful quitters, but that the true figure could be as high as 142 using alternative methods of estimation.<sup>(129)</sup> However, the latter figure was considered a probable over-estimate, and a more likely estimate was 29.6 quit attempts.

At any given time, the majority of smokers are thinking about quitting, and most have made multiple prior unsuccessful attempts to quit.

### **3.4.1 Harm reduction**

While there is evidence of a dose-response relationship between cigarettes consumed and risk of disease, substantial risk reduction can be achieved through cessation. For this reason, interventions can be distinguished on the basis of whether they are intended to reduce harm (for example, through reduced consumption) or intended to lead to permanent smoking cessation.

Thirty four percent of daily smokers and 48% of occasional smokers in Ireland were not considering quitting when asked in the 2015 Healthy Ireland survey. In the absence of a desire to quit, a policy of harm reduction through reduced consumption of cigarettes may be considered worthwhile from a public health perspective. However, there is little evidence to support the efficacy of this approach and it may not have any clinically relevant impact.<sup>(130)</sup> Despite fears that harm reduction may reduce willingness to attempt cessation, evidence suggests that it may improve the likelihood and success of quit attempts in the longer term.<sup>(128, 131)</sup> As noted however, this HTA focused on interventions aimed at increasing the probability of successful cessation in individuals making a quit attempt.

### **3.4.2 Methods used for cessation**

As described in Chapter 2, a wide range of interventions is available to support smokers attempting to quit. The interventions are intended to improve the likelihood of successful quitting over and above what can be achieved unassisted. A systematic review of studies of unassisted quit attempts found that the percentage of quit attempts that were unassisted ranged from 41% to 95%.<sup>(132)</sup> However, there was a clear temporal trend that the prevalence of quit attempts was declining over time, most likely due to the increasing availability of effective cessation aids. Those who choose to attempt quitting unassisted do so for many reasons, including autonomy and self-control, and it is likely that many smokers will continue to make quit attempts unassisted.<sup>(133)</sup> In fact, the majority of ex-smokers quit unassisted and the majority of current smokers will attempt to quit unassisted.<sup>(134)</sup>

An international review of tobacco dependence treatment guidelines found that 75% of high-income countries had treatment guidelines in place.<sup>(135)</sup> The main

interventions recommended in guidelines were brief advice (93%), intensive specialist support (93%), medications (96%), and telephone helplines (66%). Intensive specialist support was not clearly defined, but was assumed here to include counselling and behaviour support interventions. It is apparent that there is widespread support for most of the main therapies available.

The World Health Organization (WHO) Framework Convention on Tobacco Control (FCTC) requires Parties to the Convention (including Ireland) to take effective measures to promote smoking cessation.<sup>(136)</sup> A 2011 survey of countries found that only 56% of high-income countries promoted or encouraged brief advice in existing services.<sup>(137)</sup> Although 75% of high-income countries had a telephone quitline, only 36% had nationwide specialised tobacco dependence treatment facilities.

The extent to which different smoking cessation aids will be used in a population depends on numerous factors, including awareness, availability, acceptability, and cost. Quitlines, which are provided widely in high-income countries, may provide information of pharmacological cessation aids which may be available over-the-counter or require a prescription. Some of the nicotine replacement therapies (NRT), for example, are available for sale in general grocery and retail outlets and therefore do not require consultation with a healthcare practitioner prior to purchase. The need for a prescription and interaction with a clinician should ensure provision of brief advice and may increase the likelihood of accessing other supportive interventions. However, the need to consult with a clinician may also represent a barrier for some, on cost grounds or otherwise. Consultation with a clinician is also premeditated, and may not be as widely adopted amongst smokers making spontaneous quit attempts. The relative popularity of different pharmacological cessation aids has changed over time, and individual products may appeal differentially to different population subgroups.<sup>(138)</sup> Data from the UK indicate that the total number of pharmacological treatment items prescribed peaked in the year 2010 to 2011, and that the popularity of each of the three listed therapies (NRT, bupropion and varenicline) is declining.<sup>(139)</sup>

A recent and substantial change to the smoking cessation landscape has been the development of electronic nicotine delivery systems (ENDS) and electronic non-nicotine delivery systems (ENNDS), also known as e-cigarettes. As they are not a tobacco product, they are not subject to tobacco control legislation, and in many jurisdictions are therefore not expressly banned in indoor public spaces and can be advertised in mainstream media. Use of e-cigarettes is controversial for many reasons. There are concerns that they act as a gateway to cigarette smoking in adolescents, that the adverse effects and safety profile are not well known, and, as they are unregulated, the composition and effects of the inhaled vapour are not well known. Despite these concerns, e-cigarettes have become increasingly popular as an

aid to smoking cessation. Data on use of e-cigarettes for smoking cessation was first recorded in England in 2009, and was associated with less than 3% of quit attempts. Popularity began to grow in 2011 and by early 2016, approximately 40% of quit attempts in England involve the use of e-cigarettes. The increasing popularity of e-cigarettes coincides with a declining use of pharmacological aids, although the two patterns may be unrelated.

Both varenicline and bupropion are contraindicated in pregnant women, and, as nicotine may be harmful in pregnancy, there may also be some reluctance to prescribe NRT to pregnant women.<sup>(140)</sup> NRT is considered safer than tobacco smoke during pregnancy, but there may be a clinical preference for non-pharmacological smoking cessation interventions during pregnancy. A detailed assessment of the safety of smoking cessation interventions in pregnancy is presented in Chapter 5.

The prevalence of smoking is higher and successful quit rates are lower in people with mental health issues than in those without.<sup>(141)</sup> A US survey found that those with mental health issues were more likely than those without to use NRT and to receive advice.<sup>(142)</sup> The number of past quit attempts was similar in both groups. Enacting the Tobacco-Free Campus Policy was a key action of the Tobacco Control Framework 2010. There are a number of issues that complicate smoking cessation management in patients with mental health issues. As noted in Section 2.1.1.3, bupropion (Zyban®) is contraindicated in bipolar affective disorder as this antidepressant can precipitate a manic, mixed, or hypomanic episode. Warnings in relation to clinically significant neuropsychiatric events associated with varenicline administration in those with pre-existing psychiatric conditions were reversed in May 2016 by the European Medicines Agency. This followed the publication of safety and efficacy data from the EAGLES trial which found no increased incidence of adverse neuropsychiatric effects in patients with or without pre-existing psychiatric disorders. Cigarette smoking increases the metabolism of some antipsychotic drugs by inducing the cytochrome P450 enzyme system, resulting in lower therapeutic blood levels and decreased effectiveness.<sup>(91)</sup> Smoking cessation must be accompanied by a review of **a patient's medication to avoid the risk of adverse effects due to overdosing.** The safety of smoking cessation interventions in the mental health population is assessed in detail in Chapter 5.

### **3.4.3 Predictors of successful cessation**

There is a substantial body of literature regarding the clinical effectiveness of different smoking cessation interventions, and is reviewed in Chapter 4. Estimates of clinical effectiveness are preferably derived from randomised controlled trials (RCTs) and provide data on how well an intervention might work under ideal conditions of adherence and compliance to therapy. An alternative approach is to review



observational data, such as surveys, to determine the factors that influence successful quit attempts. The major distinction is that in surveys, respondents have not been randomised to different smoking cessation interventions, but have self-selected to participate. This means measures of effectiveness will be confounded by other factors and individual characteristics such as motivation to quit. For example, analysis of the data from the adult Special Eurobarometer for Tobacco survey demonstrated that the percentage of adults reporting having ever used an e-cigarette increased from 7.2% in 2012 to 11.6% in 27 EU member states in 2014.<sup>(24)</sup> Certain groups were found to be more likely to have tried e-cigarettes (younger age, living in urban areas and higher educational level).<sup>(24)</sup> Further analysis from this survey, based on all 28 member states, found that 10.6% of those who had ever attempted to quit smoking, and 27.4% of those who did so using a cessation aid, had experimented with e-cigarettes as a cessation aid.

Unassisted quitting was common — 61.4% of current and ex-smokers who had ever attempted to quit reported not using any cessation aid. However, experimentation with e-cigarettes as a cessation aid was noted to have more than doubled in just two years, with 43.6% of current smokers reporting its use as an aid in 2014. Use for this purpose was more common among younger smokers (aged 15 to 24 years) compared with those aged 55 years and older (odds ratio (OR) 5.29) and those who reported financial difficulties (OR 1.33). While use of e-cigarettes as a potential cessation aid has increased, half (50.7%) of those who did so reported that they did not help them reduce smoking or that they smoked more after trying them. Those with a higher educational level were more likely to self-report being successful (OR 2.23).<sup>(143)</sup>

An analysis of survey data on quit attempts in the US, UK, Canada and Australia found that using medication to support a quit attempt was not predictive of abstinence at six months after adjusting for age, sex, socio-economic status and level of nicotine dependence.<sup>(126)</sup> The same study found that reducing smoking to quit was more predictive of abstinence than abrupt quitting. Those with moderate or high nicotine dependence were less likely to have successfully quit than those with low dependence.

An Australian study assessed the success rate of quitting smoking for a range of cessation interventions.<sup>(144)</sup> Based on data after the introduction of bupropion, the success rate was 40.2% for no help, 20.8% for bupropion, 39.0% for GP support, 21.5% for nicotine patches, and 11.4% for nicotine gum. Individual characteristics such as age and socio-economic status were not accounted for in the analysis.

A large observational study of over 46,000 supported quit attempts in the UK found that those using medication were more likely to successfully quit at four weeks than



those using no medication.<sup>(145)</sup> Male clients and those paying for a prescription were more likely to succeed. However, when heaviness of smoking was taken into account, single NRT was no longer associated with a higher quit rate relative to no medication. It should be noted that as the standard treatment course for varenicline and bupropion is 12 weeks and seven to nine weeks, respectively, the quit rate at six or 12 months would be more meaningful than the quit rate at four weeks.

A systematic review of 17 articles examining predictors of quit attempts and successful quitting provides information on the heterogeneity in study findings.<sup>(146)</sup> For example, some studies reported that older smokers were more likely to have made a quit attempt while other studies found the reverse. Some of the more consistent findings included a negative correlation between cigarette consumption and quit attempts, and that past quit attempts predicted future quit attempts. There was some evidence to suggest that people of higher socio-economic status were more likely to succeed in quitting, as were people with lower levels of nicotine dependence. There is a potentially complex relationship between history of quit attempts and successful quitting, in that some studies found a negative association. It is possible that some smokers make many quit attempts without utilising appropriate supports or learning from previous failures.

Observational studies tend to be impacted by a number of important confounders, and the results may not be applicable to other settings. The choice of smoking cessation therapy may be strongly linked to both individual characteristics and wider issues such as affordability and ease of access. As such, it is important to consider the available data for Ireland.

#### **3.4.4 Smoking cessation in Ireland**

There is a wide range of smoking cessation supports available through the health services in Ireland. These include brief interventions, pharmacological therapies, counselling, online and social media supports, quitline services, courses, and specialist quit clinics.<sup>(147)</sup> Tobacco cessation services are available nationwide from trained health professionals who provide behavioural support to those attempting to quit. The service is intended to provide structured support either through individual or group sessions, and the service can also be accessed through telephone or online support. A full description of the organisation of quit services in Ireland is provided in Chapter 7.

Data supplied by 12 HSE smoking cessation service providers show that of almost 3,000 people accessing those providers in 2015, three out of four (75%) had a Medical Card. In the period 2013 to 2015, the providers experienced a 13% increase in the number of clients attending. Data were also provided on people that undertook a pre-quit consultation in the period January 2015 to early June 2016. In

the 17 month period there were 1,943 interactions with the service. There was substantial regional variation in the uptake of this particular service.

The 2015 Healthy Ireland survey collected data on quit attempts in the last 12 months by current and former smokers. Of current smokers or those that had smoked within the previous 12 months, half (50.0%) had stopped smoking for a day or more in the previous 12 months as part of an attempt to quit smoking. Within the survey, respondents could report the cessation approach they took, choosing from the **range of options outlined in Table 3.6. The option of 'no help'** was interpreted here as using willpower alone. A total of 13.4% of respondents reported making a quit attempt in the 12 months leading up to the survey. The most common approach, used by half (50%) of respondents, was to have no help, followed by e-cigarettes (29%) and NRT (12%) (Table 3.6).

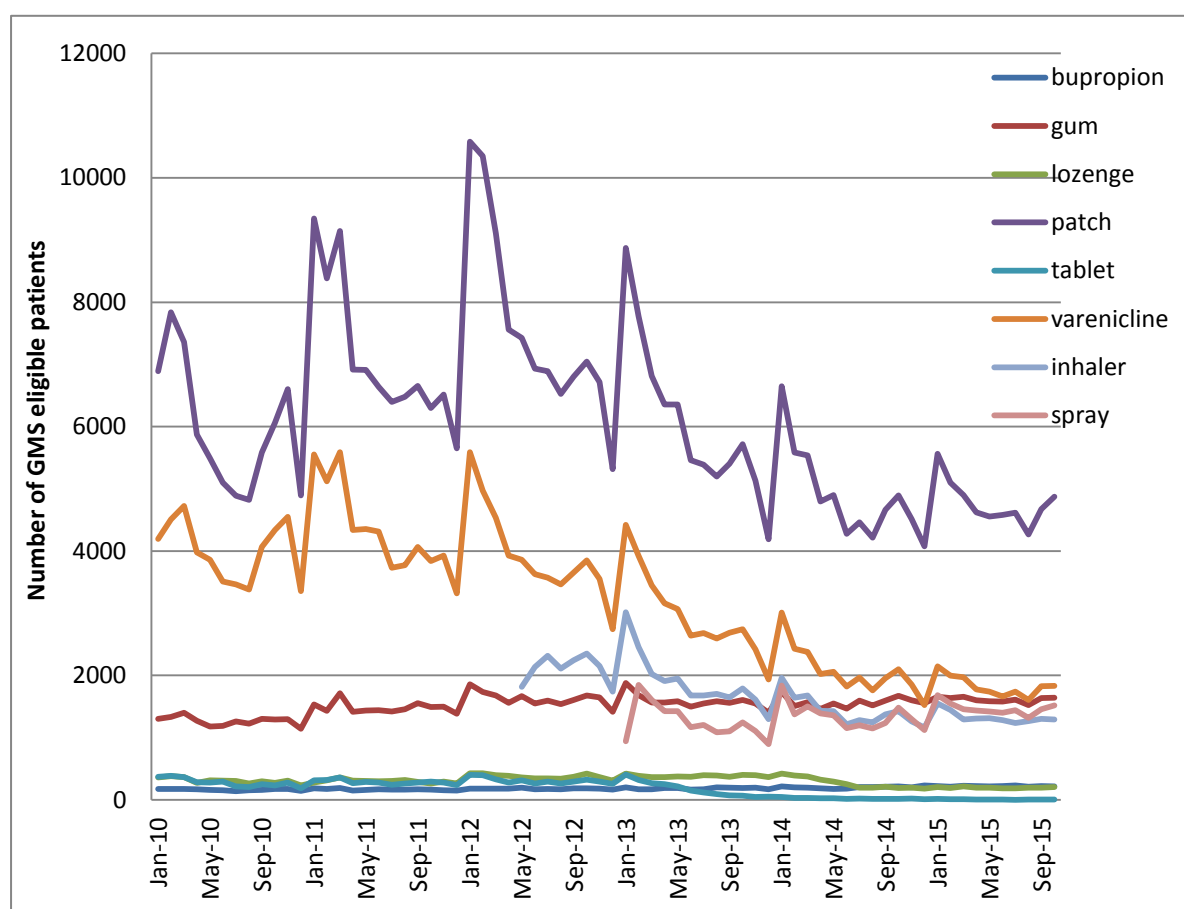
**Table 3.6 Use of different smoking cessation supports in Ireland Healthy Ireland Survey 2015)**

Help used in quitting	Percentage	Population*
No help used	50.3%	242,858
E-cigarettes	28.7%	138,389
NRT (Nicotine patches, gum, lozenges, spray)	12.0%	57,725
Varenicline(Champix®) or bupropion (Zyban™)	3.5%	17,051
Other aid, help, support	2.7%	12,805
www.quit.ie	1.0%	4,642
Acupuncture	0.6%	3,030
Smokers telephone Quitline/Helpline	0.1%	663
www.facebook.com/HSEquit	0.1%	542

\* Estimated number of people who used this intervention in a period of 12 months

The Healthy Ireland results do not provide a further breakdown within product categories to give the relative popularity of products within a group. The number of eligible Medical Card holders redeeming prescriptions for a variety of smoking cessation products was used to estimate the relative popularity of NRT, varenicline and bupropion (Figure 3.3). Half (50.8%) of NRT prescriptions were for patches, 17.4% for gum, 15.4% for sprays, and 14.2% for inhalers. The remaining 2.2% were for lozenges and tablets. In terms of prescriptions for the other pharmacological cessation aids, 89.2% were for varenicline and 10.8% for bupropion. In other words, there were just over eight people prescribed varenicline for every one patient prescribed bupropion.

**Figure 3.3 Trends in redemption of prescriptions for NRT and other smoking cessation products by Medical Card holders, 2010 to 2015**



Index: Six different formulations of nicotine replacement therapy (NRT) are included: gum, lozenge, patch, tablet, inhaler and spray.

Between January 2010 to October 2015, the total expenditure by the HSE on prescribed smoking cessation products for Medical Card holders was €46.64 million. Annual expenditure for this cohort peaked in 2012 at €9.38 million, declining to €6.96 million in 2014. Intervention costs depend on the cost of the individual product and the duration of treatment.

Primary Care Reimbursement Service (PCRS) data for Medical Card holders indicate that the average duration of bupropion prescriptions was 119 days (median 37 days) for the period 2010 to 2014, while for varenicline it was 65 days (median 28) and 51 days (median 28) for NRT patches. As noted in Chapter 2.1.1.3, the recommended treatment course for bupropion is nine weeks while that of varenicline is 12 weeks. Prescriptions for Medical Card holders are typically dispensed in one month aliquots. Using gaps of at least 90 days to indicate a new treatment episode, PCRS data from 2010 to 2014 suggest that 53% of bupropion treatment episodes and 62% of

treatment episodes were for a period of six weeks or less. It is not known if the failure to redeem additional prescriptions was because patients had successfully quit smoking and no longer needed support, or that treatment was discontinued due to lack of effect or intolerance. Again, assuming a gap of at least 90 days to indicate a switch to therapy, data from the period 2010 to 2015 indicates that 8% of patients switched therapies, with switches from varenicline to NRT patch (28%) and from NRT patches to varenicline (21%) being the most common switches made.

The Healthy Ireland survey comprises data for a mix of current and former smokers, allowing the factors associated with successful quit attempts to be assessed. In analysing these data, it must be noted the sample size is relative small. Those self-reporting as former smokers may only have quit recently, and are at substantial risk of relapse. Furthermore, there are no data on quantity of smoking for respondents classified as former smokers. Using a logistic regression model to analyse the data, the Evaluation Team estimated the probability of quitting as a function of age, gender, Medical Card status, area deprivation, and method of quitting. Women are more likely to succeed in a quit attempt, as are younger people, although age and gender were not statistically significant predictors. Those with no Medical Card and those from less deprived areas were more likely to have succeeded in quitting, and in both cases the coefficients were statistically significant.

Medical Card status can act as a socio-economic indicator, but the fact that it remains a significant predictor after adjusting for deprivation is noteworthy. The majority of the cost of prescriptions for Medical Card holders is absorbed by the HSE. **Patients pay a €2.50 charge per item, with a maximum charge of €25 per family per month.**<sup>(11)</sup> The cost of treatment should therefore not be a barrier to Medical Card holders, and yet Medical Card holders have a lower quit success rate. Due to the reported low uptake of some smoking cessation supports (for example, acupuncture and quit services), the coefficients associated with those supports are subject to substantial error. However, a hierarchy can be observed for the other supports. Relative to NRT, using no help or e-cigarettes are both statistically significantly associated with a greater likelihood of quitting. Pharmaceutical supports (varenicline and bupropion) are associated with a non-statistically significant increased likelihood of quitting, and other unspecified supports are associated with a statistically significant increased likelihood of quitting relative to NRT. Although the model had a classification accuracy of 78%, the area under the receiver-operator characteristic curve was 0.63, indicating relatively poor predictive power. It is also important to remember that smokers self-select what cessation supports they may avail of.

The study of pregnant women at the Coombe Women and Infants University Hospital in Dublin recorded information on attempts to quit during pregnancy.<sup>(120)</sup> Change in smoking status was recorded at the booking interview compared with six

months previously. Of those who attempted to quit, 81% used no help, and 12.5% used NRT. Seventy two percent of those who used no help classified themselves as an ex-smoker, compared with 17% of those who used NRT.

No data were retrieved in relation to use of smoking cessation interventions in those with serious mental health conditions in Ireland. International data suggest that the decline in prevalence of smoking in the general population has not been matched in those with serious and enduring mental illnesses. It is known that cognitive deficits coupled with disorganised thinking and poor task persistence and a higher prevalence of depression and substance misuse may contribute to a lower motivation to stop smoking for smokers with schizophrenia. However, according to international research, the sustained high prevalence of smoking in this cohort has partly been attributed to a failure of providers to offer smoking cessation interventions and advice to those with serious mental illness, despite emerging evidence that those with serious mental illness are motivated to quit and can achieve comparable abstinence rates to those without comorbid psychiatric disease in clinical trial settings.<sup>(88, 107, 148)</sup>

### **3.4.5 E-cigarette use in Ireland**

Although e-cigarettes have been available since the mid-2000s, acknowledgement of their use in smoking cessation is more recent. The English smoking statistics have recorded data on e-cigarette use for cessation since 2009. Since August 2014, the HSE Smoking Prevalence Tracker survey has included a question on e-cigarette usage. Based on this data, the proportion of the population in Ireland using e-cigarettes has been relatively stable from August 2014 to March 2016, with between two and three percent of the population aged over 15 years using them on a daily basis, and between one and three percent using them less than daily. Market penetration therefore appears to be relatively stable.

From the Healthy Ireland survey data it is apparent that e-cigarettes have become a popular aid for smoking cessation, with almost 29% of quit attempts supported through e-cigarette usage. Unfortunately, these data on e-cigarette use in cessation are limited to a snapshot, and it is therefore not possible to analyse the trends in relation to cessation in Ireland. UK data suggest the use of e-cigarettes for cessation is increasing. Almost all (98%) of e-cigarette users are smokers and former smokers, with the prevalence of e-cigarette usage at approximately 6% in both groups. There is no evidence to suggest that the quantity of cigarettes smoked is less in smokers who also use e-cigarettes compared with smokers who do not use e-cigarettes. Seventy one percent of current smokers who also use e-cigarettes attempted quitting in the previous 12 months, compared with 43% of current smokers who do not use e-cigarettes. Similarly, 66% of current smokers who also use e-cigarettes

are either trying to or actively planning to quit, compared with 30% of smokers who do not use e-cigarettes. It is not possible to state whether the higher intention to quit and likelihood of a quit attempt in the previous 12 months is associated with e-cigarette use or whether it reflects demographic or other factors of the cohort who are more likely to use e-cigarettes.

E-cigarettes are not provided through the health services, so it is possible that they are not being used in conjunction with specialist advice on smoking cessation. Data from the UK show use of e-cigarettes as a smoking cessation support is increasing, but that use of pharmacological therapies and GP-triggered quit attempts are decreasing. It was not possible to determine the extent to which these trends are related or whether they reflect the changing demographics of the cohort of smokers.

### **3.4.6 Inequalities in smoking cessation**

The HSE Smoking Prevalence Tracker and Healthy Ireland survey data include data on socio-economic status of individuals. Table 3.5 shows that there is a socio-economic gradient in smoking, with a higher prevalence of smoking in lower socio-economic groups. The higher rate of smoking persists after adjusting for age, sex, and Medical Card status. The average number of cigarettes smoked per day also increases with lower socio-economic status. The higher prevalence and intensity of smoking in people with lower socio-economic status creates challenges for smoking cessation services.

Inequalities in smoking cessation, whereby people with lower socio-economic status are less successful at quitting, have been widely studied. An analysis of smoking cessation across Europe found that inequalities increased in the 2000s.<sup>(149)</sup> Of the 11 countries analysed, the largest increase in inequalities between 2002 and 2012 was observed in Ireland. The findings of the study suggest that cessation rates in low socio-economic groups stabilised at the end of the 1990s whereas they have continued to increase in high socio-economic status groups. Data from the International Tobacco Control Four Country Survey, comprising survey data among smokers in Canada, the US, the UK, and Australia, indicates that those of moderate and high education and income levels are more likely to be planning to quit than those of low education and income level. Furthermore, those with a high education level are more likely to have attempted to quit than those of low education status.

A UK study analysed the completion and success of over 550,000 quit attempts in relation to neighbourhood deprivation and individual characteristics.<sup>(150)</sup> After adjusting for age, sex, occupation, nicotine dependence and intervention characteristics, higher neighbourhood deprivation was associated with a lower likelihood of treatment completion and of successful quitting. Reduced success was not fully explained by reduced completion of treatment, indicating that other factors

also affect successful quitting. The study highlighted the need for ensuring that smokers in the most deprived areas receive the most effective interventions to maximise the likelihood of successful quitting.

Some tobacco control policies, not limited to cessation interventions, may contribute to increasing cessation inequalities. For example, workplace smoking bans have been found to have a neutral or negative impact on cessation inequalities.<sup>(149)</sup> Socio-economic inequalities in cessation may therefore be due to a range of factors including difficulties accessing services, barriers to completion of treatment, and lower probability of success due to higher nicotine dependency. Some of the inequalities may be addressed by ensuring equitable access to smoking cessation services. One proposed method to combat cessation inequalities is to incorporate an equity element into performance measurement in the quit services.<sup>(151)</sup>

An increase in cessation inequalities does not imply that cessation has declined in those of lower socio-economic status. Cessation can increase in all groups, but a higher rate of cessation in those of higher socio-economic status is resulting in greater disparity. Increased inequalities may be due to higher motivation to quit in more affluent individuals combined with fewer barriers to accessing effective interventions. Achieving a reduction in cessation inequalities may require substantial positive inequalities in access to cessation services. On the basis of the data from the sample of Irish smoking cessation services, the disproportionate number of GMS clients suggests the presence of a positive inequality in access. It should be borne in mind that 79% of quit attempts do not involve State-supported interventions, as they involve either no support or the use of e-cigarettes. An effort to reduce cessation inequalities will require other approaches to be considered to reduce barriers to successful quitting, such as increasing motivation to quit, providing interventions not currently reimbursed, or providing them free at the point of care.

### **3.5 Discussion**

This chapter has reviewed some of the key epidemiological issues in relation to smoking and smoking cessation, with particular attention to the prevalence of smoking in Ireland and the current approach to cessation.

Cigarette smoking can have major implications for the health of both current smokers, former smokers, and those exposed to second-hand smoke. Cigarette smoking results in a significant burden on morbidity and mortality, with implications for quality of life and health service utilisation. Smoking cessation substantially reduces the risk of disease and can, over time, result in relative risks similar to that of people who have never smoked for a range of conditions.



The prevalence of smoking in Ireland has been in long-term decline. The extent to which that decline will continue without changes to service provision is difficult to determine. As prevalence declines, it is possible that the remaining cohort of smokers comprises those with high nicotine dependence and, or those who face barriers to accessing effective services. The inequalities in smoking cessation are such that smoking prevalence is highest and successful quit attempts are lowest for smokers in the lowest socio-economic groups. As the overall prevalence of smoking declines, and the rate of new smokers also declines, the demography of current smokers will shift. This may require different approaches to cessation services in terms of both how they are delivered, and which interventions are provided or favoured.

Data from the Healthy Ireland survey provide information on smoking behaviour and quit attempts in the Irish population. Ninety one percent of quit attempts use either **'no help' (50%)**, e-cigarettes (29%), or NRT (12%). A brief analysis suggested that those with no Medical Card and those from less deprived areas were more likely to have succeeded in quitting. These data also suggest that when compared with NRT, using no help, e-cigarettes, and other unspecified supports are associated with a greater likelihood of quitting. Pharmaceutical supports (varenicline and bupropion) are associated with a non-statistically significant increased likelihood of quitting.

It must be noted that smokers self-select what supports they will use when attempting to quit, and those using particular supports may have a higher likelihood of success irrespective of the intervention used. However, evidence suggests that there may be issues of compliance and completion of therapy in certain subgroups, and this should be considered when evaluating the applicability of clinical effectiveness data.

The Healthy Ireland data on cessation interventions used in Ireland does not provide information on what those interventions involve. For example, it is unclear what proportion of people using NRT is also provided with advice or counselling. Variability in how patients access therapies and what those therapies include may also contribute to reduced effectiveness relative to trial data.

The fact that half of quit attempts are made without support is noteworthy and echoes what has been observed in other countries. The use of no support may not capture what interventions those people have used on previous quit attempts. Most smokers attempt to quit, and most do so more than once a year. Over time, smokers will typically make many attempts to quit before succeeding. Those who make attempts without support may have used support previously and are therefore not necessarily without knowledge or understanding of what is involved. It is also



possible that some smokers may classify brief advice as no support, although there is no evidence to confirm or refute this.

There have been numerous legislative or policy interventions in Ireland to reduce the exposure to smoke and smoking, such as the bans on advertising, sales to minors, workplace smoking, and smoking in cars carrying minors. These policies are likely to have impacted on smoking either by stimulating quit attempts or by reducing the quantity of cigarettes smoked. These population-level interventions ultimately support a move to a tobacco-free country. The interventions considered in this report were those that support successful smoking cessation in individuals. As such, the individual-level factors that impact on successful quitting should be taken into account when considering how cessation services might be provided and organised to maximise successful cessation.

### **3.6 Key messages**

- There is a direct causal link between smoking and numerous diseases including a range of cancers, and respiratory and circulatory diseases. Smoking increases the risk of acquiring these diseases. While smoking cessation reduces the risk of these diseases, former smokers continue to have an elevated risk of disease compared to those who have never smoked.
- Smoking causes disease through the inhalation of cigarette smoke, which contains over 70 carcinogens. Cigarette smoke can be inhaled directly through smoking or second-hand through environmental tobacco smoke, such as the smoke produced by a smouldering cigarette.
- Using estimates of the proportion of disease attributable to smoking, each year in Ireland approximately 29,000 inpatient discharges and 11,000 day cases are due to smoking.
- Smoking is associated with an increased risk of mortality. More than 5,400 deaths in Ireland each year are due to smoking. When deaths due to second-hand smoke are included, approximately 20.5% of deaths each year are due to tobacco smoke.
- Smoking during pregnancy is harmful. It is associated with an increased risk of congenital anomalies, preterm birth, intrauterine fetal growth restriction, placental abruption, stillbirth, sudden infant death syndrome, respiratory infection, adverse cognitive and behavioural outcomes in infancy and the development of chronic disease in adulthood.
- Smokers with mental health disorders smoke more heavily, are more nicotine dependent, and have smoked for longer than the general population. The factors linking mental health conditions and cigarette smoking are varied and complex. Recent evidence suggests that quitting smoking may improve mental health symptoms.

- The prevalence of smoking in Ireland is 22.7% in people aged 15 years and over. The prevalence is higher in men (24.3%) than in women (21.2%), and in people aged 25 to 29 years (33.4%). Smoking prevalence follows a socio-economic gradient, whereby the prevalence is highest in those of the lowest socio-economic group.
- There are limited Irish data regarding the prevalence of smoking in pregnancy and in those with mental health disorders. Smoking prevalence is noted to be correlated with the severity of the mental illness, with prevalence rates of 33% to 70% and 45% to 88% reported for those with bipolar disorder and schizophrenia, respectively.
- Data tracking smoking behaviour in Ireland shows that the prevalence of smoking in Ireland and the quantity of cigarettes smoked has been in decline over the last decade, continuing the long-term trend for reducing prevalence.
- At any given time, the majority of smokers are thinking about quitting, and most have made multiple prior unsuccessful attempts to quit. In Ireland, half of those attempting to quit do so unaided. A further 29% of smokers trying to quit use e-cigarettes (alone or in combination with another intervention) as an aid. Approximately 16% of quit attempts are made using some form of pharmacotherapy (for example, nicotine replacement therapy).

## 4 Clinical effectiveness

This chapter summarises the available evidence on the clinical effectiveness of each of the smoking cessation interventions included in this health technology assessment (HTA). Effectiveness was considered using the outcome of long-term (greater than or equal to six months) smoking cessation. This assessment focused on the unselected adult smokers population, which is the group broadly targeted by national quit campaigns and which accounts for the majority of those utilising existing smoking cessation services. Other subgroups of interest that were examined separately include pregnant women and those accessing secondary mental health services. Safety considerations are reviewed separately in Chapter 5.

Much has been done to combine the substantial amount of scientific evidence on smoking cessation interventions that has been generated over the last number of decades, particularly through the efforts of the Cochrane Tobacco Addiction Group (TAG).<sup>(152)</sup> This HTA considered this work in order to estimate the relative effectiveness of the interventions of interest. High-quality reviews were used, where appropriate, to identify relevant studies to include in this HTA.

### 4.1 Methods

#### 4.1.1 Criteria for considering studies for this review

##### 4.1.1.1 Types of studies

Randomised controlled trials (RCTs) were considered in this review.

##### 4.1.1.2 Types of participants

The primary population of interest in this analysis is unselected adult smokers. Two additional populations were considered: users of secondary mental health services and pregnant women.

The study populations are described as follows:

- Unselected adult smokers

Adult smokers (aged 18 years or older) drawn from a general population, rather than being defined by a particular diagnosis (for example, schizophrenia, chronic obstructive pulmonary disease (COPD), and so on), or recruited from a population attending services for people with a particular disease or range of diseases (for example, cardiovascular wards, pre-operative patients, and so on).

- Users of secondary mental health services

Smokers aged 18 years or older who are users of secondary mental health services. These typically include patients with psychotic disorders, schizophrenia or schizoaffective disorder, current depression or bipolar disorder.

- Pregnant women

Women, not limited to those aged 18 and above, who smoke during pregnancy. Participants could be recruited in any trimester of pregnancy.

#### 4.1.1.3 Types of interventions

As noted in Chapter 2, given the vast array of treatments that could potentially be provided to individual smokers, it was necessary to prioritise those that are most relevant to policy makers, patients and the Irish health system. To identify treatments for inclusion in this HTA, recently published overviews of the area were combined with data on the most commonly used treatments in Ireland and advice from the Expert Advisory Group.

Studies were eligible for inclusion if they compared any of the following interventions with either no treatment (or placebo) or another eligible intervention:

- nicotine replacement therapy (NRT) such as chewing gum, transdermal patches, nasal and oral spray, inhalers, tablets and lozenges, as monotherapy or combination (dual) therapy
- electronic cigarettes, or e-cigarettes
- nicotine receptor partial agonists (cytisine or varenicline only)
- antidepressants (bupropion only)
- motivational interviewing
- brief physician advice
- telephone-based interventions
- mobile phone-based interventions
- Internet-based interventions
- individual behaviour counselling
- group behaviour therapy
- acupuncture
- Allen Carr method
- financial incentives (for pregnant women only).

The interventions can be broadly grouped into pharmacological and behavioural interventions. An individual attempting to quit smoking may use multiple interventions in a single quit attempt, or combine pharmacological and behavioural interventions. Studies that assessed the provision of multiple interventions were included.

#### 4.1.1.4 Types of outcome measures

For studies of unselected adults and users of secondary mental health services, the primary outcome of interest was long-term smoking cessation rates, as indicated by quit rates at greater than or equal to six months ( $\geq 6$  months). Biochemically verified results were preferred to self reports, and continuous or prolonged abstinence was preferred to abstinence at a particular point in time (point prevalence abstinence). Analyses were based on intention-to-treat (ITT) principles; this means that participants lost to follow up who could not definitively be classified as non-smokers were counted as smokers. Participants were retained in the groups to which they were randomised irrespective of adherence.

For studies of pregnant women, the primary outcome of interest was abstinence from smoking during pregnancy, measured at the latest point prior to birth. Continuous abstinence measures timed from the date of randomisation, where available, were used in preference to point prevalence abstinence (7-day or 30-day abstinence) measures. Biochemically validated abstinence data, where available, were used in preference to self-reported data.

Adverse outcomes are considered separately in Chapter 5 Safety.

As noted in Chapter 2, this HTA does not examine the impact of treatments in terms of any potential harm reduction associated with their use, such as helping people to reduce the number of cigarettes smoked per day, or reducing exposure to second-hand smoke, or as relapse prevention measures. Neither does it extend to examining the relative effectiveness of different patient recruitment strategies that may be employed with various treatment modalities.

#### 4.1.2 Search methods for identification of studies

Searches were carried out for recent Cochrane systematic reviews of eligible smoking cessation interventions in populations which could be compared with Ireland. Where Cochrane systematic reviews were available for relevant interventions, these were used to identify studies matching the inclusion criteria outlined above. The Cochrane reviews were updated to identify any additional studies that had emerged since the original review was published. Systematic reviews published through the Cochrane Collaboration are recognised as being of

high quality. In the absence of a Cochrane systematic review for a given intervention, Medline and Embase were searched for relevant systematic reviews.

Where no previous Cochrane or other high-quality systematic review was available for an intervention, electronic searches were conducted in Medline, Embase and the Cochrane Register of Controlled Trials to identify RCTs comparing that intervention with another eligible intervention or no treatment. Table 4.1 outlines the PICOS criteria (population, intervention, comparator, outcome, study design) for study eligibility for unselected adults.

**Table 4.1 PICOS criteria for study eligibility – unselected adults**

<b>Population</b>	Adult smokers (aged 18 years or older) drawn from a general population, rather than being defined by a particular diagnosis (for example schizophrenia, COPD), or recruited from a population attending services for people with a particular disease or range of diseases (for example, cardiovascular wards, pre-operative patients, and so on).
<b>Intervention</b>	<ul style="list-style-type: none"> <li>■ nicotine replacement therapy (NRT), such as chewing gum, transdermal patches, nasal and oral spray, inhalers, tablets and lozenges, used as monotherapy or combination (dual) therapy</li> <li>■ electronic cigarettes, e-cigarettes</li> <li>■ nicotine receptor partial agonists (cytisine or varenicline only)</li> <li>■ antidepressants (bupropion only)</li> <li>■ motivational interviewing</li> <li>■ brief physician advice</li> <li>■ telephone-based interventions</li> <li>■ mobile phone-based interventions</li> <li>■ Internet-based interventions</li> <li>■ individual behaviour counselling</li> <li>■ group behaviour therapy</li> <li>■ acupuncture</li> <li>■ Allen Carr method.</li> </ul>
<b>Comparator</b>	No treatment (or placebo) or another eligible intervention.
<b>Outcomes</b>	Primary outcome of interest was long-term smoking cessation rates, as indicated by quit rates at greater than or equal to six months ( $\geq 6$ months). Biochemically verified

	results were preferred to self-reports, and continuous or prolonged abstinence was preferred to abstinence at a particular point in time.
<b>Study design</b>	Randomised controlled trials.

### 4.1.3 Data collection and analysis

#### 4.1.3.1 Identification and selection of systematic reviews

Given the volume of systematic reviews available, the initial search was restricted to the Cochrane library to identify reviews of interventions of interest. While potentially more up-to-date reviews of the same intervention may have been available, this HTA used the relevant Cochrane reviews as a basis for identifying studies that matched our inclusion criteria and updated these reviews where appropriate. This decision was based on the following criteria:

- the approach to systematic reviewing used by the Cochrane group is identified in national guidelines<sup>(153)</sup> as representing best practice;
- the reviews identified used inclusion and exclusion criteria (based on included study designs, populations, follow up, and outcomes) that encompassed those relevant to this assessment;
- the risk of bias assessment using the Cochrane Risk of Bias tool was reported for each of the randomised controlled trials (RCTs) included;
- and the quality of the reviews were rated as good (or more favourable than other reviews for the same population and, or intervention).

De novo quality assessment of the Cochrane reviews was not undertaken, as a quality rating of each of the reviews identified was reported in a 2015 review of reviews of behavioural and pharmacotherapy interventions for tobacco cessation for the US Preventive Services Task Force.<sup>(154)</sup> These quality assessments, which used a modified version of the Assessing the Methodological Quality of Systematic Reviews (AMSTAR) tool to quality rate the reviews, were accepted for use in this report on the basis that they met best practice.

#### 4.1.3.2 Selection of studies

Where an existing high-quality systematic review existed for a given intervention, all included studies were re-assessed using **this HTA's** inclusion criteria to identify relevant studies.

For search updates or de novo searches to identify new studies not included in these reviews, all returned citations were first screened by one reviewer to eliminate

clearly irrelevant studies. Two people then independently reviewed the remaining citations per the inclusion criteria, with any disagreements being resolved by discussion, or, if necessary, a third reviewer.

#### 4.1.3.3 Data extraction and management

Data extraction from newly identified study reports was carried out independently by two people to reduce the likelihood of errors, with any disagreements being resolved by discussion or a third reviewer, if necessary.

Where the HTA updated a previous systematic review, data were extracted from the systematic review rather than from the primary studies. In general, if the data extraction method used in the review was consistent with that which would have been used had an original search been conducted (that is, extracted independently by two people and cross checked, as above), re-extraction of the primary study data was not performed unless there was a specific reason to warrant it. For example, in some cases, two systematic reviews might report different numbers for the same study. Data for these studies were re-extracted independently by two reviewers, with any inconsistencies resolved through discussion or via a third party.

For quality assurance purposes, a random sample of one in 10 studies was selected from the systematic reviews and data extraction from the primary studies was carried out. By comparing the data extraction from the primary studies to the data presented in the systematic reviews, it was possible to determine if there were any inconsistencies.

#### 4.1.3.4 Assessment of risk of bias in included studies

Risk of bias was assessed using the Cochrane risk of bias tool for randomised controlled trials. This was performed on all reports of studies by two people independently, with any disagreement being resolved by discussion or a third party.

Where the HTA updated a previous systematic review that used the Cochrane risk of bias tool, an assessment of the quality and rigour of that systematic review was carried out to decide if re-assessment was necessary. If the review used a different method of assessing risk of bias, then the risk of bias analysis was carried out again using the Cochrane approach.

For all interventions, small study bias was assessed using a funnel plot in combination with multiple tests for asymmetry (including the **Harbord and Egger's** tests).<sup>(155)</sup> Due to the low power of such tests when there are few studies, this was only performed for comparisons involving 10 or more studies. Small study bias was interpreted as a potential indicator of publication bias. Where evidence of small study bias was detected, the trim and fill approach was used to determine the



treatment effect adjusted for missing studies.<sup>(156)</sup> This approach was used to give an estimate of the impact of small study bias, but not used for final treatment effect estimates.

#### 4.1.3.5 Measures of treatment effect and data synthesis

Effect sizes were expressed as the relative risk (RR) of a smoker having abstained from smoking for six months or longer in the intervention group compared with the comparison group(s).

Preference was given to random effects meta-analysis, due to the variability in trial populations and how interventions were delivered. For example, study participants had different mean ages and levels of smoking dependency across studies. Both fixed and random effect estimates were computed in all cases, and the differences considered. In cases of fewer than five studies in a comparison, the fixed effect estimate is reported, as it was considered that there were insufficient data to support a reliable estimate of between-study variance. For head-to-head comparisons, the Mantel-Haenszel method was used to calculate the fixed effect estimate and the DerSimonian-Laird method was used to estimate the random effects estimate.

Where there was sufficient indirect and direct evidence and the assumption of transitivity was justified, a network meta-analysis approach was considered. In the case of a network meta-analysis, the consistency model was used.<sup>(157)</sup> An unrelated mean effects (UME) model, also referred to as an inconsistency model, was also applied.<sup>(158)</sup> A random effects model was used. The node splitting approach was used to compare direct and indirect evidence, and an examination of deviance statistics was used to identify studies that were providing potentially inconsistent estimates.<sup>(159, 160)</sup> Node splitting generates separate models for direct and indirect evidence, and the network evidence is not a mathematical combination of the two. Some multi-arm trials may be excluded from the node splitting analysis if they provide both direct and indirect evidence for a given comparison. Node splitting has only been applied to comparisons for which there is both direct and indirect evidence.

Meta-regression approaches were also applied to determine if study-level covariates could explain some of the observed variance. Models were compared using the Deviance Information Criterion (DIC). Network meta-analysis models were run using package *gemtc* 0.8.1<sup>(161)</sup> in R 3.3.1. Models were run with a burn-in of 20,000 iterations followed by 50,000 iterations on four chains. Model convergence in the adaption phase was checked using the Gelman and Rubin convergence diagnostic.

Treatment effect estimates based on head-to-head evidence only were computed using Frequentist methods and are reported with associated confidence intervals. For network meta-analyses, which were based on Bayesian methods, treatment effects are reported with associated credible intervals. The two intervals have different interpretations reflecting the underlying methodology. A confidence interval is a statement of how frequent the true treatment effect lies in the confidence interval when the experiment is repeated a large number of times, each time with a different sample of data from the same underlying population. A credible interval is a statement of the range of values for which the treatment effect remains plausible given the particular sample of data that have actually been observed. The credible interval has a more intuitive interpretation for decision-making, as a statement can be made that 'there is a 95% probability that the true treatment effect lies within the credible interval'.

For both confidence and credible intervals, the reported range relates to the average treatment effect. Prediction intervals for some analyses are also reported. A prediction interval provides an estimate of the range of values that the treatment effect could take in a future study. Prediction intervals tend to be wider than confidence or credible intervals. When there are substantial differences, the prediction intervals may be very wide. For decision-making at a national level regarding smoking cessation, it may be more appropriate to focus on the confidence bounds or credible interval associated with the average treatment effect. The heterogeneity observed across studies reflects differences in study design, setting, participants, and implementation of the interventions. Such heterogeneity is likely to also be observed if cessation programmes are implemented across Ireland, but overall a treatment effect similar to the average observed across trials is anticipated.

The difference between efficacy and effectiveness also needs to be considered. Efficacy refers to the performance of an intervention under ideal and controlled circumstances, whereas **effectiveness refers to its performance under typical or 'real-world' conditions.** Effectiveness takes into account the fact that not all people will receive an intervention as intended. The systematic reviews undertaken for this chapter were restricted to data from randomised controlled trials (RCTs). Although evidence from RCTs may often be considered as measuring efficacy, many of the included trials could be more accurately described as measuring effectiveness. This is because the interventions were evaluated under circumstances that more closely approach real-world practice, such as more heterogeneous patient populations, less-standardised treatment protocols, and delivery in routine clinical settings.

#### 4.1.3.6 Assessment of heterogeneity

An assessment of clinical heterogeneity was carried out based on the description of the interventions within each group. Statistical heterogeneity was examined using the  $I^2$  statistic. An  $I^2$  value of less than 50% was taken to indicate a low degree of heterogeneity and  $I^2$  values greater than 70% indicate substantial heterogeneity. Interpretation was based on both the point estimate of  $I^2$  and also the associated confidence bounds. If the point estimate for  $I^2$  suggested substantial heterogeneity but the lower bound for  $I^2$  was low, for example 10%, then it was considered evidence of moderate heterogeneity. Where substantial heterogeneity was observed, it was investigated using subgroups analysis or meta-regression, as appropriate. The coherence of the network of evidence was also considered by comparing the effect size estimates obtained from direct and indirect comparisons.

Where there was evidence of heterogeneity, meta-regression with study-level covariates (such as year of publication, quality, length of follow up, measure of abstinence, and abstinence verification) was used to explore to whether heterogeneity could be explained. The risk of bias assessment was used as a proxy for study quality. It is appreciated that risk of bias was evaluated based on a limited set of study characteristics, and that a study at low risk of bias is not necessarily a high quality study.

## 4.2 Clinical effectiveness in unselected adults

The primary population of interest in this analysis is unselected adult smokers. This population group underpins the majority of published research on smoking cessation.

### 4.2.1 Identified systematic reviews

A total of 13 systematic reviews were identified that were relevant to the interventions considered in this HTA (Table 4.2). All of the identified reviews were Cochrane reviews. No review was identified for the Allen Carr method. These reviews are limited to those assessing the effectiveness of a pharmacological or behavioural intervention. Reviews of the effectiveness of combination therapy (that is, a pharmacological intervention with adjunctive behavioural therapy) are considered separately in Section 4.2.7.

**Table 4.2 Identified systematic reviews**

Review (year)	Intervention	Primary studies
<b>White et al. (2014)<sup>(45)</sup></b>	Acupuncture	38
<b>Hughes et al. (2014)<sup>(28)</sup></b>	Antidepressants (bupropion)	65
<b>McRobbie et al. (2014)<sup>(25)*</sup></b>	Electronic cigarettes	2
<b>Stead and Lancaster (2005)<sup>(59)</sup></b>	Group behaviour therapy	53
<b>Lancaster and Stead (2005)<sup>(56)</sup></b>	Individual behavioural counselling	30
<b>Civiljak et al. (2013)<sup>(55)</sup></b>	Internet-based interventions	28
<b>Whittaker et al. (2016)<sup>(54)</sup></b>	Mobile phone-based	12
<b>Lindson-Hawley et al. (2015)<sup>(49)</sup></b>	Motivational interviewing	28
<b>Cahill et al. (2016)<sup>(38)</sup></b>	Nicotine receptor partial agonists (cytisine and varenicline)	41
<b>Stead et al. (2012)<sup>(7)</sup></b>	Nicotine replacement therapy (NRT)	150
<b>Rice et al. (2013)<sup>(162)</sup></b>	Nursing interventions	49
<b>Stead et al. (2013)<sup>(52)</sup></b>	Physician advice	42
<b>Stead et al. (2013)<sup>(52)</sup></b>	Telephone counselling	77

\* An update of this review was published in September 2016 following search updates for this HTA.<sup>(163)</sup> No additional studies were identified.

While the majority of the identified reviews were no more than three years old, two of the reviews were published over 10 years ago. Not all of the primary studies included in the identified reviews were considered relevant to this HTA. Some studies appeared in multiple systematic reviews, as certain interventions could legitimately appear in multiple reviews (for example, motivational interviewing, a

behavioural intervention provided by a physician, could appear in both the motivational interviewing and physician advice reviews) or individual arms of multi-arm studies could be applicable to multiple reviews.

#### **4.2.2 Identified trials**

The identified systematic reviews were updated (search dates 18 July 2016 to 13 August 2016). A de novo search was carried out to identify trials evaluating the Allen Carr method on 20 May 2016. However, no studies evaluating the efficacy and safety of the Allen Carr method for smoking cessation that were eligible for inclusion in this HTA were identified (see Appendix 8, Figure 8.1).

Trials that compared different intensities of the same intervention (for example, different doses of nicotine replacement therapy [NRT]) were excluded under the assumption that the choice of intensity was related to the level of dependence in the smokers receiving therapy. Based on subgroup analyses in the included Cochrane reviews, there was no evidence of a dose-response relationship for implementing more intense interventions. Trial arms that evaluated different intensities of the same intervention were collapsed into a single arm. If the trial did not include other interventions then it was excluded as it was effectively considered a single-arm trial.

A total of 313 relevant studies were identified, published between 1971 and 2016 (Table 4.3). Data were only extracted for study arms that were relevant to this HTA. The relevant number of trial participants ranged from 32 to 6,451 (mean 592, standard deviation 763). In terms of the number of included trial arms, we identified studies with two (n=283), three (n=25), four (n=4), and five (n=1) arms. Due to the large number of studies identified, they are listed in full in Appendix 8.

The duration of follow up varied across trials, although most reported cessation rates at six months (n=113; 36%) and 12 months (n=170; 54%). Behavioural and pharmacological interventions had similar proportions of trials reporting six-month follow ups. Twenty-five studies reported greater than 12-months follow up, with two studies providing cessation rates at five years. The majority of studies with more than 12-months follow up were for behavioural interventions (n=20).

Studies were also graded on quality, based on assessments using the Cochrane risk of bias tool. Studies at low risk of bias were considered high quality. Overall, just over one in four (26% or n=80) studies were considered high quality. More studies of pharmacological interventions were rated as high quality (31%) than studies of behavioural intervention (20%).

Studies recorded smoking cessation through either self-reports or some form of biochemical verification, such as cotinine levels. Biochemical verification is the

preferred measure of cessation as it is less prone to bias. Almost two out of three studies (65%) used biochemical verification, although the percentage varied between studies of pharmacological agents (86%) and behavioural interventions (38%).

Finally, abstinence from smoking was measured as either cessation from the quit date or abstaining at a particular point in time (also known as point prevalence). Measuring continued abstinence from the quit date gives a better indication of the true quit rate. Continuous abstinence was reported in 58% of studies, although this outcome was more typically used in pharmacological studies (69%) than in behavioural studies (41%).

**Table 4.3 Identified primary studies and main characteristics**

Intervention	Studies (n)	Participants (n) <sup>†</sup>	Follow up*, n (%)				High quality n (%)		Biochemically verified n (%)		Continuous abstinence n (%)		Mean (SD) years since publication	
			6 months		≥12 months									
	Behavioural therapies													
Acupuncture <sup>(164-174)</sup>	13	1,194	7	(54)	6	(46)	4	(31)	3	(23)	6	(46)	27.2	(8.2)
Group behaviour therapy <sup>(167, 168, 173, 175-198)</sup>	27	5,497	10	(37)	17	(63)	2	(7)	13	(48)	7	(26)	22.9	(7.9)
Individual counselling <sup>(178, 183, 192, 198-209)</sup>	15	3,646	9	(60)	6	(40)	5	(33)	10	(67)	6	(40)	17.3	(7.4)
Intensive advice <sup>(179, 181, 187, 205, 209-241)</sup>	37	11,210	18	(49)	18	(49)	8	(22)	19	(51)	13	(35)	15.6	(9.9)
Internet-based <sup>(242-250)</sup>	9	5,677	6	(67)	2	(22)	6	(67)	1	(11)	4	(44)	4.8	(2.8)
Mobile phone-based <sup>(243, 251-253)</sup>	4	923	4	(100)	0	(0)	3	(75)	1	(25)	2	(50)	2.8	(1.7)
Telephone support <sup>(204, 206, 211, 218, 235, 254-293)</sup>	45	26,426	10	(22)	33	(73)	7	(16)	13	(29)	24	(53)	13.0	(6.1)
	Pharmacotherapies													
Bupropion <sup>(294-327)</sup>	34	8,341	13	(38)	21	(62)	12	(35)	32	(94)	23	(68)	9.3	(4.2)
Combination NRT <sup>^</sup> (312, 313, 315, 328-336)	13	3,240	5	(38)	8	(62)	4	(31)	12	(92)	7	(54)	10.1	(7.6)
Cytisine <sup>(41, 337-339)</sup>	4	1,732	2	(50)	2	(50)	2	(50)	2	(50)	3	(75)	15.0	(20.1)
Electronic cigarettes <sup>(340, 341)</sup>	2	489	1	(50)	1	(50)	2	(100)	1	(50)	2	(100)	3.0	(0)
NRT <sup>(172, 197, 203, 205, 208, 212, 241, 296, 302, 303, 312, 313, 320, 324, 327-336, 339, 340, 342-445)</sup>	133	33,556	44	(33)	88	(66)	30	(23)	110	(83)	88	(66)	18.7	(9.2)

Notes: \*a small number of studies ran for more than six months, but less than 12 months; ^Combination NRT refers to using more than one form of NRT (for example, transdermal patch plus gum). <sup>†</sup>Participants' refers to number receiving the intervention and excludes control arm participants.

**Table 4.3 continued. Identified primary studies and main characteristics**

Intervention	Studies (n)	Participants (n) <sup>†</sup>	Follow up*, n (%)				High quality n (%)		Biochemically verified n (%)		Continuous abstinence n (%)		Mean (SD) years since publication	
			6 months		≥12 months									
NRT + bupropion <sup>(311-313, 320, 324, 358, 398)</sup>	7	1,509	4	(57)	3	(43)	0	(0)	6	(86)	4	(57)	8.3	(5)
NRT + varenicline <sup>(446, 447)</sup>	2	392	2	(100)	0	(0)	2	(100)	2	(100)	2	(100)	2.0	(0)
Varenicline <sup>(295, 305, 315, 318, 319, 327, 335, 342, 345, 350, 395, 396, 441, 446-458)</sup>	26	6,903	14	(54)	12	(46)	15	(58)	24	(92)	20	(77)	4.9	(3.7)
Varenicline + bupropion <sup>(453)</sup>	1	249	0	(0)	1	(100)	1	(100)	1	(100)	1	(100)	2.0	NA

Notes: \*a small number of studies ran for more than six months, but less than 12 months; ^Combination NRT refers to using more than one form of NRT (for example, transdermal patch plus gum). <sup>†</sup>Participants' refers to number receiving the intervention and excludes control arm participants.



### **4.2.3 Classification of interventions**

The definitions of interventions were very heterogeneous in the studies included in the systematic reviews. In particular, this is evident in behavioural interventions. Interventions could be provided at a variety of frequencies and intensities. If a dose-response relationship exists, then treatment effects may vary by frequency and intensity. However, the identified Cochrane reviews included subgroup analyses that provided little evidence that treatment effect was related to the frequency and intensity of interventions.

Some interventions could be interpreted in different ways. For example, a motivational interviewing intervention delivered by nurses could appear in both the motivational interviewing and nursing intervention reviews. Where possible, the Evaluation Team used a simplified categorisation. For interventions delivered by a healthcare professional, the Team did not distinguish between physicians or nurses. Based on the Cochrane review and exploratory analysis, it was assumed that the different forms of NRT (for example, transdermal patch, gum, and so on) are equally effective.

It is possible to distinguish between different implementations or versions of cessation interventions based on intervention characteristics. For example, telephone support can be provided as reactive (in response to contact by the person seeking to quit smoking) or proactive (where the provider makes several calls to the person seeking to quit). Interventions that are different versions of a common concept have been grouped together when the supporting systematic review showed no evidence of differing treatment effect in subgroup analyses. For example, motivational interviewing, motivational support, and physician or nurse support bore many similarities in terms of duration and frequency of sessions. As such, they have been amalgamated in this analysis into a grouping called intensive advice.

The interventions could be briefly defined as:

- Nicotine replacement therapy (NRT): a range of replacement therapies (chewing gum, transdermal patches, nasal and oral spray, inhalers, tablets and lozenges; as monotherapy or combination therapy) that provide nicotine by means other than tobacco.
- Electronic cigarettes (e-cigarettes): electronic devices with the ability to heat a liquid - usually comprising propylene glycol and glycerol, with or without nicotine and flavours, and stored in disposable or refillable cartridges or a reservoir - into an aerosol for inhalation.
- Nicotine receptor partial agonists (cytisine or varenicline only).
- Antidepressants (bupropion only).

- Brief physician advice: **verbal instructions from the physician with a 'stop smoking' message**, irrespective of whether or not information was provided about the harmful effects of smoking.
- Telephone-based interventions: provision of proactive or reactive telephone counselling to assist smoking cessation, to any population.
- Mobile phone-based: any type of mobile phone-based intervention for smoking cessation based around delivery via mobile phone, and using any functions or applications that could be used or sent via a mobile phone.
- Internet-based interventions: interactive, personalised and non-interactive interventions, focused on standard approaches to information delivery though the Internet.
- Intensive advice: combining interventions of motivational interviewing (a brief psychotherapeutic intervention intended to increase the likelihood that a person will make an attempt to change their harmful behaviour) and clinician support (more intensive than brief advice
  - but less intensive than individual counselling in terms of frequency and duration of interaction).
- Individual behaviour counselling: a face-to-face encounter between a smoking patient and a counsellor trained in assisting smoking cessation.
- Group behaviour therapy: scheduled meetings of smokers including some form of behavioural intervention, such as information, advice and encouragement or cognitive behavioural therapy (CBT) delivered over at least two sessions.
- Acupuncture: non-pharmacological stimulation interventions involving needle puncture, finger pressure or laser therapy in areas of the body described as acupuncture points.
- Allen Carr method: a behavioural intervention as described by Allen Carr in a series of publications.

#### **4.2.4 Networks of evidence**

The identified interventions could be broadly grouped into behavioural interventions and pharmacotherapy interventions. For this analysis, e-cigarettes are considered as a pharmacotherapy as the intervention is similar to nicotine replacement therapy.

Generally, drug trials include some form of behavioural therapy, however limited. But since this is provided to participants in all arms of the trial, the only difference between intervention and control groups is the use of the drug or drugs, thereby allowing its effect to be observed. The situation is reversed for trials of behavioural supports which involve a group that is provided with a given behavioural intervention (who are generally free to use some form of pharmacological cessation

aid) compared to a group that receive another, usually less intense, behavioural support (who are also free to use some form of pharmacological intervention).

In addition to supportive care, most pharmacotherapy trials include use of placebo in the control arm. For example, in a trial of NRT gum, the control arm participants are typically provided with gum with no nicotine, or with a sufficiently small dose of nicotine to be considered placebo. For behavioural therapies there is, in most cases, no equivalent to placebo. Control arms are a mixture of 'do nothing' or minimal supportive care that is provided in all trial arms, such as brief advice or written materials.

Although the patient populations were comparable in terms of age, sex and nicotine dependency, some of the populations in behavioural trials were not selected on the basis of an expressed desire to make a quit attempt, as the intervention may be designed to address the barriers smokers experience that prevent them making a quit attempt. On the other hand, all participants in drug trials must agree to receive the treatment (active or placebo), indicating a willingness to quit. As such, it is not clear that people who participated in all behavioural therapy trials can be compared to those in the pharmacotherapy trials. Only one randomised controlled trial directly compared a pharmacological intervention to a behavioural intervention.

Two studies directly compared pharmacological interventions to behavioural interventions.<sup>(459, 460)</sup> Both studies included an NRT arm and a group behaviour therapy arm. NRT was provided with brief advice in both cases. One of the studies found a statistically significant treatment effect for NRT relative to group behaviour therapy.<sup>(460)</sup> The pooled estimate showed some evidence of effect in favour of NRT (RR=1.25, 95% CI: 0.98 – 1.59; p=0.071). The conflicting evidence of these two studies that provide the only link between pharmacological and behavioural interventions is not a good basis for considering a large combined network of evidence.

For these reasons, trials evaluating behavioural interventions are considered separately from those evaluating pharmacological interventions. There were a wide range of comparisons available within those two groups, with direct evidence available between many of the interventions. As such, it was possible to consider evidence synthesis, including both direct and indirect evidence.

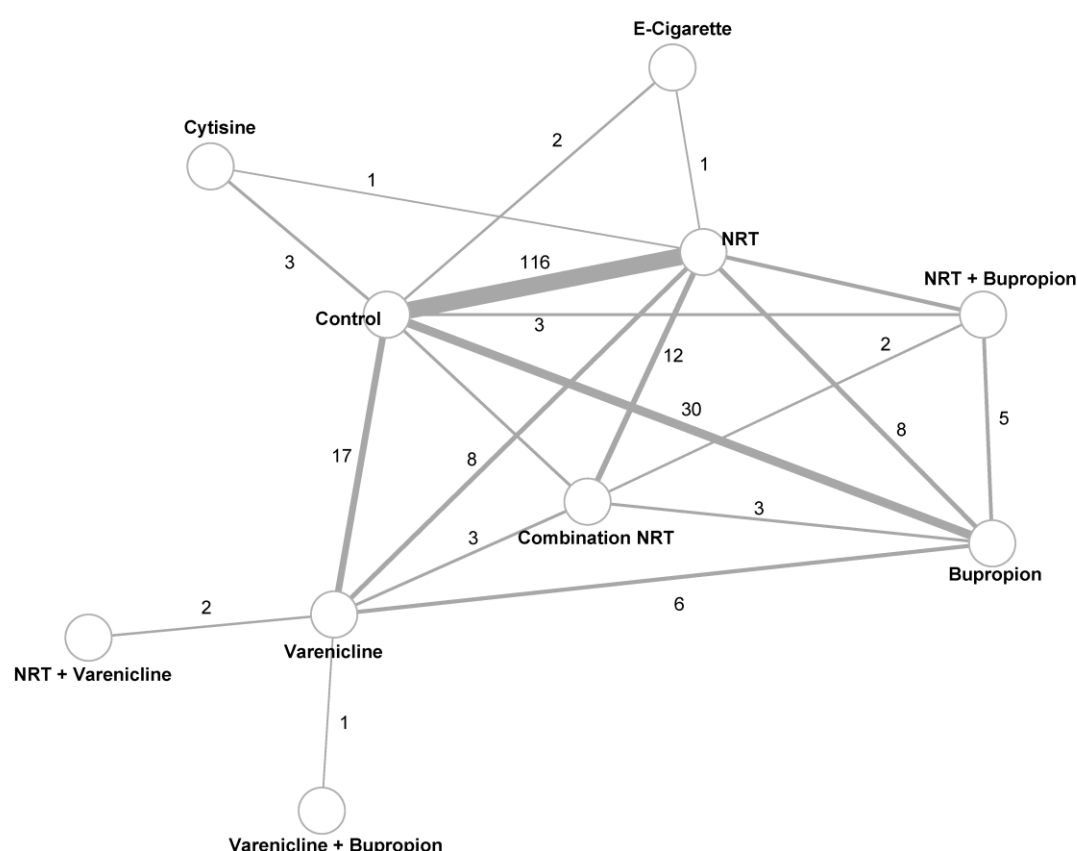
#### **4.2.5 Pharmacotherapy interventions**

There were 232 comparisons available across the 176 pharmacotherapy trials (Figure 4.1). Of those comparisons, 174 were between intervention and control. The largest quantity of evidence was for NRT, with 152 comparisons. There were 20 head-to-head comparisons between interventions in total. For the purposes of the

analysis, combinations of interventions are treated as distinct interventions. For example, NRT plus varenicline is a distinct combination therapy.

Most of the interventions appear in numerous different comparisons. Others, such as NRT plus varenicline and varenicline plus bupropion, each appear in a single comparison, although there may be multiple studies providing evidence for those comparisons.

**Figure 4.1 Network of evidence for pharmacotherapy interventions for unselected adults**



#### 4.2.5.1 Direct comparisons

The direct head-to-head evidence between interventions was investigated. The pooled direct evidence is provided in Table 4.4. Where the pooled estimates have been combined using a random effects approach, the 95% confidence bounds are associated with the mean effect. In cases where there were five or more studies in the comparison, the 95% prediction intervals were also computed, and these give an indication of the range of effect sizes that might be observed in a future study.

Relative to control, the seven interventions for which there was direct evidence all had a treatment effect that was statistically significant. That is, the intervention was better than control. It can be seen that the confidence bounds are relatively narrow

where there are many studies available. NRT and bupropion are similarly effective, with risk ratios close to 1.60. Varenicline is the most effective intervention, with a risk ratio of 2.66.

**Table 4.4 Treatment effects based on direct evidence: pharmacological interventions**

Comparison	Studies (n)	Participants (n)	Risk ratio (95% CI)	p-value	95% Prediction interval	I <sup>2</sup> (95% CI)
NRT vs Control <sup>(172, 197, 203, 205, 208, 212, 241, 296, 303, 312, 320, 327, 328, 330, 340, 342-349, 351-357, 359-394, 396, 397, 399-440, 442-445)</sup>	116	53,066	1.59 (1.50 - 1.69)	<0.001	(1.12 - 2.25)	0.34 (0.16 - 0.47)
Bupropion vs Control <sup>(294-301, 303-311, 313, 314, 316-323, 325-327)</sup>	30	13,363	1.65 (1.51 - 1.79)	<0.001	(1.47 - 1.84)	0.02 (0.00 - 0.42)
NRT + bupropion vs Control <sup>*(311, 312, 320)</sup>	3	1,240	1.73 (1.39 - 2.15)	<0.001		0.31 (0.00 - 0.93)
Combination NRT vs Control <sup>*(312, 328, 330)</sup>	3	904	1.71 (1.30 - 2.25)	<0.001		0.00 (0.00 - 0.64)
E-cigarette vs Control <sup>*(340, 341)</sup>	2	662	2.29 (1.05 - 4.96)	0.037		0.00
Cytisine vs Control <sup>*(41, 337, 338)</sup>	3	2,151	1.87 (1.48 - 2.38)	<0.001		0.68 (0.00 - 0.91)
Varenicline vs Control <sup>(295, 305, 318, 319, 327, 342, 396, 448-452, 454-458)</sup>	17	9,275	2.66 (2.25 - 3.15)	<0.001	(1.52 - 4.66)	0.58 (0.27 - 0.75)
Bupropion vs NRT <sup>(296, 302, 303, 312, 313, 320, 324, 327)</sup>	8	5,485	1.03 (0.88 - 1.21)	0.696	(0.66 - 1.61)	0.56 (0.03 - 0.80)
E-cigarette vs NRT <sup>*(340)</sup>	1	584	1.26 (0.68 - 2.34)	0.463		NA
Varenicline vs NRT <sup>(327, 335, 342, 345, 350, 395, 396, 441)</sup>	8	4,277	1.28 (1.12 - 1.47)	<0.001	(0.96 - 1.70)	0.25 (0.00 - 0.66)
NRT + bupropion vs NRT <sup>(312, 313, 320, 324, 358, 398)</sup>	6	3,277	1.29 (0.94 - 1.76)	0.109	(0.46 - 3.61)	0.81 (0.59 - 0.91)
Combination NRT vs NRT <sup>(312, 313, 328-336, 395)</sup>	12	7,239	1.31 (1.16 - 1.47)	<0.001	(1.05 - 1.62)	0.13 (0.00 - 0.53)
Cytisine vs NRT <sup>*(339)</sup>	1	1,310	1.43 (1.13 - 1.80)	0.002		NA

Notes: comparisons marked with \* are based on fixed effect model. All other treatment effect estimates are based on random effects model. The fixed effect model was used when there were fewer than five studies.

**Table 4.4 continued. Treatment effects based on direct evidence: pharmacological interventions**

Comparison	Studies (n)	Participants (n)	Risk ratio (95% CI)	p-value	95% Prediction interval	I <sup>2</sup> (95% CI)
NRT + bupropion vs Bupropion <sup>(311-313, 320, 324)</sup>	5	2,644	1.15 (0.93 - 1.42)	0.210	(0.56 - 2.34)	0.64 (0.04 - 0.86)
Combination NRT vs Bupropion <sup>*(312, 313, 315)</sup>	3	1,216	1.27 (1.08 - 1.50)	0.003		0.64 (0.00 - 0.90)
Varenicline vs Bupropion <sup>(295, 305, 315, 318, 319, 327)</sup>	6	3,994	1.42 (1.29 - 1.57)	<0.001	(1.24 - 1.63)	0.00 (0.00 - 0.62)
Combination NRT vs NRT + bupropion <sup>*(312, 313)</sup>	2	1,076	1.06 (0.89 - 1.26)	0.512		0.63
Varenicline vs Combination NRT <sup>*(315, 335, 395)</sup>	3	1,511	1.04 (0.88 - 1.23)	0.628		0.68 (0.00 - 0.91)
Varenicline + bupropion vs Varenicline <sup>*(453)</sup>	1	506	1.26 (0.95 - 1.68)	0.109		NA
NRT + varenicline vs Varenicline <sup>*(446)</sup>	2	787	1.42 (1.13 - 1.79)	0.003		0.60

Notes: comparisons marked with \* are based on fixed effect model. All other treatment effect estimates are based on random effects model. The fixed effect model was used when there were fewer than five studies.

Varenicline, cytisine and combination NRT show a statistically significant treatment benefit when compared with NRT monotherapy. Relative to bupropion, varenicline was shown to have a statistically significant treatment effect. On the basis of a fixed effect estimate, combination NRT was also shown to have a statistically significant treatment effect relative to bupropion.

The direct evidence shows a hierarchy where the least effective pharmacotherapies are NRT monotherapy and bupropion, which are similarly effective. There is a small additional benefit to using NRT monotherapy and bupropion in combination. Varenicline is the most effective monotherapy, and has a small, but not statistically significant treatment benefit compared to combination NRT. It is noted that, from a pharmacological perspective, the combination of nicotine replacement therapy with a nicotine receptor partial agonist may appear counter-intuitive. A number of hypotheses have been proposed as to why this combination may improve smokers' chances of quitting, including that 'varenicline does not completely saturate nicotinic acetylcholine receptors leading to incomplete reward response and incomplete blockade of continuing smoking reinforcement; and/or [that] varenicline incompletely replaces the dopaminergic effect of smoking leading to a continued craving to smoke'.<sup>(461)</sup>

The data on e-cigarettes is less clear, influenced by the small number of studies and comparisons available. Relative to control, there was statistically significant treatment effect, although the confidence bounds were wide. Relative to NRT monotherapy, there was a small but not statistically significant treatment benefit.

The evidence in many of the comparisons was subject to heterogeneity, although the bounds in many cases suggest that it was not substantial. The comparisons for which heterogeneity was a concern were varenicline versus control ( $n=17$ ,  $I^2=0.58$ ), and NRT monotherapy plus bupropion versus NRT monotherapy ( $n=6$ ,  $I^2=0.81$ ). Other comparisons also showed potentially substantial heterogeneity, but the bounds for the estimate of  $I^2$  included values of low heterogeneity. In the comparison of varenicline versus control, there were sufficient studies to investigate whether study-level covariates might explain some of the heterogeneity (Figure 4.2).

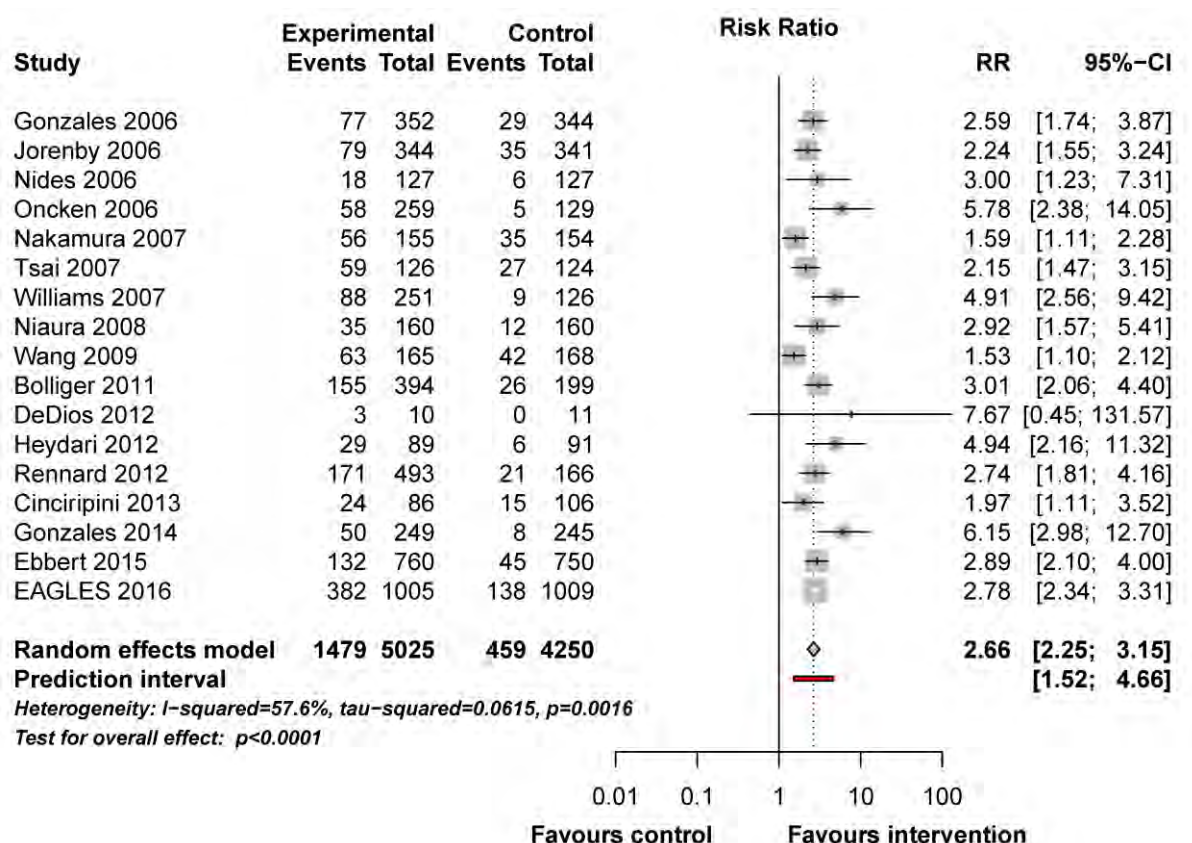
Only continuous abstinence was associated with a statistically significant effect, whereby studies that used continuous abstinence observed a smaller treatment effect associated with the intervention. An assessment of influence statistics did not identify any single study that contributed to heterogeneity, and a leave-one-out analysis had only a small impact on the pooled treatment effect.

Fixed effect and random effects models generated very similar point estimates of treatment effect for all but one comparison: cytisine versus control. The random effects estimate ( $RR=2.59$ , 95% CI: 1.19 to 5.65) was larger than the fixed effect



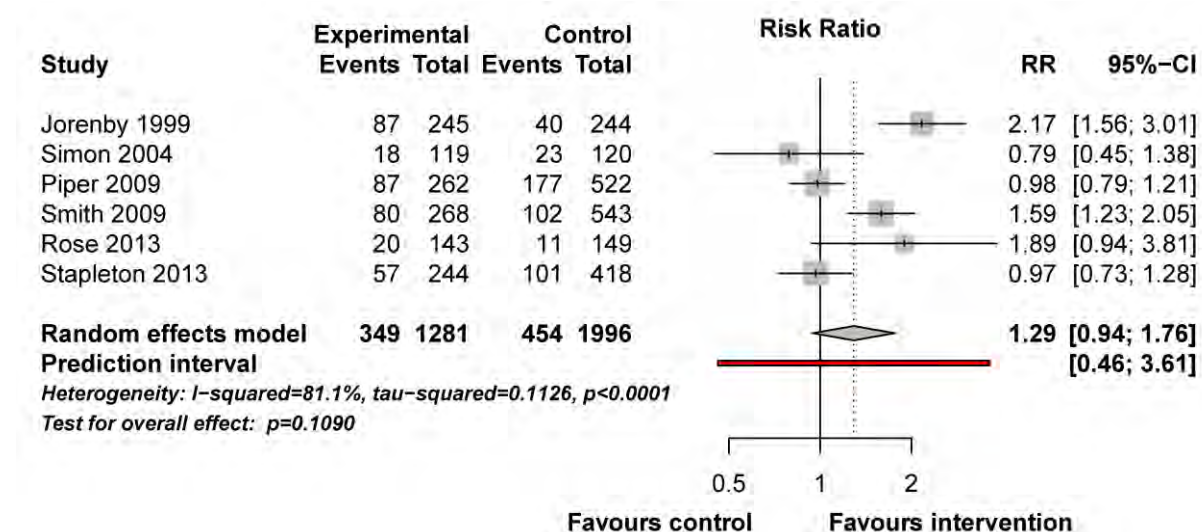
estimate (RR=1.87, 95% CI: 1.48 to 2.38). With only three studies available, the estimate of between study variance is likely to be unreliable, and the random effects result may over-estimate the treatment effect. There are a further four comparisons for which the fixed effect estimate is associated with a statistically significant treatment effect, but the random effects estimate does not.

**Figure 4.2 Forest plot of studies comparing varenicline versus control**



There were insufficient studies in the comparison of NRT monotherapy plus bupropion versus NRT monotherapy to consider a meta-regression. An inspection of the forest plot demonstrates the substantial heterogeneity (Figure 4.3). A review of the main study characteristics does not suggest a common feature to the studies that reported lower effect sizes.

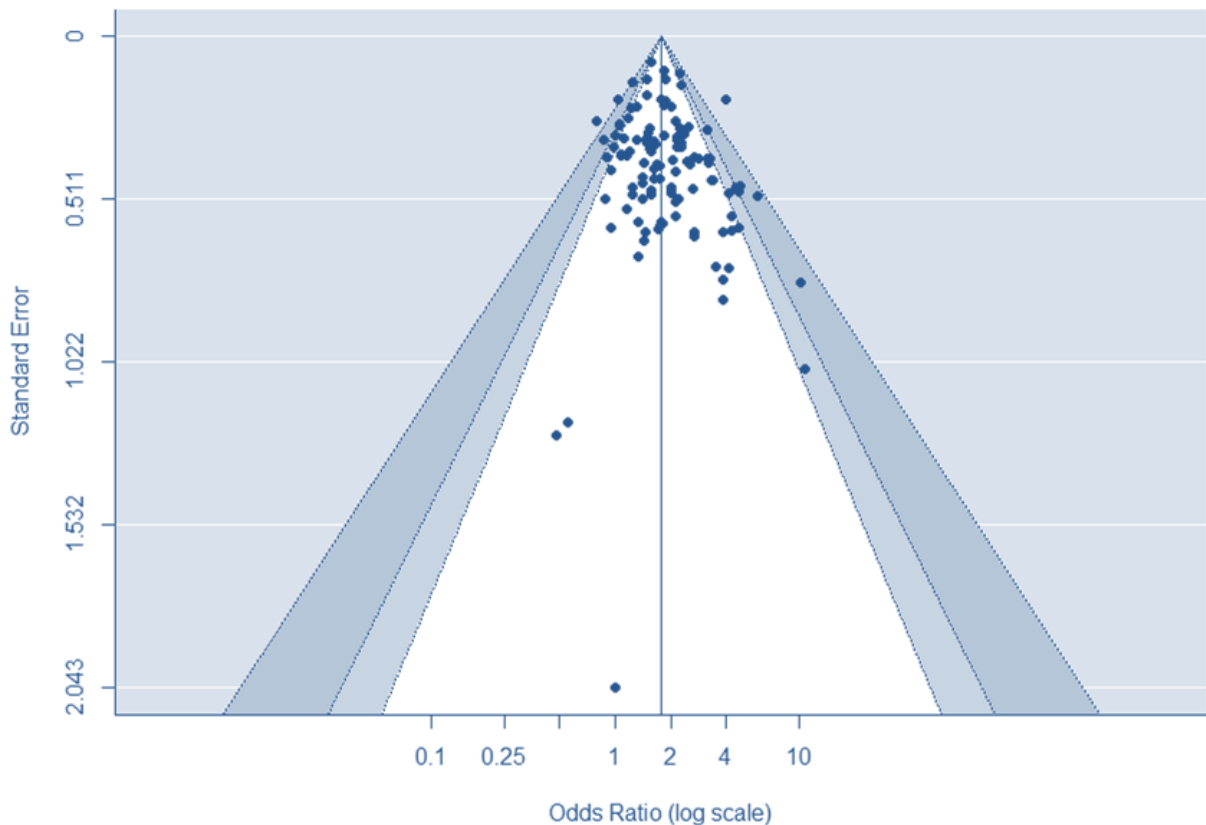
**Figure 4.3 Forest plot of studies comparing NRT plus bupropion versus NRT**



The potential for small study bias was also investigated using funnel plots for comparisons with 10 or more studies. There was some evidence of small study bias **in the comparison of NRT versus control based on the Egger's test ( $p=0.073$ )**, but not based on the Harbord test ( $p=0.508$ ). A visual inspection of the funnel plot shows that there may be a tendency towards greater treatment effects being observed in smaller studies. However, the three studies with largest standard errors contradict this finding (Figure 4.4).

Of note, when studies were split into two-arm and multi-arm trials, there was no evidence of small study bias in multi-arm trials that compared NRT monotherapy to control. Analysing only two-arm trials resulted in statistically significant evidence of **funnel plot asymmetry based on the Egger's test but not the Harbord test**. The trim and fill method was applied to estimate what the treatment effect might be in the absence of such a small study effect. The treatment effect for NRT monotherapy reduced from 1.59 (95% CI: 1.50 - 1.69) to 1.52 (95% CI: 1.42 - 1.63). This suggests a potentially modest impact and would not change the interpretation that NRT monotherapy is superior to control. However, it should be noted that the application of trim and fill widened the prediction intervals to encompass no treatment effect.

**Figure 4.4 Funnel plot of studies comparing NRT versus control**



#### 4.2.5.2 Direct and indirect comparisons

Given the available network of evidence and apparent consistency of evidence, the analysis of pharmacological interventions was extended to include both direct and indirect evidence. Direct evidence allows estimation of treatment effect between two interventions using head-to-head trials. Indirect evidence supports an estimate of treatment effect between two interventions using a common comparator. In the absence of any direct comparison between treatments A and B, it is possible to estimate the effect if there are trials comparing A to C and B to C. In a network meta-analysis, both direct and indirect evidence is combined to derive an estimate of treatment effects. Treatment effects were calculated on the log odds scale and then finally converted to risk ratios using the assumed control risk, which was calculated as the risk of smoking cessation pooled across the control arms.

The first step was to estimate treatment effects using both consistency and inconsistency models to determine whether the assumption of consistency has a substantial impact on estimates of treatment effect. The consistency and inconsistency models produced very similar estimates of treatment effect, agreeing in terms of direction and magnitude of effect. All of the estimates from the consistency model were well within the confidence bounds for the corresponding inconsistency model estimates. The Deviance Information Criterion (DIC) was

marginally lower for the consistency model (639.2 versus 643.9), although the difference ( $<5$ ) was not large enough to be considered important. The random effects standard deviation was 0.236 (95% CI: 0.173 to 0.303) for the consistency model, and 0.239 (95% CI: 0.215 to 0.238) for the inconsistency model. As such, the consistency model was considered appropriate.

An analysis of heterogeneity estimated a global  $I^2$  of 29%. Based on an analysis of heterogeneity, potential issues were identified for two comparisons: varenicline versus control ( $p=0.077$ ) and varenicline versus NRT monotherapy ( $p=0.054$ ). A node-splitting analysis was used to investigate the contribution of direct and indirect evidence to treatment effect estimates (Table 4.5). There was no statistically significant difference in the direct and indirect evidence for any of the comparisons. For almost all comparisons, the direct and indirect treatment effects were in agreement in terms of direction and, for the most part, in terms of magnitude, although there were some differences. For example, the direct evidence showed combination NRT to be better than NRT monotherapy. The indirect evidence showed a non-significant treatment benefit associated with the monotherapy. The pooled estimate was driven by the direct evidence.

For the estimate of varenicline versus control, the summary treatment effect was closer to that of the direct evidence. For the comparison of varenicline versus NRT monotherapy, the treatment effect estimate was more influenced by the indirect evidence.

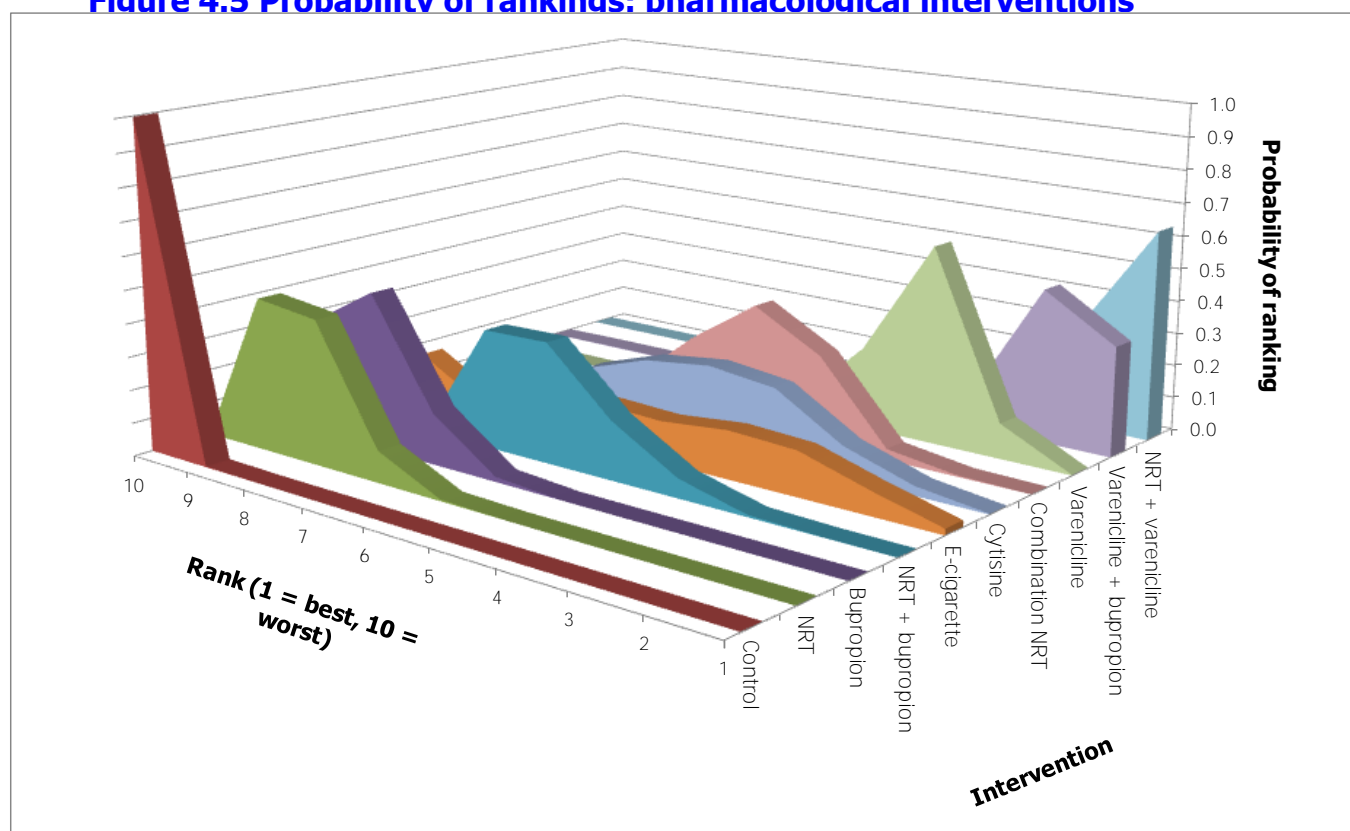
The 10 interventions in the network of pharmacological treatments were analysed in terms of their likely ranking (from best treatment to worst treatment) (Figure 4.5). There was a probability of 1 that control was the least effective treatment. Only two therapies had a probability of being most effective: combined varenicline and NRT monotherapy (probability = 0.64) and combined varenicline and bupropion (probability = 0.34). E-cigarettes and cytosine both had wide ranges of potential rankings, highlighting the uncertainty in relation to their effectiveness.

**Table 4.5 Comparison of direct and indirect treatment effect estimates: pharmacological interventions**

Comparison	Risk ratio						p-value
	Direct estimate (95% CI)		Indirect estimate (95% CI)		Network estimate (95% CI)		
Bupropion vs Control	1.67	(1.49 to 2.18)	1.67	(1.27 to 2.53)	1.70	(1.54 to 2.16)	0.98
Cytisine vs Control	2.10	(1.49 to 3.55)	2.28	(1.50 to 4.64)	2.20	(1.68 to 3.55)	0.66
NRT vs Control	1.67	(1.56 to 2.05)	1.78	(1.47 to 2.51)	1.68	(1.58 to 2.05)	0.53
NRT + bupropion vs Control	1.85	(1.34 to 2.97)	2.07	(1.60 to 3.25)	2.02	(1.70 to 2.97)	0.60
Combination NRT vs Control	1.82	(1.19 to 3.25)	2.28	(1.96 to 3.25)	2.21	(1.93 to 2.97)	0.28
Varenicline vs Control	2.83	(2.45 to 3.88)	2.23	(1.78 to 3.55)	2.64	(2.28 to 3.55)	0.10
NRT vs Bupropion	0.97	(0.78 to 1.33)	1.00	(0.86 to 1.30)	0.99	(0.88 to 1.25)	0.80
NRT + bupropion vs Bupropion	1.18	(0.92 to 1.67)	1.17	(0.66 to 2.28)	1.21	(0.99 to 1.67)	0.98
Combination NRT vs Bupropion	1.36	(0.97 to 2.12)	1.38	(1.12 to 1.96)	1.34	(1.13 to 1.82)	0.90
Varenicline vs Bupropion	1.58	(1.24 to 2.30)	1.60	(1.33 to 2.26)	1.60	(1.38 to 2.12)	0.91
NRT vs Cytisine	0.67	(0.40 to 1.24)	0.78	(0.51 to 1.32)	0.74	(0.53 to 1.13)	0.65
NRT vs E-cigarette	0.79	(0.36 to 1.87)	0.60	(0.17 to 1.87)	0.76	(0.41 to 1.53)	0.68
NRT + bupropion vs NRT	1.33	(1.06 to 1.89)	1.02	(0.58 to 1.92)	1.22	(1.01 to 1.67)	0.35
Combination NRT vs NRT	1.37	(1.16 to 1.86)	0.89	(0.47 to 1.84)	1.37	(1.17 to 1.79)	0.18
Varenicline vs NRT	1.38	(1.09 to 1.94)	1.72	(1.49 to 2.36)	1.62	(1.43 to 2.10)	0.09
Combination NRT vs NRT + bupropion	1.07	(0.74 to 1.75)	1.15	(0.84 to 1.76)	1.11	(0.88 to 1.58)	0.77
Varenicline vs Combination NRT	1.16	(0.83 to 1.82)	1.20	(0.95 to 1.70)	1.19	(0.99 to 1.63)	0.88

Notes: NRT refers to NRT monotherapy (only one pharmaceutical form used); Combination NRT refers to use of more than one formulation (e.g., transdermal patch plus gum or spray). CI, credible interval. The direct, indirect and network evidence are created from three different models, and the network estimate was not a weighted average of the indirect and direct studies. Results are presented for studies where there was both direct and indirect evidence not limited to data from a single multi-arm study).

**Figure 4.5 Probability of rankings: pharmacological interventions**



Note: the graph shows the probability of a given intervention being ranked from 1 (most effective intervention) to 10 (least effective intervention). A high probability reflects greater certainty about the ranking of a particular intervention. For example, it is almost certain that 'control' is the least effective intervention with a probability of 0.997 of being ranked tenth. There is a probability of 0.64 that varenicline plus NRT dual therapy is the most effective intervention.

The 95% credible intervals provided with the treatment effects indicate the bounds for the mean treatment effect. It is also possible to consider the prediction intervals which provide an indication of what might be observed in a future study (Table 4.6). When considered in terms of prediction intervals, all of the pharmacological interventions are associated with a statistically significant treatment effect relative to control.

**Table 4.6 Treatment effect relative to control: pharmacological interventions**

Intervention	Risk ratio	95% CI	95% PI
Control	Reference		
NRT	1.68	(1.58 - 1.78)	(1.14 - 2.41)
Bupropion	1.70	(1.53 - 1.87)	(1.13 - 2.44)
NRT + bupropion	2.02	(1.70 - 2.40)	(1.31 - 2.92)
E-cigarettes	2.14	(1.26 - 3.35)	(1.10 - 3.60)
Cytisine	2.20	(1.68 - 2.83)	(1.37 - 3.24)
Combination NRT	2.22	(1.91 - 2.55)	(1.48 - 3.18)
Varenicline	2.57	(2.32 - 2.85)	(1.74 - 3.60)
Varenicline + bupropion	3.20	(2.05 - 4.60)	(1.80 - 4.82)
NRT + varenicline	3.54	(2.57 - 4.61)	(2.28 - 5.03)

Abbreviations: CI, credible interval; PI, prediction interval; NRT, nicotine replacement therapy.

From the rankings and the estimated effectiveness (Table 4.7), it is apparent that all active treatments are better than control. That is, the evaluated pharmacological interventions result in higher rates of long-term (six months or longer) smoking cessation than control. NRT monotherapy and bupropion are similarly effective. Used in combination they are more effective than when used as monotherapies, although the improved effect is only statistically significant compared to NRT monotherapy alone. Varenicline, either as monotherapy or combined with NRT monotherapy or bupropion is more effective than NRT monotherapy or bupropion as monotherapy. Cytisine and e-cigarettes are similarly effective. They are both supported by limited evidence and as such the confidence bounds around the average treatment effect are wide.

**Table 4.7 Network meta-analysis treatment effect estimates: pharmacological interventions**

Risk ratio (95% credible interval)									
	Control	Bupropion	Cytisine	E-cigarette	NRT	NRT + bupropion	NRT + varenicline	Combination NRT	Varenicline
Bupropion	1.70 (1.53 - 1.87)								
Cytisine	2.20 (1.68 - 2.83)	1.33 (0.97 - 1.81)							
E-cigarette	2.14 (1.26 - 3.35)	1.29 (0.72 - 2.20)	0.97 (0.49 - 1.80)						
NRT	1.68 (1.58 - 1.78)	0.99 (0.88 - 1.11)	0.73 (0.53 - 1.00)	0.76 (0.41 - 1.34)					
NRT + bupropion	2.02 (1.70 - 2.40)	1.21 (0.99 - 1.48)	0.91 (0.62 - 1.30)	0.94 (0.50 - 1.68)	1.23 (1.01 - 1.48)				
NRT + varenicline	3.54 (2.57 - 4.61)	2.33 (1.58 - 3.27)	1.80 (1.08 - 2.81)	1.86 (0.93 - 3.30)	2.35 (1.61 - 3.28)	1.96 (1.27 - 2.89)			
Combination NRT	2.22 (1.91 - 2.55)	1.35 (1.12 - 1.60)	1.01 (0.70 - 1.41)	1.04 (0.57 - 1.84)	1.36 (1.16 - 1.58)	1.11 (0.88 - 1.40)	0.53 (0.33 - 0.86)		
Varenicline	2.57 (2.32 - 2.85)	1.60 (1.39 - 1.84)	1.21 (0.87 - 1.65)	1.25 (0.69 - 2.13)	1.61 (1.43 - 1.83)	1.33 (1.06 - 1.65)	0.65 (0.42 - 0.99)	1.20 (0.99 - 1.44)	
Varenicline + bupropion	3.20 (2.05 - 4.60)	2.07 (1.22 - 3.25)	1.58 (0.85 - 2.75)	1.64 (0.75 - 3.20)	2.08 (1.24 - 3.27)	1.73 (0.98 - 2.86)	0.87 (0.43 - 1.69)	1.57 (0.90 - 2.61)	1.32 (0.77 - 2.18)

Note: NRT, nicotine replacement therapy. Shaded cells indicate statistically significant treatment effect.



The impact of treatment combinations relative to an assumption of an additive effect is worth noting. For example, NRT monotherapy plus varenicline has a risk ratio of 3.54. However, if assuming an additive effect on the log scale, the combined treatments should have a risk ratio of 4.32. Similarly for the other available combinations, two treatments together are less effective than if the two individual effects are combined. This apparent loss of effect is plausible. If the effects were additive on the log scale, it assumes that there is no overlap in effect. That is, none of the people benefitting from therapy A benefit from therapy B, and vice versa. To illustrate, consider a control arm quit rate of 10%. We would expect to observe, on average, quit rates of 16.8% with NRT and 25.7% with varenicline. Multiplying the relative risks generates an expected quit rate of 43.2% when using NRT in conjunction with varenicline. It is more plausible that combining the therapies means that some recipients would quit on either, and therefore do not gain additional benefit from dual therapy, while others benefit from one therapy, but not the other. In other words, the benefit of dual therapy is greater than for either therapy alone, but not equivalent to an additive effect.

#### 4.2.5.3 Sensitivity analysis

The previous analyses have estimated treatment effect in terms of the risk ratios. It is useful to consider the absolute quit rates across the different study arms and how that relates to the length of follow up. Table 4.8 shows the pooled quit rates by study arm and by six-month and 12-month follow up. These estimates include only studies using exactly six or 12-month follow up. There was substantial and statistically significant evidence of heterogeneity for all estimates with three or more studies. In most cases the pooled quit rate is lower at 12 months than at six months. This is consistent with relapse occurring between six and 12 months. Notably for NRT, the quit rates at six and 12 months are almost unchanged. The quit rates in the two e-cigarette trials are much lower than any of the other active interventions. One e-cigarette trial involved no behavioural support, while the other included responsive telephone support. Given the widespread provision of supportive therapy in other pharmacological trials, the minimal support in the e-cigarette trials may partly explain the low absolute quit rates observed.

**Table 4.8 Absolute quit rates across study arms: pharmacological interventions**

Intervention	6-month follow up			12-month follow up		
	studies	quit	95% CI	studies	quit	95% CI
Control	47	0.11	(0.09 - 0.14)	102	0.11	(0.10 - 0.12)
NRT	44	0.19	(0.16 - 0.23)	84	0.18	(0.16 - 0.20)
Bupropion	13	0.25	(0.21 - 0.30)	21	0.18	(0.16 - 0.21)
NRT + bupropion	4	0.25	(0.18 - 0.33)	3	0.23	(0.13 - 0.37)
E-cigarettes	1	0.07	(0.05 - 0.11)	1	0.11	(0.07 - 0.16)
Cytisine	2	0.15	(0.06 - 0.33)	1	0.08	(0.06 - 0.12)
Combination NRT	5	0.29	(0.17 - 0.44)	8	0.15	(0.10 - 0.21)
Varenicline	14	0.35	(0.30 - 0.41)	12	0.23	(0.19 - 0.27)
Varenicline + Bupropion	0			1	0.31	(0.25 - 0.37)
NRT + varenicline	2	0.32	(0.28 - 0.37)	0		

Notes: CI, credible interval.

The average absolute quit rate across control arms is 11% at both six and 12 months. It should be noted that almost all trials provided some form of supportive care to both the intervention and control arms. Typically, this was some form of behavioural therapy, such as individual counselling or group behaviour therapy. Studies were classified on the basis of the type of supportive care provided. A meta-regression of quit rates was used across control arms to explore how supportive care may impact on quit rates. Data from the 174 control arms was used, including covariates of intervention, length of follow up, and type of supportive care. The type of intervention had no statistically significant impact on the quit rate in control arms. Length of follow up did not have a statistically significant impact ( $p=0.10$ ) but was included in the model.

Twelve-month quit rates in control arms were predicted for each type of supportive care (Table 4.9). The control arm quit rates were statistically significantly higher relative to placebo-controlled in studies that used individual counselling or group behaviour therapy as a supportive care. That is, control arm quit rates are higher in pharmacological intervention studies that provide individual counselling or group behaviour therapy to all study arms.

Trials that provide individual counselling or group behaviour therapy have a higher control arm quit rate. In turn, this may impact on the potential treatment effect of the intervention. With a control arm quit rate of 11%, an intervention that achieved a 100% quit rate would have a risk ratio of 9. Considering an extreme, if the control arm quit rate was, for example, 50%, then the maximum possible risk ratio would be

2. Thus it is plausible that providing an effective supportive care to all trial arms may diminish the observed relative effectiveness of the active intervention.

**Table 4.9 Predicted 12-month quit rates in control arms by type of supportive care**

Supportive care	Quit rate	(95% CI)
Placebo	0.08	(0.06 - 0.10)
Brief advice/written materials	0.07	(0.05 - 0.09)
Intensive advice	0.10	(0.08 - 0.12)
Individual counselling	0.11	(0.10 - 0.13)
Group behaviour therapy	0.16	(0.14 - 0.19)
Other	0.07	(0.05 - 0.10)

Notes: CI, credible interval.

The network meta-analysis was also run as a network meta-regression to determine if certain study-level characteristics might be acting as effect modifiers. Six different covariates were considered: two continuous variables (study year, length of follow up) and four dichotomous variables (high quality, biochemical verification of abstinence, continuous abstinence, and no provision of supplementary care). The meta-regression assumed a shared effect across treatments. Longer follow up was associated with a reduced effect size, while measuring continuous abstinence (rather than point prevalence) was associated with a larger effect size (Table 4.10). The other covariates were not associated with statistically significant effects. Inclusion of covariates did not impact on the Deviance Information Criterion (DIC).

**Table 4.10 Network meta-regression results**

Covariate	Coefficient	(95% CI)	DIC	Random effects SD
No covariates	-	-	639.2	0.24 (0.17 to 0.30)
Study year	0.12	(-0.03 to 0.27)	640.7	0.22 (0.16 to 0.29)
Follow up	-0.12	(-0.25 to 0.00)	639.8	0.22 (0.16 to 0.29)
High quality	0.02	(-0.13 to 0.16)	640.4	0.24 (0.17 to 0.30)
Biochemically verified	0.11	(-0.08 to 0.31)	640.1	0.23 (0.17 to 0.30)
Continuous abstinence	0.17	(0.03 to 0.31)	638.3	0.22 (0.16 to 0.29)
No supplementary care	0.06	(-0.17 to 0.29)	640.2	0.24 (0.17 to 0.30)

Notes: CI, credible interval; DIC, Deviance Information Criterion; SD, standard deviation.

The impact on treatment effects (relative to control) of including covariates in the model are shown in Table 4.11. Including length of follow up reduces the effect size for all interventions apart from cytisine. Including continuous abstinence increases the treatment effect for all interventions. The addition of covariates has a negligible impact on DIC and random effects standard deviation, indicating that inclusion of covariates has a small impact on reducing heterogeneity.

**Table 4.11 Impact on treatment effect (relative to control) of including covariates in analysis**

Intervention	No covariate		Follow up = 12 months		Continuous abstinence	
	RR	(95% CI)	RR	(95% CI)	RR	(95% CI)
Bupropion	1.70	(1.53 - 1.87)	1.65	(1.49 - 1.82)	1.76	(1.59 - 1.94)
Cytisine	2.20	(1.68 - 2.83)	2.31	(1.78 - 2.95)	2.34	(1.80 - 3.00)
E-cigarette	2.14	(1.26 - 3.35)	2.09	(1.25 - 3.28)	2.19	(1.32 - 3.42)
NRT	1.68	(1.58 - 1.78)	1.64	(1.54 - 1.75)	1.76	(1.64 - 1.88)
NRT + bupropion	2.02	(1.70 - 2.40)	1.97	(1.65 - 2.33)	2.12	(1.78 - 2.50)
NRT + varenicline	3.54	(2.57 - 4.61)	3.44	(2.51 - 4.49)	3.60	(2.66 - 4.65)
Combination NRT	2.22	(1.91 - 2.55)	2.16	(1.87 - 2.49)	2.30	(2.00 - 2.64)
Varenicline	2.57	(2.32 - 2.85)	2.49	(2.24 - 2.78)	2.63	(2.37 - 2.91)
Varenicline + bupropion	3.20	(2.05 - 4.60)	3.11	(2.01 - 4.46)	3.26	(2.13 - 4.61)

Notes: RR, risk ratio; CI, credible interval.

The impact of length of follow up suggests that if all trials followed up to 12 months, the treatment effects observed would be lower. This is plausible if the rate of failure (that is to say, recommencing smoking) is different in the control and intervention arms after six months. Given that the pharmacological treatments typically last for up to 12 weeks, it is possible that those in the intervention arm reach the point of no nicotine or active treatment three months after the participants in the control arm, and the failure curve may therefore be different.

The influence of continuous abstinence implies that studies that record cessation on the basis of continuous abstinence observe a greater treatment effect than those using a point prevalence estimate. Continuous abstinence is considered a better measure of smoking cessation, as point prevalence does not account for those who have short-term relapses. People with short relapses may be less likely to succeed in long-term quitting. How the choice of abstinence measure might lead to a consistent bias is unclear.

The meta-regression results should be interpreted with caution. The inclusion of covariates has a negligible impact on model fit, and the estimated impact may be influenced more by certain comparisons than others. For example, the use of continuous abstinence is least common in NRT trials, which also contribute the most evidence to the network. The potentially counter-intuitive findings, particularly with regard to continuous abstinence, may be an artefact or proxy for some other study feature.

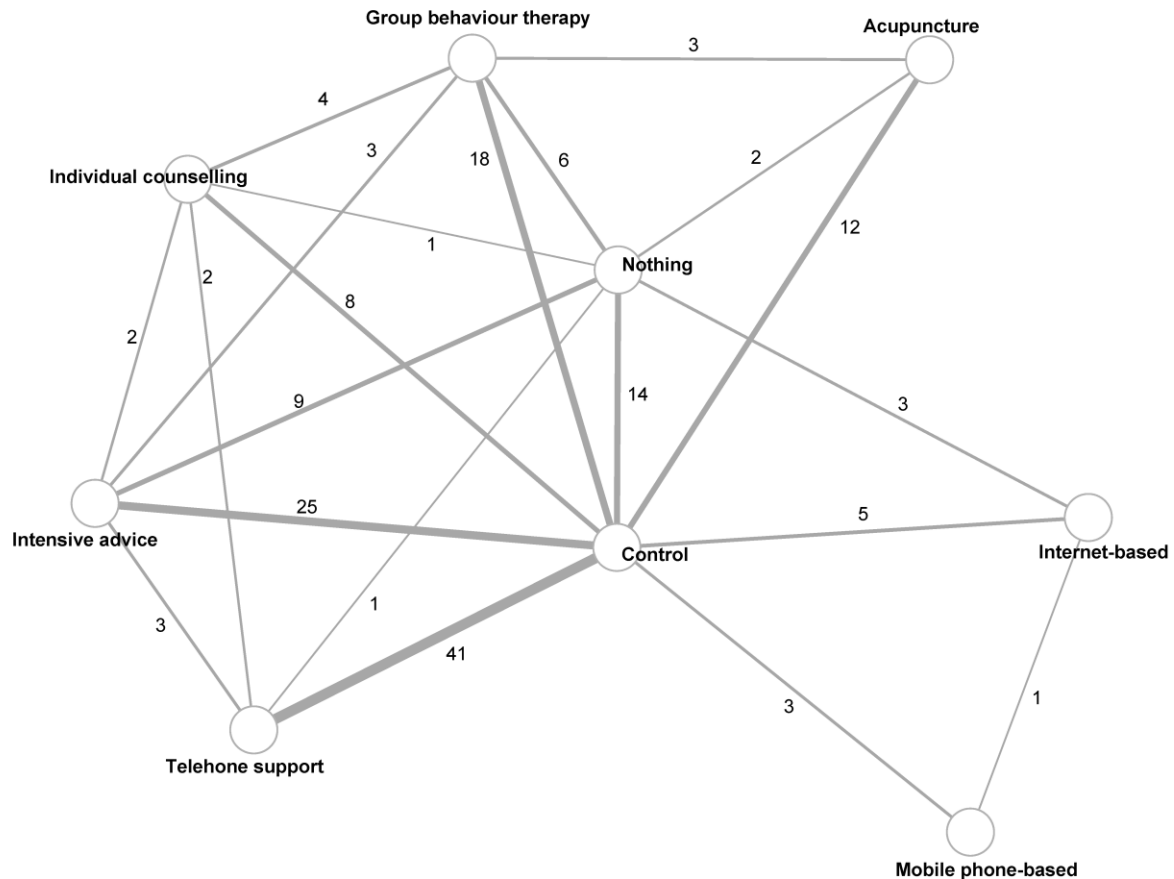
#### **4.2.6 Behavioural interventions**

There were 166 comparisons available across 143 behavioural intervention trials (Figure 4.6). There were 112 comparisons of active intervention to control, and a further 22 comparisons of active control to **'do nothing'**. **Fourteen trials provided data comparing control to 'do nothing'**. The control arms are based on participants receiving either brief advice or written materials, as this is presumed to constitute the standard of care for those seeking to quit **smoking**. The **'do nothing'** arms are typically waiting list control or no further contact other than at follow up to **determine smoking status**. **Both control and 'do nothing' arms have been included as separate arms in the following analyses**, as they are distinct and provide contextual information when considering how effective behavioural interventions are.

There were 47 comparisons involving telephone support, 42 involving intensive advice, and 34 involving group behaviour therapy. The majority of the studies were two-arm trials (n=127), but three-arm (n=12) and four-arm (n=4) trials were also included. There were only 19 head-to-head comparisons between the included interventions.

Combinations of therapies were excluded from this analysis. There were a variety of combinations reported, typically combining telephone or Internet-based support with individual counselling. In some cases, the combination of therapies in both the control and intervention arms was unique, and therefore the trial could not link into the evidence network. For other combinations there was insufficient evidence regarding the use of those combinations in smoking cessation attempts in Ireland, and therefore the evidence would not contribute to the economic evaluation of this report.

**Figure 4.6 Network of evidence for behavioural interventions for unselected adults**



#### 4.2.6.1 Direct comparisons

The pooled direct evidence for behavioural interventions is provided in Table 4.12. As for the comparison of pharmacotherapies, the pooled estimates have been combined using a random effects approach and the 95% confidence bounds are associated with the mean effect. In cases where there were five or more studies in the comparison, the 95% prediction intervals were also computed, and these give an indication of the range of effect sizes that might be observed in a future study.

**Relative to 'do nothing', four of the five behavioural interventions evaluated had a statistically significant treatment benefit.** Telephone support, based on a single trial, did not show a statistically significant treatment benefit.

**Control and 'do nothing' are clearly different, as is evidenced by the relative effectiveness observed across head-to-head comparisons** (RR=1.67, 95%CI: 1.34 - 2.07). A total of 14 trials included arms with no intervention and also arms that could be considered control on the basis of minimal intervention. As inclusion of some form of placebo is problematic for many of the behavioural interventions, the

alternative is providing some form of minimal intervention to all study arms. Pooling control and 'do nothing' could create biased estimates, particularly if some interventions are more likely to be compared to minimal intervention than 'do nothing'.

The direct evidence suggests a somewhat consistent picture whereby 'do nothing' is less effective than control or active intervention, apart from the single telephone support study. Acupuncture and mobile phone-based interventions appear to have similar effectiveness to control. The remaining five interventions (intensive advice, telephone support, Internet-based, individual counselling, and group behaviour therapy) are superior to control and, based on limited evidence, there is no statistically significant evidence of any one offering a treatment benefit over another.

Four of the included comparisons showed evidence of substantial heterogeneity. Two of the comparisons included sufficient studies to consider meta-regression. The comparison of telephone support versus control included 41 studies ( $I^2=64\%$ ). When study-level characteristics were used as covariates, two were identified as statistically significant effect modifiers: length of follow up ( $p=0.0194$ ), and continuous abstinence ( $p=0.0002$ ). Increased follow up was associated with a reduced treatment effect. The mean follow up was 12 months, and the overall treatment effect (risk ratio = 1.35) reflects the effect at 12 months. At six months follow up the estimated treatment effect was 1.54. In terms of continuous abstinence, the estimated treatment effect was 1.60 with, and 1.11 without continuous abstinence. For the comparison of group behaviour therapy versus control ( $n=18$ ,  $I^2=66\%$ ), only biochemical verification was a significant effect modifier. In contrast to the overall effect of 1.80, the effect sizes were 2.46 with biochemical verification and 1.19 without. In other words, studies using self-reported abstinence had a lower effect size.

Two further comparisons had substantial heterogeneity, but insufficient studies for meta-regression: group behaviour therapy versus 'do nothing' ( $n=6$ ,  $I^2=69\%$ ), and Internet-based versus control ( $n=5$ ,  $I^2=70\%$ ). The forest plots for these two comparisons are provided in Figures 4.7 and 4.8. The heterogeneity in group behaviour therapy versus 'do nothing' is largely driven by two studies (from 1983 and 1985) that found a modest treatment effect that was not statistically significant. In terms of Internet-based interventions versus control, a 2011 study found a non-statistically significant treatment benefit for the control arm. In fact, a statistically significant treatment benefit was only found in two studies from 2008.



**Table 4.12 Treatment effects based on direct evidence: behavioural interventions**

Comparison	Studies	Participants (n)	Risk ratio (95% CI)	p-value	95% Prediction interval	I <sup>2</sup> (95% CI)
Individual counselling vs Nothing <sup>*(199)</sup>	1	155	0.85 (0.27 – 2.63)	0.772		NA
Telephone support vs Nothing <sup>*(275)</sup>	1	1821	1.11 (0.74 - 1.67)	0.621		NA
Internet-based vs Nothing <sup>*(242, 248, 249)</sup>	3	3671	1.46 (1.18 – 1.81)	0.001		0.61 (0.00 - 0.89)
Control vs Nothing <sup>(173, 215, 223, 240, 353, 462-469)</sup>	14	9720	1.67 (1.34 - 2.07)	<0.001	(0.97 - 2.85)	0.31 (0.00 - 0.64)
Intensive advice vs Nothing <sup>(187, 215, 224, 225, 229, 231, 233, 234, 240)</sup>	9	6707	1.74 (1.36 - 2.24)	<0.001	(0.96 - 3.15)	0.36 (0.00 - 0.71)
Acupuncture vs Nothing <sup>*(167, 173)</sup>	2	243	2.49 (1.23 – 5.02)	0.011		0.00
Group behaviour therapy vs Nothing <sup>(167, 173, 177, 182, 187, 190)</sup>	6	846	3.16 (1.26 - 7.90)	0.014	(0.19 - 53.03)	0.69 (0.28 - 0.87)
Acupuncture vs Control <sup>(164-166, 168-174)</sup>	12	2249	1.03 (0.83 - 1.29)	0.778	(0.76 - 1.40)	0.03 (0.00 - 0.60)
Mobile phone-based vs Control <sup>*(251-253)</sup>	3	1112	1.18 (0.88 - 1.60)	0.272		0.51 (0.00 - 0.86)
Intensive advice vs Control <sup>(210, 212-223, 226-228, 230, 232, 235-241)</sup>	25	16196	1.19 (1.05 - 1.35)	0.008	(0.84 - 1.67)	0.28 (0.00 - 0.56)
Telephone support vs Control <sup>(218, 235, 254-274, 276-293)</sup>	41	44218	1.35 (1.21 - 1.51)	<0.001	(0.78 - 2.35)	0.64 (0.49 - 0.74)
Internet-based vs Control <sup>(244-247, 250)</sup>	5	5128	1.43 (1.02 - 2.00)	0.041	(0.45 - 4.51)	0.70 (0.23 - 0.88)
Individual counselling vs Control <sup>(178, 192, 200-203, 207, 208)</sup>	8	3696	1.48 (1.17 - 1.85)	0.001	(1.11 - 1.96)	0.00 (0.00 - 0.57)
Group behaviour therapy vs Control <sup>(168, 173, 175, 176, 178, 180, 184-186, 188, 189, 191-197)</sup>	18	5072	1.80 (1.36 - 2.40)	<0.001	(0.66 - 4.92)	0.66 (0.45 - 0.79)
Individual counselling vs Telephone support <sup>*(204, 206)</sup>	2	1226	1.02 (0.74 - 1.42)	0.884		0.22
Intensive advice vs Telephone support <sup>*(211, 218, 235)</sup>	3	2869	1.11 (0.77 - 1.59)	0.572		0.00 (0.00 - 0.88)
Mobile phone-based vs Internet-based <sup>*(243)</sup>	1	755	1.43 (0.88 - 2.31)	0.151		NA

Notes: comparisons marked with \* are based on fixed effect model, all other treatment effect estimates based on random effects model.

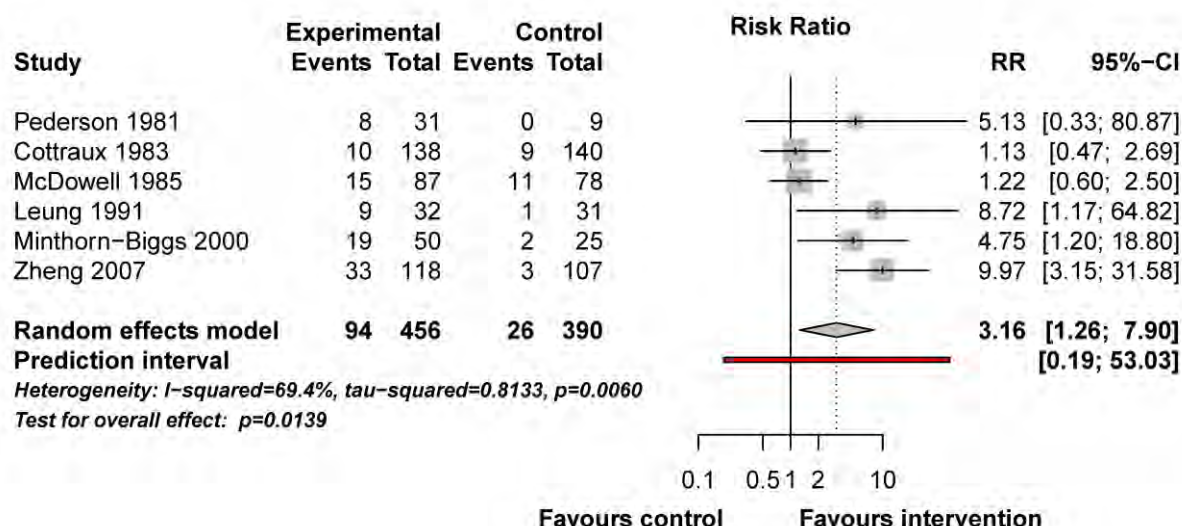
**Table 4.12 continued. Treatment effects based on direct evidence: behavioural interventions**

Group behaviour therapy vs Individual counselling* <sup>(178, 183, 192, 198)</sup>	4	2854	1.10	(0.87 - 1.40)	0.426	0.42	(0.00 - 0.81)
Intensive advice vs Individual counselling* <sup>(205, 209)</sup>	2	1028	1.40	(1.08 – 1.80)	0.010	0.85	
Intensive advice vs Group behaviour therapy* <sup>(179, 181, 187)</sup>	3	351	1.05	(0.63 - 1.75)	0.853	0.00	(0.00 - 0.33)
Acupuncture vs Group behaviour therapy* <sup>(167, 168, 173)</sup>	3	396	1.34	(0.80 – 2.24)	0.270	0.64	(0.00 - 0.90)

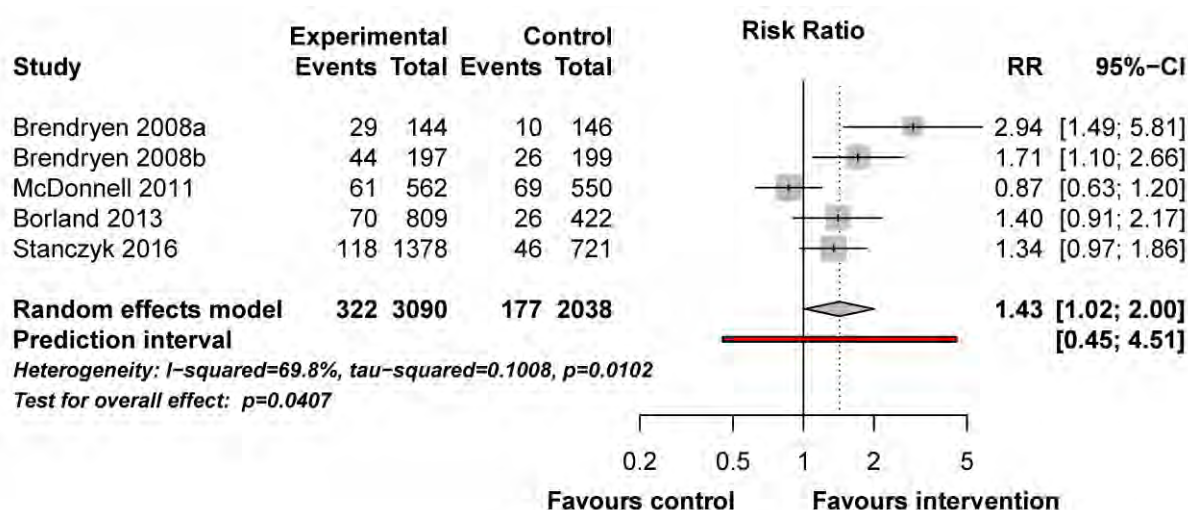
Notes: comparisons marked with \* are based on fixed effect model, all other treatment effect estimates based on random effects model.

For the comparison of group behaviour therapy versus control, the fixed effect estimated (RR=1.45, 95%CI: 1.27 to 1.66) was lower than the random effects estimate (RR=1.80, 95% CI: 1.36 to 2.40). Given that the comparison was supported by 18 studies and there was evidence of substantial heterogeneity, the random effects analysis was considered more appropriate.

**Figure 4.7 Forest plot of studies comparing group behaviour therapy versus 'do nothing'**



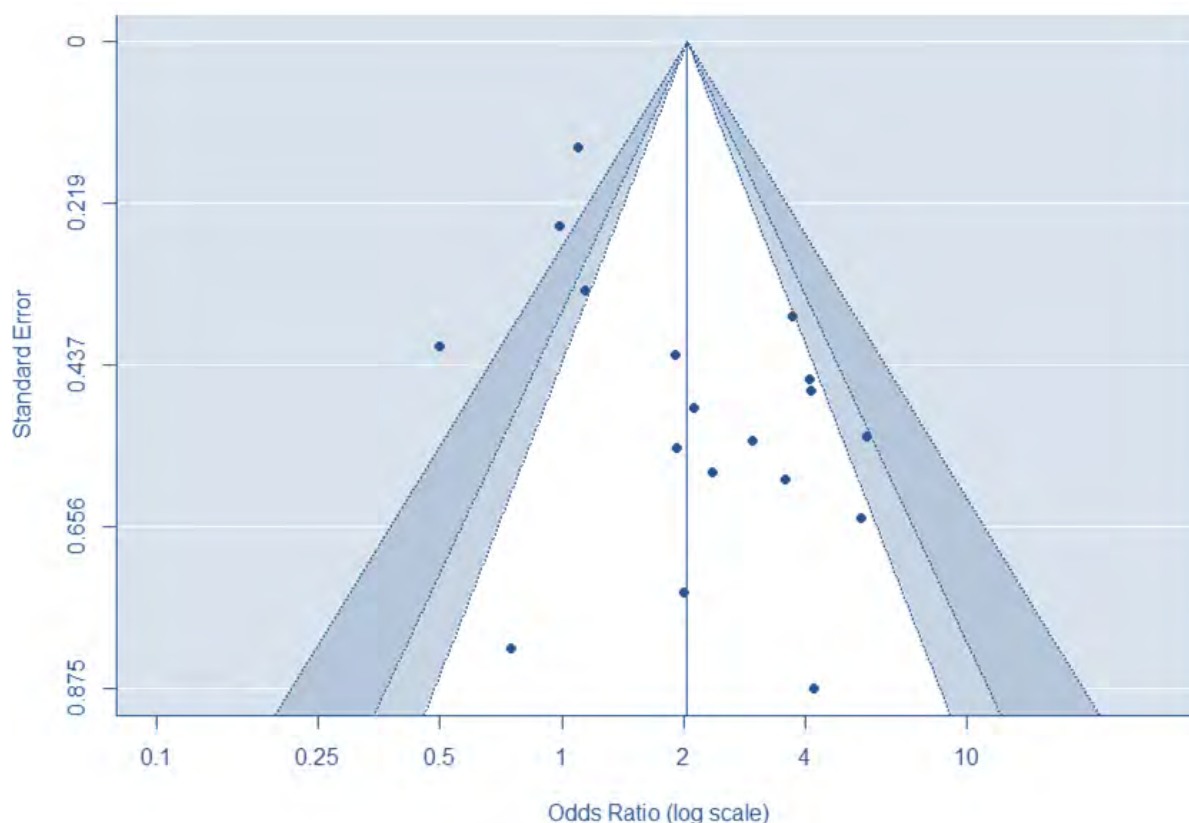
**Figure 4.8 Forest plot of studies comparing Internet-based interventions versus control**



The possible presence of small study bias was investigated using funnel plots for cases where there were 10 or more studies. In two comparisons there was statistically significant evidence of bias using both the Harbord and Egger's tests: group behaviour therapy versus control (Harbord test:  $p=0.025$ ; Egger's test:  $p=0.008$ ), and intensive advice versus control (Harbord test:  $p=0.023$ ; Egger's test:

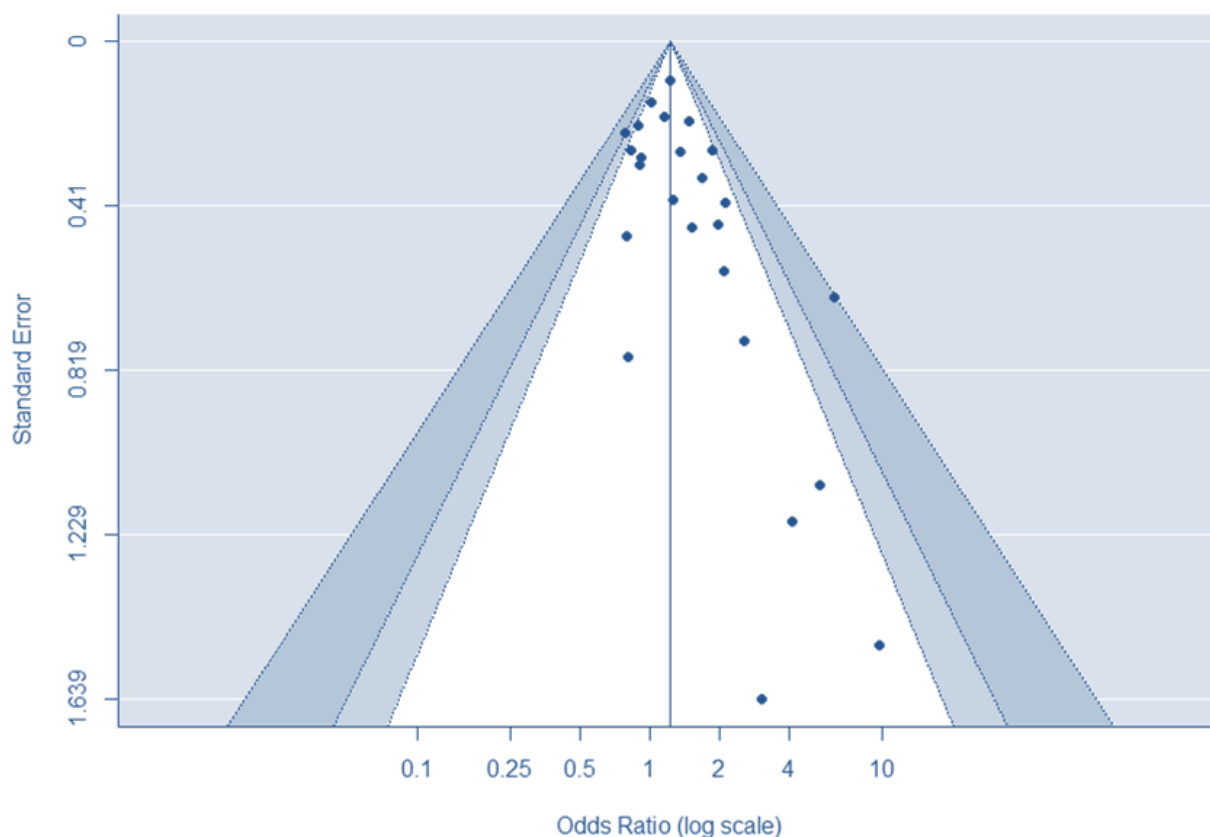
$p=0.021$ ). The evidence of bias in both cases is consistent with the concept of publication bias – smaller studies are associated with a larger effect size in favour of the intervention.

**Figure 4.9 Funnel plot of studies comparing group behaviour therapy versus control**



The trim and fill technique was applied to both comparisons to determine the potential impact of small study bias on the estimated treatment effect. For the comparison of group behaviour therapy versus control, the risk ratio decreased from 1.80 (95% CI: 1.36 to 2.40) to 1.36 (95% CI: 1.04 to 1.79). The reduction in treatment effect is quite marked, although the mean treatment effect is still superior to control. In the comparison of intensive advice versus control, the application of trim and fill reduced the treatment effect from 1.19 (95% CI: 1.05 to 1.35) to 1.14 (95% CI: 0.99 to 1.31). The treatment effect size is only reduced by a modest amount, but the confidence bounds for the effect estimate include the possibility of no treatment effect.

**Figure 4.10 Funnel plot of studies comparing intensive advice versus control**



#### 4.2.6.2 Direct and indirect comparisons

As with the analysis of pharmacological interventions, it was considered appropriate to extend the analysis of behavioural interventions to include both direct and indirect evidence. Treatment effects were again calculated on the log odds scale and then converted to risk ratios using the assumed control risk, which was calculated as the risk of smoking cessation pooled across the control arms.

Treatment effects were first estimated using both consistency and inconsistency models to determine whether the estimates of treatment effect were sensitive to the assumption of consistency. The consistency and inconsistency models produced similar estimates of treatment effect in most cases. Four comparisons disagreed in the direction of effect. However, all of the estimates from the consistency model were well within the confidence bounds for the corresponding inconsistency model estimates. Comparing the models on the basis of DIC, the consistency model produced a DIC of 528.7 and the inconsistency model a DIC of 533.3. The credible intervals around treatment effect were larger in the inconsistency model than the corresponding comparisons in the consistency model. The random effects standard deviation was 0.36 (95% CI: 0.28 to 0.44) for the consistency model and 0.35 (95% CI: 0.26 to 0.44) for the inconsistency model.

An analysis of heterogeneity estimated a global  $I^2$  of 54%. Based on an analysis of heterogeneity, potential issues were identified for four comparisons:

- **telephone support versus 'do nothing' (p=0.077),**
- acupuncture versus control (p=0.005),
- Internet-based versus control (p=0.077),
- and individual counselling versus intensive advice (p=0.082).

Using a node-splitting analysis to investigate the contribution of direct and indirect evidence to treatment effect estimates, there was one comparison with a statistically significant difference in the direct and indirect evidence (Table 4.13). In the comparison of group behaviour therapy versus acupuncture, the direct evidence suggested a treatment benefit associated with acupuncture that was not statistically significant (based on three studies). The indirect evidence suggested a statistically significant treatment benefit for group behaviour therapy. Given that the direct evidence suggests that acupuncture has a similar effect to control, and that group behaviour therapy provides a statistically significant treatment benefit over control, the limited direct evidence between acupuncture and group behaviour therapy appears to contradict the general findings.

Other comparisons associated with some evidence of inconsistency included: telephone support versus **'do nothing' (p=0.087)**, **individual counselling versus control (p=0.083)**, and individual counselling versus intensive advice (p=0.098). In these cases the general interpretation was not changed by the addition of indirect evidence.

For almost all other comparisons the direct and indirect treatment effects were in agreement in terms of direction and magnitude, although there were some differences. There were four instances of a difference in direction of effect, although the difference was not statistically significant due to the wide credible intervals.

**Table 4.13 Comparison of direct and indirect treatment effect estimates: behavioural interventions**

Comparison	Risk ratio						p-value
	Direct estimate (95% CI)		Indirect estimate (95% CI)		Network estimate(95% CI)		
Control vs Nothing	1.69	(1.32 to 2.15)	1.37	(1.06 to 1.76)	1.49	(1.25 to 1.79)	0.242
Acupuncture vs Nothing	2.56	(1.13 to 5.04)	1.59	(1.08 to 2.29)	1.75	(1.26 to 2.37)	0.302
Internet-based vs Nothing	1.49	(0.98 to 2.24)	2.06	(1.43 to 2.98)	1.81	(1.37 to 2.37)	0.242
Telephone support vs Nothing	1.10	(0.52 to 2.22)	2.08	(1.70 to 2.56)	1.98	(1.62 to 2.37)	0.087
Intensive advice vs Nothing	1.88	(1.42 to 2.56)	2.10	(1.62 to 2.77)	2.00	(1.64 to 2.37)	0.600
Individual counselling vs Nothing	0.85	(0.20 to 2.98)	2.13	(1.62 to 2.77)	2.06	(1.56 to 2.77)	0.166
Group behaviour therapy vs Nothing	2.98	(1.90 to 4.48)	2.56	(2.03 to 3.45)	2.77	(2.13 to 3.45)	0.615
Acupuncture vs Control	1.04	(0.74 to 1.42)	1.01	(0.24 to 3.21)	1.18	(0.87 to 1.59)	0.959
Internet-based vs Control	1.44	(1.02 to 2.01)	0.93	(0.59 to 1.42)	1.21	(0.93 to 1.59)	0.113
Mobile phone-based vs Control	1.17	(0.70 to 1.87)	1.78	(0.76 to 3.69)	1.31	(0.86 to 1.96)	0.389
Telephone support vs Control	1.37	(1.21 to 1.55)	1.13	(0.70 to 1.82)	1.35	(1.19 to 1.52)	0.431
Intensive advice vs Control	1.29	(1.08 to 1.55)	1.56	(1.15 to 2.10)	1.36	(1.17 to 1.59)	0.313
Individual counselling vs Control	1.70	(1.20 to 2.37)	1.12	(0.79 to 1.55)	1.39	(1.09 to 1.78)	0.083
Group behaviour therapy vs Control	1.82	(1.46 to 2.27)	2.15	(1.48 to 2.98)	1.85	(1.53 to 2.26)	0.472
Group behaviour therapy vs Acupuncture	0.79	(0.39 to 1.59)	1.95	(1.32 to 2.77)	1.59	(1.14 to 2.20)	0.025
Internet-based vs Mobile phone-based	0.70	(0.29 to 1.59)	1.08	(0.60 to 1.84)	0.93	(0.57 to 1.47)	0.397
Telephone support vs Intensive advice	0.99	(0.56 to 1.76)	0.99	(0.79 to 1.22)	0.99	(0.81 to 1.20)	0.993
Individual counselling vs Intensive advice	0.69	(0.39 to 1.20)	1.17	(0.86 to 1.57)	1.03	(0.78 to 1.36)	0.098
Telephone support vs Individual counselling	0.96	(0.52 to 1.66)	0.97	(0.70 to 1.30)	0.96	(0.73 to 1.25)	0.996
Intensive advice vs Group behaviour therapy	1.06	(0.50 to 2.18)	0.67	(0.51 to 0.88)	0.72	(0.55 to 0.92)	0.243
Individual counselling vs Group behaviour therapy	0.83	(0.52 to 1.31)	0.68	(0.47 to 1.00)	0.74	(0.54 to 0.98)	0.527

Notes: CI, credible interval. The direct, indirect and network evidence are created from three different models, and the network estimate was not a weighted average of the indirect and direct studies. Results are presented for studies for which there was both direct and indirect evidence not limited to data from a single multi-arm study).

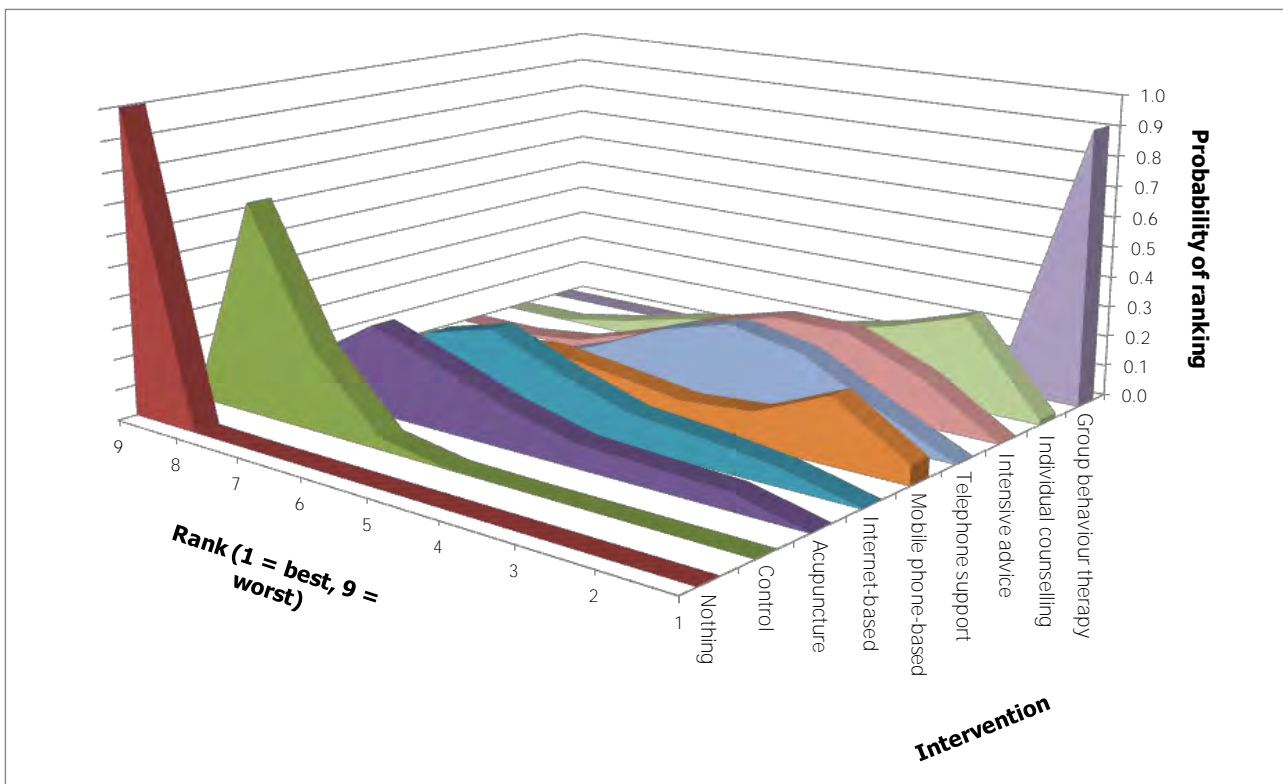


The nine interventions in the network of behavioural treatments were analysed in terms of their likely ranking from best treatment to worst treatment (Figure 4.11).

**There was a probability of 1 that 'do nothing' was the least effective treatment.**

Group behaviour therapy had the highest probability of being most effective (probability = 0.91). Individual counselling and intensive advice were the next highest ranked treatments. Intensive advice, telephone support and mobile phone-based interventions had wide ranges of probable rankings, indicating uncertainty in their effectiveness compared with the other interventions.

**Figure 4.11 Probability of rankings: behavioural interventions**



Note: the graph shows the probability of a given intervention being ranked from 1 (most effective intervention) to 10 (least effective intervention). A high probability reflects greater certainty about the ranking of a particular intervention. For example, it is almost certain that 'nothing' is the least effective intervention with a probability of 0.997 of being ranked tenth. There is a probability of 0.91 that group behaviour therapy is the most effective intervention.

When considered in terms of prediction intervals, none of the behavioural interventions are associated with a statistically significant treatment effect relative to control (Table 4.14). In other words, the expectation is that futures studies for any of the behavioural interventions may show no treatment benefit relative to control.



**Table 4.14 Treatment effect relative to control: behavioural interventions**

Intervention	Risk ratio	95% CI	95% PI
Do nothing	0.66	(0.54 - 0.79)	(0.32 - 1.26)
Control	Reference		
Acupuncture	1.17	(0.86 - 1.58)	(0.59 - 2.52)
Internet-based	1.22	(0.93 - 1.58)	(0.60 - 2.23)
Mobile phone-based	1.31	(0.84 - 1.97)	(0.61 - 2.69)
Telephone support	1.34	(1.19 - 1.51)	(0.70 - 2.47)
Intensive advice	1.35	(1.16 - 1.58)	(0.72 - 2.35)
Individual counselling	1.39	(1.10 - 1.76)	(0.74 - 2.63)
Group behaviour therapy	1.85	(1.53 - 2.23)	(0.95 - 3.20)

Notes: CI, credible interval; PI, prediction interval.

The network meta-analysis provides estimates of the relative effectiveness of each intervention compared to each of the others in the network (Table 4.15). The general hierarchy observed in the direct evidence is apparent in the combined direct and indirect evidence, with the distinction being that group behaviour therapy has a statistically significant treatment benefit over all interventions other than mobile phone-based interventions. It should be noted that there were only four studies providing data on mobile phone-based interventions, and the effectiveness of the intervention has wide credible intervals.

**Table 4.15 Network meta-analysis treatment effect estimates: behavioural interventions**

Intervention	Risk ratio (95% credible interval)							
	Nothing	Control	Acupunctur e	Internet- based	Mobile phone- based	Telephone support	Intensive advice	Individual counselling
<b>Control</b>	1.50 (1.26 - 1.79)							
<b>Acupuncture</b>	1.74 (1.25 - 2.39)	1.17 (0.86 - 1.58)						
<b>Internet-based</b>	1.81 (1.38 - 2.35)	1.22 (0.93 - 1.58)	1.04 (0.69 - 1.55)					
<b>Mobile phone- based</b>	1.93 (1.24 - 2.89)	1.31 (0.84 - 1.97)	1.12 (0.65 - 1.86)	1.07 (0.66 - 1.70)				
<b>Telephone support</b>	1.98 (1.63 - 2.41)	1.34 (1.19 - 1.51)	1.15 (0.82 - 1.59)	1.11 (0.82 - 1.47)	1.03 (0.65 - 1.61)			
<b>Intensive advice</b>	2.00 (1.66 - 2.41)	1.35 (1.16 - 1.58)	1.16 (0.82 - 1.62)	1.12 (0.82 - 1.51)	1.04 (0.65 - 1.64)	1.01 (0.83 - 1.23)		
<b>Individual counselling</b>	2.05 (1.57 - 2.66)	1.39 (1.10 - 1.76)	1.19 (0.81 - 1.74)	1.14 (0.80 - 1.63)	1.07 (0.64 - 1.73)	1.04 (0.80 - 1.34)	1.03 (0.78 - 1.34)	
<b>Group behaviour therapy</b>	2.67 (2.15 - 3.30)	1.85 (1.53 - 2.23)	1.60 (1.14 - 2.22)	1.54 (1.12 - 2.10)	1.43 (0.90 - 2.25)	1.39 (1.11 - 1.75)	1.38 (1.09 - 1.75)	1.35 (1.02 - 1.77)

Note: shaded cells indicate a statistically significant treatment effect.

The majority of evidence in the network relates to comparisons between active **interventions and control or 'do nothing'**. The number of head-to-head trials providing direct comparisons between behavioural therapies is very limited. Of the 166 comparisons included, only 18 were head-to-head between behavioural interventions. Therefore, it is apparent that combined direct and indirect evidence is **influenced primarily by the evidence relative to control and 'do nothing'**.

**The concept of 'do nothing' does not exist in the network of pharmacological treatments.** In relation to behavioural interventions, 'do nothing' is clearly different to receiving brief advice or written materials. As control has been defined here to include brief advice or written materials, the finding of a treatment benefit relative to **'do nothing' is consistent with the findings of the Cochrane review of brief advice.** All of the behavioural interventions reviewed provide a treatment effect benefit over the **alternative of 'do nothing'**.

#### 4.2.6.3 Sensitivity analysis

Quit rates at six and 12 months were pooled across the different study arms (Table 4.16). There are no studies with 12-months follow up for mobile phone-based interventions. All estimates with three or more studies, with the exception of acupuncture and group behaviour therapy at six months, show substantial and statistically significant evidence of heterogeneity. In almost all cases the pooled quit rate is lower at 12 months than at six months, which is consistent with there being relapse between six and 12 months. There is an apparent increase in quit rates for acupuncture between the six and 12-month follow-up data, and for individual counselling the rates are unchanged.

**Table 4.16 Absolute quit rates across study arms: behavioural interventions**

Intervention	6-months follow up			12-months follow up		
	studies	quit	95% CI	studies	quit	95% CI
Do nothing	11	0.07	(0.04 - 0.11)	15	0.04	(0.03 - 0.06)
Control	43	0.10	(0.08 - 0.12)	54	0.08	(0.06 - 0.09)
Acupuncture	7	0.09	(0.06 - 0.13)	3	0.24	(0.12 - 0.43)
Internet-based	6	0.13	(0.07 - 0.24)	2	0.08	(0.07 - 0.10)
Mobile phone-based	4	0.13	(0.08 - 0.21)	0		
Telephone support	10	0.16	(0.10 - 0.24)	22	0.10	(0.08 - 0.13)
Intensive advice	18	0.15	(0.12 - 0.18)	15	0.08	(0.06 - 0.11)
Individual counselling	9	0.13	(0.07 - 0.21)	4	0.12	(0.06 - 0.23)
Group behaviour therapy	10	0.26	(0.22 - 0.31)	16	0.17	(0.13 - 0.23)

Notes: CI, credible interval.

Network meta-regressions were carried out using study-level covariates, as per the approach used for the analysis of studies including pharmacological interventions.

Five different covariates were considered: two continuous variables (study year, length of follow up) and three dichotomous variables (high quality, biochemical verification of abstinence, and continuous abstinence). The meta-regression assumed a shared effect across treatments. As for the network meta-regression of pharmacological interventions, length of follow up was the only covariate associated with a reduced effect size (Table 4.17). Although none of the covariates were associated with statistically significant effects, some of the effect sizes were potentially large. Including covariates did not impact substantively on the Deviance Information Criterion (DIC), or the random effects standard deviation.

**Table 4.17 Network meta-regression results**

Covariate	Coefficient	(95% CI)	DIC	Random effects SD
No covariates	-	-	528.7	0.36 (0.28 to 0.44)
Study year	0.11	(-0.12 to 0.34)	529.1	0.36 (0.28 to 0.45)
Follow up	-0.15	(-0.45 to 0.14)	530.1	0.35 (0.27 to 0.44)
High quality	0.07	(-0.17 to 0.32)	528.8	0.36 (0.28 to 0.45)
Biochemically verified	0.19	(-0.02 to 0.39)	527.4	0.35 (0.28 to 0.44)
Continuous abstinence	0.13	(-0.05 to 0.32)	529.8	0.35 (0.27 to 0.44)

Notes: CI, credible interval; DIC, Deviance Information Criterion; SD, standard deviation.

The impact on treatment effects (relative to control) of including covariates in the model are shown in Table 4.18. The inclusion of biochemical verification and continuous abstinence increases the treatment effect for all interventions.

**Table 4.18 Impact on treatment effect (relative to control) of including covariates in analysis of behavioural interventions**

Intervention	No covariate		Biochemical verification		Continuous abstinence	
Acupuncture	1.17	(0.86 - 1.58)	1.34	(0.96 - 1.86)	1.25	(0.91 - 1.69)
Group behaviour therapy	1.85	(1.53 - 2.23)	2.00	(1.62 - 2.47)	1.99	(1.61 - 2.46)
Intensive advice	1.35	(1.16 - 1.58)	1.48	(1.23 - 1.77)	1.47	(1.22 - 1.77)
Individual counselling	1.39	(1.10 - 1.76)	1.51	(1.17 - 1.93)	1.51	(1.16 - 1.95)
Mobile phone-based	1.31	(0.84 - 1.97)	1.48	(0.95 - 2.26)	1.36	(0.88 - 2.04)
Telephone support	1.34	(1.19 - 1.51)	1.51	(1.27 - 1.80)	1.42	(1.23 - 1.64)
Internet-based	1.22	(0.93 - 1.58)	1.41	(1.03 - 1.90)	1.30	(0.98 - 1.71)

The analysis shows that if all studies used biochemical verification, then larger treatment effects would be expected. Similarly, if all studies used continuous abstinence rather than self-reported abstinence, greater treatment effects would be expected.

As with pharmacological interventions, the meta-regression results should be interpreted with caution. The inclusion of covariates has a negligible impact on model fit and the observed effects may be overly influenced by certain comparisons.

#### 4.2.7 Behavioural interventions as an adjunct to pharmacotherapy

The systematic review of smoking cessation interventions in unselected adults found separate evidence regarding pharmacotherapy and behavioural interventions. With

the exception of two studies, there was no evidence directly comparing pharmacological and behavioural interventions. However, it was clear that the majority of pharmacological interventions included some form of behavioural support intervention provided to both the control and intervention study arms. The **behavioural interventions assessed offered a treatment benefit relative to 'do nothing' and, to a lesser extent, relative to control** in the form of brief advice or written materials. It is therefore possible that combining pharmacotherapy with a behavioural intervention may lead to an increased treatment effect relative to pharmacotherapy or a behavioural intervention as a single intervention.

#### 4.2.7.1 Identification of studies

Two systematic reviews investigated the clinical effectiveness of behavioural therapy with pharmacotherapy. The first review considered behavioural therapy as an adjunct to pharmacotherapy.<sup>(470)</sup> Studies were included if all patients were provided with pharmacotherapy, and if the intervention arm participants received more intensive behavioural therapy than the control arm participants. The second review considered behavioural therapy in combination with pharmacotherapy.<sup>(471)</sup> Studies were included if all patients received behavioural therapy and all intervention arm participants were offered pharmacotherapy. Pharmacotherapy was offered as an adjunct to behavioural therapy in the second review. This HTA was restricted to the studies identified in those reviews, and the search was not updated given the recent publication date of the identified reviews.

Of the 176 pharmacological intervention trials, only 12% did not include supportive care in all arms. Almost three out of four (73%) trials provided intensive advice, individual counselling or group behaviour therapy to all participants. However, only 31 of 143 behavioural therapy studies clearly stated the provision of pharmacotherapy to participants. This HTA was primarily interested in behavioural therapy as an adjunct to pharmacotherapy as this is a common feature of these studies. Understanding the impact of behavioural support on the clinical effectiveness of pharmacotherapy is relevant as the provision of behavioural therapy may be incorporated into the product license requirements or guidelines.

#### 4.2.7.2 Available evidence

The systematic review of behavioural therapy as adjunct to pharmacotherapy identified 47 trials, of which 36 were considered applicable to the review in this HTA. The remaining 11 did not meet the inclusion criteria for this review, mainly due to the study population not being applicable. The included studies were published between 1985 and 2014, and 42% (n=15) were considered at low risk of bias. The majority (n=26) used biochemical verification, but only 19% (n=7) recorded continuous abstinence. The pharmacological interventions used in the trials included

NRT (n=24), bupropion (n=5), choice of pharmacotherapy (n=4), NRT plus bupropion (n=2), and varenicline (n=1). The review included studies that compared adjunct behavioural therapy either to no adjunct behavioural therapy (n=6), or to alternative configurations of low intensity (n=13) or high-intensity behavioural therapy (n=17).

#### 4.2.7.3 Results

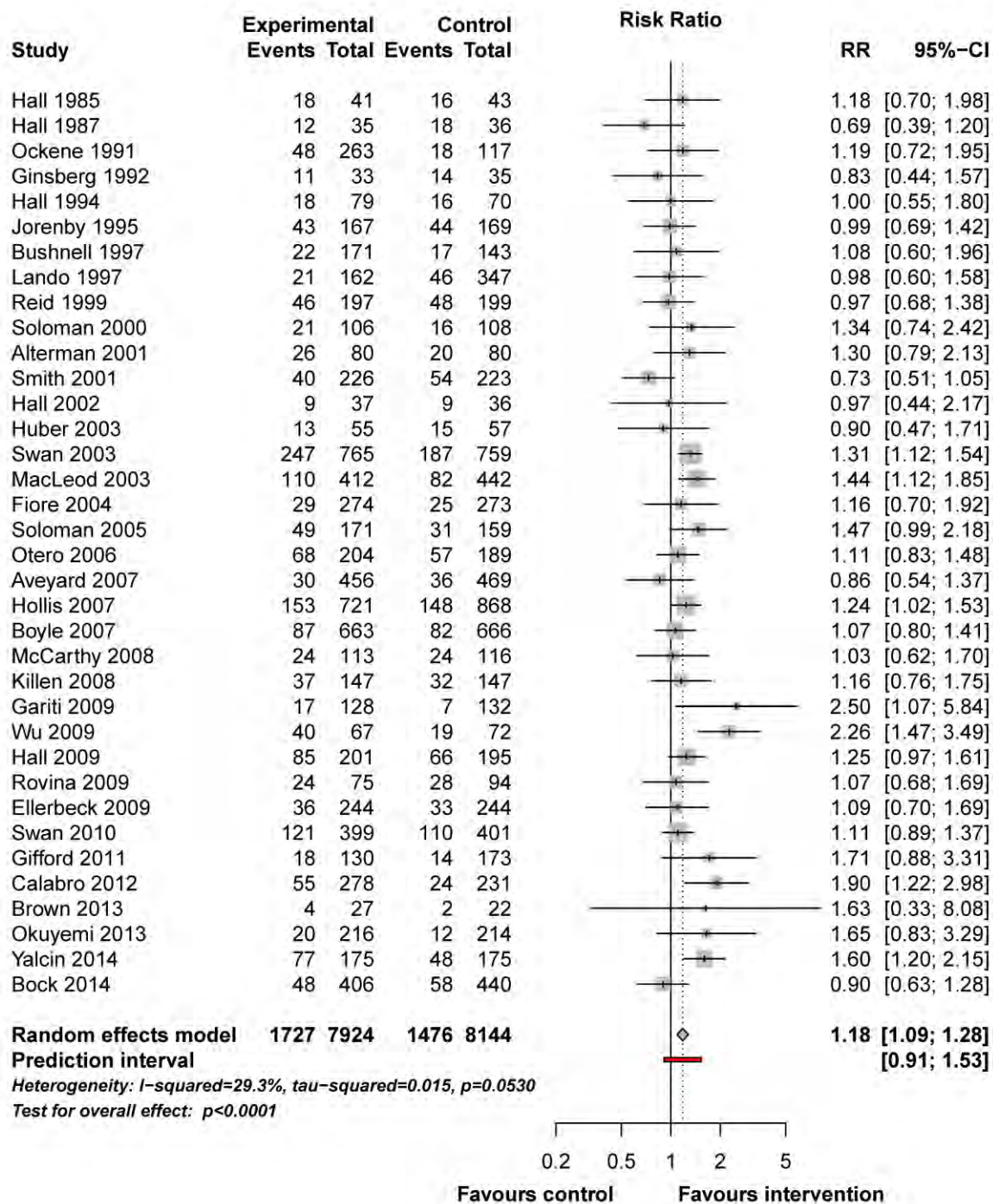
There was no statistically significant difference in treatment effect by type of pharmacological intervention or by the type of supportive care used in the control arms of the studies (Figure 4.12). There was moderate heterogeneity in the full analysis ( $I^2=29.3\%$ ,  $p=0.053$ ). The overall treatment effect of providing behavioural therapy as an adjunct to pharmacotherapy was modest, with a risk ratio of 1.18 (95% CI: 1.09 to 1.28). A risk ratio of less than 1 was estimated in 10 of the 36 studies, indicating the uncertainty of treatment effect. The prediction intervals for the treatment effect were correspondingly wide (95% prediction interval: 0.91 to **1.53**). **There was no evidence of funnel plot asymmetry using either Egger's test** ( $p=0.23$ ) or the Harbord test ( $p=0.29$ ).

Meta-regression was used to determine if there was an association between study-level covariates and treatment effect. Only study year was a statistically significant effect modifier, with more recent studies showing a greater treatment effect ( $p=0.0148$ ). The predicted effect for a study published in 2014 was a risk ratio of 1.35 (95% CI: 1.19 to 1.55).

On average, the addition of behavioural therapy to pharmacotherapy results in an increased treatment effect over and above pharmacotherapy alone. In the main analysis, the treatment effect of NRT relative to control was an estimated risk ratio 1.68, and the treatment effect of individual counselling was 1.39. If the treatment effects were additive on the log scale, then risk ratio for NRT plus individual counselling relative to NRT alone would be 1.39. The estimated risk ratio of 1.18 is somewhat less than that, suggesting a loss of effect. This could also be seen for combination pharmacotherapies where the risk ratio for NRT plus varenicline was less than the combination of effect sizes for NRT and varenicline individually.



**Figure 4.12 Behavioural support as an adjunct to pharmacotherapy**



Although the use of pharmacotherapy as an adjunct to behavioural therapy is not being considered as a distinct intervention in this HTA, it is useful to briefly consider the findings of the published systematic review. The review included studies that compared behavioural support with the option of pharmacological interventions to usual care or some lower intensity of behavioural support. While 53 studies were identified, one was considered an outlier and removed from the analysis. The review reported a risk ratio of 1.83 (95% CI: 1.68 to 1.98), indicating that behavioural



support with optional pharmacological intervention was more effective than usual care or lower intensity behavioural support. Due to the criterion of lower intensity support and no systematic availability of pharmacological intervention in the control arms, it is unclear how the findings of this review may be interpreted.

#### **4.2.9 Summary**

Based on updating 13 systematic reviews, we identified 313 studies that met the inclusion criteria for an unselected adult population. Half of the studies had been published in the year 2000 or more recently. Sixty two percent of the studies had 12 months or longer follow up for estimating abstinence. A quarter of the studies were considered at low risk of bias. Almost two out of three (65%) studies used biochemical verification of quitting, and 58% measured continuous abstinence as distinct from point prevalence.

Interventions could be broadly classified as pharmacological and behavioural interventions. While the definitions of pharmacological interventions were clear, behavioural interventions tended to be quite heterogeneous. In addition, many pharmacotherapy trials provided supportive care in the form of a behavioural intervention to both the control and intervention arm participants.

Both direct and indirect evidence were considered when evaluating the relative effectiveness of interventions. Due to differences in the trial participants and lack of direct evidence, pharmacotherapy and behavioural interventions were analysed separately.

Direct evidence was available for many of the possible comparisons between pharmacological interventions. All of the interventions were found to be superior to the control group. The results of a network meta-analysis suggest that varenicline is the most effective monotherapy, and that dual therapy varenicline plus NRT is the most effective pharmacotherapy. NRT monotherapy and bupropion are similarly effective. The direct and indirect evidence were broadly in agreement.

The evidence regarding dual therapy varenicline plus NRT was based on two trials, both of which used NRT in the form of patches. There are 18 ongoing trials of smoking cessation in unselected adults that have an intervention arm including dual therapy varenicline plus NRT. In 11 trials, the NRT therapy is specified as patch, in four it is unspecified, and in three it is explicitly as combination NRT or in a form other than patch. Based on the outcome of a Cochrane review, we assumed that NRT is equally effective irrespective of the form in which it is used.<sup>(7)</sup> While the evidence base for combination therapy using varenicline plus NRT will continue to be entirely or predominantly based on NRT in patch form, there is no clear basis to assume that the effectiveness will be different if a different type of NRT is used.

The relative effectiveness of e-cigarettes was estimated using data from two trials: a three-arm trial comparing e-cigarettes with NRT and with placebo e-cigarettes<sup>(472)</sup>; and a two-arm trial comparing e-cigarettes with placebo e-cigarettes.<sup>(473)</sup> The three-arm trial couriered e-cigarettes to participants, while those in the NRT arm were provided with vouchers that could be redeemed for NRT patches at a pharmacy. This approach may have introduced a barrier for those in the NRT arm, in which the quit rate at six months was 5.8%, well below the average six month quit rate of 19% seen in the NRT arms of studies (Table 4.8). The two-arm study did not provide any supportive care in conjunction with the intervention, and the control arm quit rate at 12 months was 4%. In both trials, the devices were first-generation devices providing low doses of nicotine.

It is unclear to what extent the results of the trials apply to more recent generations of e-cigarettes. As the technology has developed, nicotine delivery has improved creating a closer approximation to smoking conventional cigarettes. This could plausibly reduce the effectiveness of e-cigarettes for cessation, as stopping may be associated with greater withdrawal symptoms, as would be experienced when quitting conventional cigarettes. However, it may also make it easier for smokers to transition to e-cigarettes before reducing nicotine intake as part of a quit attempt. Using the GRADE system, the Cochrane review of e-cigarettes for smoking cessation described the level of evidence as low. These caveats should be borne in mind when considering the clinical effectiveness of e-cigarettes for smoking cessation.

There are a number of ongoing trials evaluating the effectiveness of e-cigarettes for smoking cessation, and on completion these may well change the estimates of effectiveness. Although e-cigarettes are a popular smoking cessation aid, this is not necessarily considered in their design. Given that the technology is developing and may become more or less effective for smoking cessation, this is particularly relevant. Given the paucity of evidence regarding e-cigarettes, the evolving evidence base for both effectiveness and safety should be monitored and re-evaluated to support decisions regarding their promotion for smoking cessation.

There are six ongoing trials involving e-cigarettes that will provide further evidence in relation to their use to aid smoking cessation in unselected adults. These are due to be completed between 2017 and 2022. The ongoing trials all include e-cigarettes compared with either usual care, NRT, nicotine-free e-cigarettes or some combination of those therapies. The two trials included in the systematic review undertaken as part of this HTA had a combined 957 participants, while the six ongoing trials will include an estimated 9,700 participants, potentially improving the precision of the effect estimates.

In terms of behavioural interventions, the majority of evidence compared **interventions to control or 'do nothing'**. For the purposes of this analysis, control was defined as minimal intervention, which usually comprised brief advice or written materials. All of the interventions and control **were more effective than 'do nothing'**. Relative to control, only four of the interventions (group behaviour therapy, individual counselling, intensive advice, and telephone support) showed a statistically significant benefit in terms of average treatment effect. When considered on the basis of prediction intervals, the confidence bounds encompassed no treatment effect for all interventions. In other words, a future study of any of the interventions has a reasonable potential to find no effect relative to control. The significance of this is apparent if it is assumed that control (brief advice or written materials) represents the standard of care for those not accessing a behavioural intervention.

Evidence of inconsistency was found when analysing the behavioural interventions. Some of this may be due to the small number of head-to-head comparisons available and relatively heterogeneity of interventions. In other words, when only one or a small number of studies are available in a given comparison, they may not **be representative of the 'average' implementation of that intervention as seen in** other comparisons.

There was some evidence that certain study-level covariates acted as effect modifiers. Most notably, studies using biochemical verification and continuous abstinence had a tendency to observe larger treatment effects in favour of the intervention. This finding may be considered counter-intuitive, as these characteristics might be expected to reduce the observed quit rates by removing bias due to deception and temporary relapses. There is no reason to expect that these differences would systematically bias against the control arms. Biochemical verification and continuous abstinence may act as measures of study quality that are not captured by the Cochrane risk of bias tool, but again that would not be expected to bias in favour of the treatment.

There was evidence of small study bias for a limited number of comparisons. Small study bias indicates that smaller studies tend to report results that favour one of the study arms, in this case the intervention. It is often interpreted as evidence of publication bias in that smaller studies are more likely to get published if they report a statistically significant finding, usually in favour of the intervention. The effect of such a bias is to inflate the estimate of treatment effect. Using the trim and fill method to estimate the treatment effects in the absence of the small study bias, it could be seen that the treatment effects would be reduced, although generally by only a modest amount. In other words, the small study bias had a limited impact on the results.

Based on the findings of a Cochrane review, the provision of behavioural support as an adjunct to pharmacotherapy increases the treatment benefit by 18%. This finding is consistent across types of supportive care and the type of pharmacological treatment. This can be interpreted as a modest additional benefit to pharmacological interventions derived from providing adjunctive behavioural therapy.

The absolute quit rates varied by intervention arm. For both pharmacotherapy and behavioural intervention studies, the control arm quit rates were approximately 10% to 11% at six months. There was some divergence at 12 months, with control arm quit rates of 11% in pharmacotherapy studies and 8% in behavioural intervention studies. These quit rates are substantially lower than those observed in the Healthy Ireland survey data (see Chapter 3). Using the Healthy Ireland survey data based on those reporting smoking in the last year and those who made a quit attempt in that year, the estimated overall quit rate was 24.0%. This includes people who quit over a 12 month period and is a point prevalence estimate. Some of those may only have quit in the previous month, and hence the estimate is potentially subject to substantial bias. As the risk of relapse is highest in the first few months following a quit attempt, the figure of 24% is likely to be an overestimate of successful quit attempts.

However, the quit rates from the Healthy Ireland data are similar for a number of methods of quitting: unassisted quitting (27.1%), e-cigarettes (26.5%), and NRT in combination with a behavioural intervention (27.7%). The quit rate associated with NRT monotherapy was only 11.2%. The Healthy Ireland data do not record number of quit attempts, and the observed cessation rates may be influenced by smokers making numerous attempts, increasing the probability of successful quitting. The trial data presumes a single quit attempt, particularly for those using the measure of continuous abstinence. Healthcare professionals are trained in the provision of brief advice for smoking cessation, and the need to quit smoking is widely publicised. Smokers and former smokers who report a quit attempt as unassisted may not consider brief advice or written materials as an intervention, even though they have been exposed to it. To estimate the clinical effectiveness of behavioural interventions, we selected a control comprising minimal intervention as the reference **for unassisted quitting, rather than 'do nothing'.**

The differences between the trial and survey data raise questions about how the trial data generalise to the real-world setting, where smokers are free to choose a method of cessation that suits them, and where they may find a preferable method through experimentation and repeated failed attempts. Behavioural interventions are designed to provide smokers with mechanisms to manage quit attempts and reduce the likelihood of relapse. The skills obtained from a quit attempt using a behavioural intervention may increase the likelihood of successful quitting in future attempts.

This may not apply to pharmacological interventions unless they are used with adjunctive behavioural support. Thus the relative effectiveness of behavioural interventions in a single quit attempt, as reported in clinical trial data, may understate their impact on further quit attempts and risk of relapse.

## **4.3 Clinical effectiveness in users of secondary mental health services**

The primary population of interest in this analysis is users of secondary mental health services.

### **4.3.1 Identified systematic reviews**

The aim of this systematic review is to assess the effectiveness of smoking cessation interventions in users of secondary mental health services.

A scoping search identified a recent high-quality systematic review of the effectiveness of smoking cessation interventions in users of secondary mental health services. The report was published by the UK Centre for Tobacco Control Studies in 2012 and was used as a starting point for this review.<sup>(474)</sup> In addition, two high-quality Cochrane reviews were found. One of these assessed smoking cessation interventions in individuals with schizophrenia and schizoaffective disorders, while the other looked at interventions in those with current and past depression. These reviews were cross-checked against the UK Centre for Tobacco Control Studies report to ensure all relevant studies were included.<sup>(475, 476)</sup> The PICOS criteria for study eligibility are included in Table 4.19.

**Table 4.19 PICOS criteria for study eligibility – users of secondary mental health services**

<b>Population</b>	Adults aged 18 years or older who are users of secondary mental health services. These typically include patients with psychotic disorders, schizophrenia or schizoaffective disorder, current depression or bipolar disorder.
<b>Intervention</b>	<ul style="list-style-type: none"> <li>■ nicotine replacement therapy (NRT), such as chewing gum, transdermal patches, nasal and oral spray, inhalers, tablets and lozenges; as monotherapy or combination (dual) therapy</li> <li>■ electronic cigarettes (e-cigarettes)</li> <li>■ nicotine receptor partial agonists (cytisine or varenicline only)</li> <li>■ antidepressants (bupropion only)</li> <li>■ motivational interviewing</li> <li>■ brief physician advice</li> <li>■ telephone-based interventions</li> <li>■ mobile phone-based interventions</li> <li>■ Internet-based interventions</li> <li>■ individual behaviour counselling</li> <li>■ group behaviour therapy</li> <li>■ acupuncture</li> <li>■ Allen Carr method.</li> </ul>
<b>Comparator</b>	No treatment (or placebo) or another eligible intervention.
<b>Outcomes</b>	Primary outcome of interest was long-term smoking cessation rates, as indicated by quit rates at greater than or equal to six months ( $\geq 6$ months). Biochemically verified results were preferred to self-reports, and continuous or prolonged abstinence was preferred to point prevalence abstinence.
<b>Study design</b>	Randomised controlled trials.

### 4.3.2 Identified trials

The UK Centre for Tobacco Control Studies review was updated by running further searches from 01 January 2012 to 18 August 2016 in Pubmed, EMBASE and the Cochrane Library, see Appendix 1 for details. The UK Centre for Tobacco Control Studies review searched a range of databases including Medline (Search date: 30 January 2012), EMBASE (Search date: 09 February 2012, date limits: 1985-2012) and the Cochrane Library (Search date: 01 January 2012). The scope of the review was broader than that specified in this HTA and included a broader set of potential smoking cessation interventions such as clozapine, naltrexone and fluoxetine. These interventions were not included in this assessment as they are not representative of smoking cessation standard of care in Ireland nor are they licensed for this purpose. The UK Centre for Tobacco Control Studies report also included a broader range of study types such as non-randomised controlled trials, controlled before-and-after studies, interrupted time series and uncontrolled before-and-after studies not eligible for inclusion in this HTA. As such, of the fifty-one studies included in the UK Centre for Tobacco Control Studies report, only eight are eligible for inclusion in this review;<sup>(477-485)</sup> the reasons for excluding the remaining studies are reported in Appendix 1. Two additional studies were retrieved in the updated search.<sup>(486, 487)</sup>

### 4.3.3 Summary of the evidence

Of the 10 included studies, nine were based in the US,<sup>(478-484, 486, 487)</sup> one of which was US and Canada based,<sup>(486)</sup> and one was based in Australia.<sup>(477)</sup> Eight studies recruited from community volunteers,<sup>(477-482, 484, 486)</sup> one study from outpatient clinics<sup>(487)</sup> and the setting was unclear in one study.<sup>(483)</sup> Six studies included populations with a DSM-IV/DSM-IV-TR (updated version) diagnosis of schizophrenia or schizoaffective disorder,<sup>(479, 481-484, 486)</sup> one of which was defined as the depressed type.<sup>(479)</sup> Two trials included people with a DSM-IV diagnosis of schizophrenia only,<sup>(478, 480)</sup> and one trial included patients with a ICD-10 diagnosis of psychotic disorder (over half of which had schizophrenia or schizoaffective disorder).<sup>(477)</sup> One trial included clinically stable adults who met the DSM-IV criteria of bipolar disorder.<sup>(487)</sup> These studies were published from 2000<sup>(483)</sup> to 2014<sup>(487)</sup> and were mainly small trials with participant numbers ranging from 19<sup>(480)</sup> to 298.<sup>(477)</sup>

All 10 trials included behavioural interventions as an adjunct to pharmacological interventions, with some form of behavioural therapy provided to both the control and intervention study arms. See Table 4.20 and 4.21.

The efficacy of bupropion as a cessation aid was investigated in five trials.<sup>(478-483)</sup> Two of these trials included adjunctive NRT (transdermal nicotine patch) in both the intervention and control arms.<sup>(478, 481)</sup> One trial also included nicotine gum, as required (that is, combination NRT as adjunctive therapy) in both arms.<sup>(478)</sup> The

efficacy of varenicline was assessed in two trials (n=1 schizophrenia or schizoaffective disorder; n=1 bipolar disorder).<sup>(486, 487)</sup> In each of these seven trials, the same behavioural intervention was delivered to both the intervention and control arm,<sup>(478-482, 486, 487)</sup> with the intensity ranging from nine to 12 once-weekly sessions.

Three trials investigated the efficacy of different behavioural interventions. The first compared two types of group behavioural therapy – a generic programme and a programme tailored to those diagnosed with schizophrenia and schizoaffective disorder. NRT transdermal patches were used as adjunctive therapy in both arms.<sup>(483)</sup> One trial compared two types of individual counselling – both tailored to the mental health population, but varied by intensity. Again, both arms received adjunctive NRT (transdermal patch).<sup>(484)</sup> The remaining trial compared the use of an NRT transdermal patch plus individual behavioural therapy programme specifically tailored for a broader psychotic disorder population (comprising motivational interviewing and cognitive behavioural therapy) with routine care.<sup>(477)</sup>

All data for the included studies were extracted. All 10 studies reported biochemically verified continuous abstinence, with five rated as having a high risk of bias, two low risk and three rated as unclear risk of bias. See Appendices 2 and 3 for full details of the included studies. Cessation interventions were classified as per Section 4.2.2.

#### **4.3.4 Results**

None of the studies identified included a mixed population attending secondary mental health services. As such, the results are presented separately for those with a diagnosis of schizophrenia and schizoaffective disorder (Section 4.3.4.1), bipolar disorder (Section 4.3.4.2) and depression (Section 4.3.4.3).

##### **4.3.4.1 Schizophrenia and schizoaffective disorder**

###### *Pharmacotherapy as an adjunct to behavioural interventions*

Five trials compared long-term smoking cessation ( $\geq 6$  months) using bupropion as an adjunct to a behavioural intervention in the schizophrenia and schizoaffective disorder population. Participant numbers were small ranging from only 19<sup>(480)</sup> to 59<sup>(481)</sup> patients, all community volunteers. The studies were based in the US and were undertaken between 2001<sup>(480)</sup> and 2008.<sup>(481)</sup> Of these, two trials also included adjunctive NRT (transdermal patch)<sup>(478, 481)</sup> or combination NRT<sup>(478)</sup> (transdermal patch plus nicotine gum up to 18mg per day as needed for cravings) in both the intervention and control arms. A transdermal patch with a dose of 21mg per day was used based on smoking rate of 21 cigarettes per day. One study inferred that the daily dose of NRT was tapered from 40mg per day down to 20mg per day over the course of the study.<sup>(478)</sup>



When used in conjunction with behavioural therapy and NRT (as mono- or dual NRT), bupropion was found to increase the likelihood of being abstinent at six months almost four-fold (RR=3.86, 95%CI: 1.01 to 14.80) in those with schizophrenia or schizoaffective disorder (Table 4.20). This was based on a small number of trials (n=2) with a small sample size (n=110), see Figure 4.13. Three earlier placebo-controlled trials showed no statistically significant effect for using bupropion as an adjunct to a behavioural intervention alone, again based on a small sample size (n=104), see Figure 4.14. Strong evidence does not exist for a difference in relative effect between bupropion as an adjunct to a behavioural intervention alone or in combination with NRT as the numbers of quitters was small across the groups. All studies included a lower initial dose (150mg per day), although one study (Evins et al. 2001) maintained this lower bupropion dose over the course of the study while the remaining studies increased to 300mg per day per licensed recommendations.<sup>(480)</sup> In addition, the one person who achieved smoking cessation in the study by Evins et al. (2001) was also on clozapine treatment. Although clozapine is not indicated for smoking cessation, there is evidence to suggest it may have an effect.<sup>(488)</sup> Removal of this study does not significantly affect the overall result.

Due to the inherent differences between the studies (with or without NRT), the five trials have not been combined in a meta-analysis. However, they have been combined in previous high-quality systematic reviews which reported that the population was three times more likely to be abstinent at six months.<sup>(474, 475)</sup> As noted, the number of quitters was small in these studies. Absolute cessation rates were lower in the control group compared with the general population, with quit rates of approximately 7% across the control arms compared with 11% for the unselected adult population (see Section 4.2.5.3). This is despite the fact that the control arm in these trials typically included an intensive behavioural intervention involving weekly sessions for several weeks, with or without NRT.

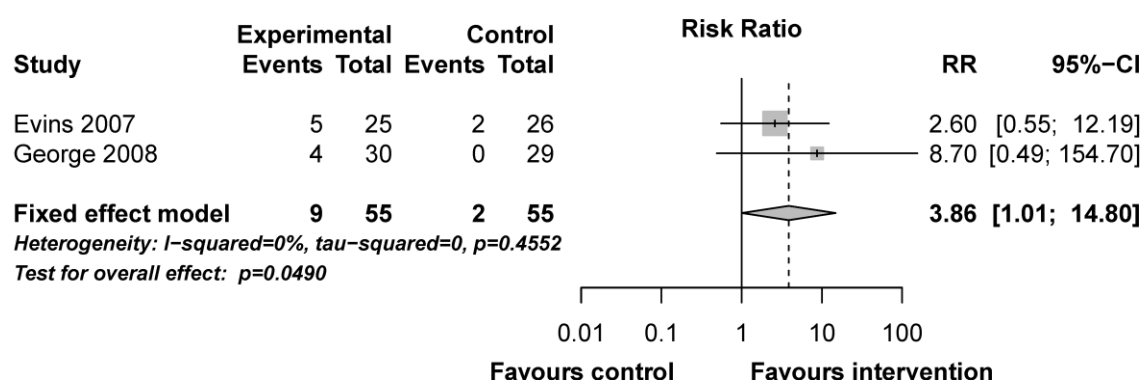
It is recommended that tests for funnel plot asymmetry are only used when there are at least 10 studies included in the meta-analysis, as the power of the tests is too low to distinguish chance from real asymmetry.<sup>(489)</sup> As such, an assessment of small study bias was not undertaken here.

**Table 4.20 Summary of findings for schizophrenia or schizoaffective disorder**

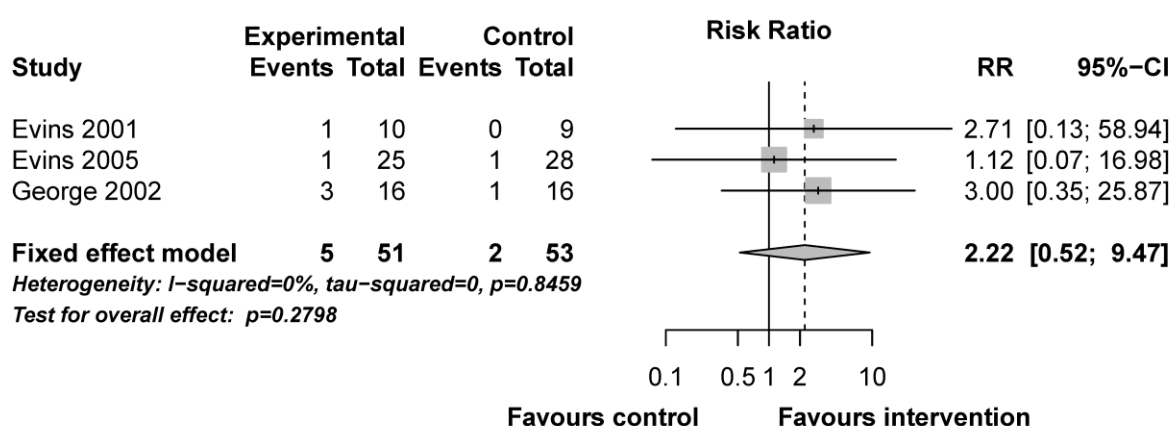
Comparator	Study (year)	Included studies (n)	Participants (n) † `	RR	P value, overall effect
Bupropion + behavioural intervention versus placebo + behavioural intervention	Evins (2001) Evins (2005) George (2002)	3	108	2.22 [0.52, 9.47]	0.28
Bupropion + behavioural intervention + NRT versus placebo + behavioural intervention + NRT (¥both arms received transdermal patch, ¢both received nicotine gum)	Evins (2007)¥,¢ George (2008) ¥	2	110	3.86 [1.01, 14.80]	0.05
Varenicline + behavioural intervention versus placebo + behavioural intervention	Williams (2012)	1	128	5.06 [0.67, 38.24]	0.12
Group behavioural intervention (generic) + NRT (transdermal patch) versus group behavioural intervention (tailored to schizophrenia) + NRT (transdermal patch)	George (2000)	1	45	0.88 [0.34, 2.23]	0.78
High-intensity individual counselling + NRT (transdermal patch) versus lower intensity individual counselling + NRT (transdermal patch) (both arms tailored to mental health)	Williams (2010)	1	100	0.86 [0.30, 2.51]	0.79
Individual counselling + NRT (transdermal patch) versus routine care (Counselling tailored to mental health)	Baker (2006)	1	298	2.84 [0.74, 10.92]	0.13

Note: Nicotine replacement therapy (NRT) was as an active comparator, that is to say, patients could not use NRT on its own. RR: Risk Ratio.

**Figure 4.13 Bupropion + behavioural intervention with NRT versus placebo + behavioural intervention with NRT in the schizophrenia and schizoaffective disorder population**



**Figure 4.14 Bupropion + behavioural intervention versus placebo + behavioural intervention in the schizophrenia and schizoaffective disorder population**



One study (Williams 2012) sponsored by Pfizer assessed the efficacy of varenicline with adjunctive behavioural therapy on long-term smoking cessation ( $\geq 6$  months) in patients with schizophrenia or schizoaffective disorder in a placebo-controlled trial.<sup>(486)</sup> Trial participant numbers were small ( $n=128$ ), recruited from community volunteers in the US. Varenicline was administered per standard licensed recommendations. The behavioural intervention comprised weekly smoking cessation counselling (less than 30 minutes per session) for 12 weeks. Varenicline was not associated with a statistically significant treatment effect compared with the placebo arm ( $n=128$ , RR 5.06, 95% CI 0.67 to 38.24,  $p=0.12$ ), see Table 4.20. The study authors noted that there were nine serious adverse events in the varenicline group, two of which were considered to be related to varenicline use. There was one serious adverse event in the control arm.

One study (George 2000) assessed the long-term ( $\geq 6$  months) smoking cessation results of two different group behavioural therapy programmes; adjunctive therapy with NRT transdermal patches was provided to both the intervention and control arms.<sup>(483)</sup> A total of 45 people who met the DSM-IV criteria for schizophrenia or schizoaffective disorder and nicotine dependence were randomised to either a cessation programme specialised to those with schizophrenia or a generic smoking cessation intervention programme developed by the American Lung Association. The generic programme comprised a standard seven-week group behavioural therapy programme followed by supportive group counselling during the remaining three weekly group sessions. Each session lasted 60 minutes. The specialised schizophrenia smoking cessation programme included three weeks of motivational enhancement therapy and seven weeks of psychoeducation, social skills training, and relapse prevention strategies. A quit date was set during week three of both programmes. There was no evidence of a treatment effect associated with specialised smoking cessation group counselling sessions at six-months follow up ( $n=45$ , RR 0.56, 95% CI 0.10 to 3.16,  $p=0.51$ ), see Table 4.20.

One study (Williams 2010) reported long-term ( $\geq 6$  months) smoking cessation results comparing two intensities of individual behavioural therapy. Adjunctive therapy with NRT transdermal patches was provided to both the intervention and control arms.<sup>(484)</sup> The study aimed to assess therapies which could be integrated into standard individual mental health treatment sessions. A total of 100 people who met the DSM-IV criteria for schizophrenia or schizoaffective disorder and nicotine dependence were included. The behavioural programmes included the Treatment of Addiction to Nicotine in Schizophrenia programme and the Medication Management programme. Treatment of Addiction to Nicotine in Schizophrenia is a high-intensity treatment of 24 sessions (45 minutes each) delivered over 26 weeks. It incorporates motivational interviewing, social skills training, use of NRT, and relapse prevention techniques. Behavioural intervention was delivered by mental health clinicians trained in smoking cessation interventions. The Medication Management programme is a moderate intensity treatment of nine sessions (20 minutes each) over 26 weeks. Brief advice on monitoring psychiatric symptoms and understanding medication interactions with tobacco is given to the patient in the Medication Management programme. A quit date was set during week five for both programmes. Both approaches used an active, educational approach and therapists were encouraged to develop a collaborative and focused working alliance with clients. Treatment manuals, training programmes, and training materials were developed to accompany the two approaches. At six-months follow up there was no statistically significant difference ( $n=76$ , 0.86 [0.30, 2.51]  $p=0.79$ ), see Table 4.20. The authors noted that participants who had better attendance at individual sessions had better outcomes in terms of smoking cessation and reduction.

Baker et al. (2006) reported long-term smoking cessation results ( $\geq 6$  months) comparing individual counselling plus NRT in the form of transdermal patches versus routine care.<sup>(477)</sup> A total of 298 people who met an ICD-10 diagnosis of psychotic disorders were included. Of these, 126 had a diagnosis of schizophrenia and 43 had a diagnosis of schizoaffective disorder (56.7%). Referrals were received from Australian community health agencies (82.2%), inpatient psychiatric units (8.3%), and the Neuroscience Institute of Schizophrenia and Allied Disorders schizophrenia register (7.0%). The behavioural programme comprised an eight-session, individually administered smoking cessation programme consisting of motivational interviewing and cognitive behaviour therapy. At six-months follow up, those receiving this combined care were more likely to be abstinent compared with routine care, although this result was not statistically significant ( $n=298$ , RR 2.84, 95% CI 0.74 to 10.92,  $p=0.13$ ), see Table 4.20. Consistent with the findings of Williams et al., the authors noted a trend towards improved smoking cessation and reduction rates in those participants who had better attendance at individual sessions.

As noted in Chapter 3, smoking cessation may have a negative effect on mental health symptoms. Limited data were reported in relation to mental health symptoms in the trials identified. George et al. (2002) reported that bupropion did not alter positive symptoms of schizophrenia, but significantly reduced negative symptoms.<sup>(482)</sup> In a later study by George et al. (2008), where NRT was provided to both study arms, they did not report a difference between positive or negative symptoms.<sup>(481)</sup>

#### **4.3.4.2 Bipolar disorder**

##### *Behavioural interventions as an adjunct to pharmacotherapy*

The UK Centre for Tobacco Control Studies review retrieved one study which assessed bupropion in patients with bipolar disorder who were attending secondary mental health services. This was limited to a pilot study of five people and did not meet our inclusion criteria.

One study (Chengappa 2014) was retrieved in the updated search. Chengappa, 2014 compared brief advice as an adjunct to varenicline in a placebo-controlled trial. A total of 60 clinically stable adults who met the DSM-IV criteria for bipolar disorder were recruited from the community in the US. The majority (82%) had bipolar I disorder. Brief advice consisted of 15 minutes of each visit dedicated to smoking cessation counselling. There was no statistically significant difference between the comparators at six-months follow up ( $n=60$ , 2.84, 95% CI 0.61 to 12.81,  $p=0.18$ ), see Table 4.21. Absolute cessation rates were lower in the control group (approximately 7%) compared with that seen in the general unselected adult population (average 11% see Section 4.2.5.3).

**Table 4.21. Summary of findings**

Comparator	Study (year)	Studies (n)	Participants (n)	RR	p value, overall effect
<b>Bipolar Disorder</b>					
Varenicline + brief advice versus placebo + brief advice	Chengappa (2014)	1	60	2.81 [0.61, 12.81]	0.18

#### 4.3.4.3 Depression

The 2012 UK Centre for Tobacco Control Studies review assessed the effectiveness of smoking cessation interventions in users of secondary mental health services, including studies for patients with a diagnosis of depression. Four of the 51 studies were for those with a diagnosis of depression. However, these have not been included on the basis of the interventions assessed (n=2), duration of follow up (n=1) and study design (n=1). See Appendices 4, 5 and 6 for full details of excluded studies.

A Cochrane review by Van der Meer et al. (2013), including a total of 49 randomised controlled trials (RCTs), reviewed a range of smoking cessation interventions in individuals with either a current (n=33) or past diagnosis of depression (n=26).<sup>(476)</sup> Some of the interventions included (for example, fluoxetine, paroxetine, naloxone) are not applicable to this review. As noted, this assessment is limited to smoking cessation interventions in those attending secondary mental health services. Studies assessing interventions for those with a past history of depression were deemed not applicable as, unless stated otherwise, it was assumed that the majority would not be attending secondary mental health services. From the studies reviewing smoking cessation interventions in those with a current diagnosis of depression, 10 met the inclusion criteria. However, it was not clear if all included populations were attending secondary mental health services. As such, these 10 studies were not included in this assessment. No additional studies were retrieved in the updated search.

#### 4.3.5 Discussion

A systematic review of the effectiveness of smoking cessation interventions in users of secondary mental health services was undertaken. Limited evidence was retrieved from mainly small trials with small participant numbers (for example, participant numbers ranged from 19 to 298). Absolute cessation rates were lower in comparison with the general population. Average quit rates in the control arms were approximately 7% versus 11% for the unselected population (see Section 4.2.5.3), despite the fact that the control arm in these studies typically included an intensive behavioural intervention with or without NRT. The combination of low control arm

cessation rates and the small numbers of participants resulted in some large, but not statistically significant treatment effects.

Relevant data were only identified for the schizophrenia and schizoaffective disorder and bipolar disorder populations. However, based on a recent Health Research Board study, these populations represent the main diagnoses associated with admissions in general hospital psychiatric units, psychiatric hospitals and independent or private charitable centres.<sup>(490)</sup> It estimates that depressive disorders amount to 29.7% of the total admissions, followed by schizophrenia, schizotypal and delusional disorders (13.1%), followed by neuroses amount (12.6%). Admission rates were higher in the private compared to the public setting for depression only.

Patients with schizophrenia or schizoaffective disorder populations who used bupropion as an adjunct to a behavioural intervention plus NRT (monotherapy or combination NRT) were found to be almost four times more likely to be abstinent at six months in placebo-controlled trials. This was based on a small number of trials (n=2) with a small total sample size (n=110). Three earlier trials showed no statistically significant effect for bupropion when used as an adjunct to a behavioural intervention only, again based on a small sample size (n=104). This review agrees with previous high-quality systematic reviews.<sup>(474, 475)</sup> A meta-analysis of these five trials was not conducted based on their inherent differences, but have been combined in previous reviews reporting that a behavioural intervention with or without NRT as an adjunct to bupropion was three times more effective in this population.

One placebo controlled trial was identified which indicated that varenicline used as an adjunct to a behavioural intervention increases abstinence rates at six months compared with behavioural therapy alone in patients with schizophrenia, although this was not statistically significant. This is in agreement with two recent systematic reviews which assessed varenicline in the schizophrenia population (2015)<sup>(491)</sup> and in a broader population of serious mental illness (2016)<sup>(492)</sup>, neither of which found evidence of effect. These reviews reported a statistically significant beneficial effect for varenicline on smoking reduction, but the results were very heterogenous ( $I^2=89\%$ ). Both reviews included additional studies which were not applicable to this review. For example, some reported short-term results or included patients with concurrent alcohol and nicotine dependence. One placebo-controlled study was identified which found no statistically significant effect for varenicline when used as an adjunct to brief advice, compared with brief advice alone in patients with bipolar disorder.

The Cochrane review by van der Meer et al. (2013) reviewed a range of interventions in both current and past depression. However, it was unclear if all



included populations were attending secondary care mental health services, so none of the studies met the inclusion criteria of this assessment. The 11 trials reported a significant positive effect for a range of behavioural interventions which they termed psychosocial mood management in the current depression population (RR 1.47, 95% CI 1.13 to 1.92, n=1,844). The interventions generally compared a standard smoking cessation counselling intervention to that alongside cognitive behavioural intervention focused on depression.

The 2012 UK Centre for Tobacco Control Studies review reported that the combination of bupropion with NRT may be effective for smoking cessation in populations with schizophrenia. However, it concluded that further high-quality research is urgently required the areas of smoking cessation, smoking reduction, and temporary abstinence in secondary mental health service settings.<sup>(474)</sup>

Clinical guidelines recommend that NRT can be used as a first line therapy for all smokers.<sup>(493)</sup> While no trials were identified that explicitly investigated the efficacy of NRT in those attending secondary mental health services, trials reporting use of NRT (as monotherapy or combination) as an adjunct to either behavioural therapy, bupropion, or a combination thereof were identified, with absolute quit rates of approximately 9% in the control arms incorporating NRT. One recent large scale and good-quality RCT, requested by the FDA (Eagles trial), reported on the neuropsychiatric safety and efficacy of varenicline, bupropion, and NRT (in the form of a transdermal patch) in smokers with (n=4,116) and without psychiatric disorders (n=4,028).<sup>(34)</sup> The cohort of psychiatric disorders included people with a primary diagnosis per DSM-IV-TR for a range of Axis I and II disorders such as mood disorders, post-traumatic stress disorder and psychotic disorders. Only patients with psychiatric disorders who were stable and treated, or who had previous psychiatric conditions that were in remission were included. This trial did not meet the inclusion criteria of this study for participants to be attending secondary mental health services.

The trial found that the odds ratios for efficacy did not differ as a function of psychiatric status.<sup>(34)</sup> More specifically, at two to six-months follow up, participants who took varenicline or bupropion or transdermal patch had a significant rate of abstinence when compared with placebo. The odds ratios were varenicline 1.77 (95% CI 1.33 to 2.36), bupropion 2.50 (95% CI 1.90 to 3.29) and transdermal patch 1.65 (95% CI 1.24 to 2.20). In addition, participants who took varenicline had a higher rate of abstinence compared to transdermal patch and compared to bupropion (OR 1.51 95% CI 1.19 to 1.93; OR 1.41 95% CI 1.11 to 1.79). No significant difference was reported between bupropion and transdermal patch. No significant increase in rates of neuropsychiatric adverse events were found with either varenicline or bupropion use relative to transdermal NRT patch or placebo.



This study, and many of the studies reviewed, included a dose of 21mg per day with taper for the mental health population. However, given the fact that this population typically has higher nicotine dependence, it is possible that the dose of NRT provided was suboptimal.

A US population survey carried out in 2012 (n=10,041) reported that individuals with a mental health condition (n=1,905) were more likely to have tried e-cigarettes (14.8%) and to be current users of e-cigarettes (3.1%) compared to the general population (6.6% and 1.1%, respectively;  $p<0.01$ ).<sup>(494)</sup> However, limited studies were retrieved which assessed e-cigarette use in the mental health population. Of those retrieved, none were applicable as for example, the trials were not focused on cessation, the participants were not attending secondary mental health services or there was no comparator group. One large scale trial carried out a secondary analysis of e-cigarettes compared with NRT in the mental health population (ASCEND trial, n=86).<sup>(495)</sup> The mental health population was defined as those reporting use of at least one medication associated with mental illness (antidepressants 72%, antipsychotics 28%, 14% hypnotics or sedatives; 9% anxiolytics, 1% addictive disorder medications). Those with uncontrolled psychiatric or current chemical dependence were excluded. No statistically significant difference in cessation rates was found at six months.

Smoking cessation has the potential to deliver significant health benefits for smokers and their families, including those with mental health problems. For those using secondary care services, there are additional advantages, such as reduced length of stay in hospital, lower drug doses, fewer complications, higher survival rates, better wound healing, decreased infections and fewer re-admissions after surgery.<sup>(496)</sup> However, the mental health population smokes more than the general population.

### **Why does the mental health population smoke more and are less likely to quit?**

A study in the US reported that the decline in smoking from 2004 to 2011 was significantly higher in the general population than in mental health populations.<sup>(125)</sup> They suggested that control policies and smoking cessation interventions for the general population were not as effective in mental health populations. Approximately one-third of people with mental health problems<sup>(497, 498)</sup> and two-thirds of people in psychiatric units smoke.<sup>(499)</sup> Smoking prevalence is particularly high in the schizophrenia population (70-80%)<sup>(477, 500)</sup> compared with other mental health diagnoses (50%).<sup>(501)</sup>

Theories to explain the high smoking prevalence and low cessation rate in serious mental illnesses They **include the belief that 'smoking improves mental health or relieves stress'**.<sup>(502, 503)</sup> This relates to the 'self-medication hypothesis', where despite

the health consequences of smoking this population may continue to smoke to alleviate symptoms associated with their disorder. Smoking is reported to increase the metabolism of some antipsychotic drugs,<sup>(89)</sup> with some smokers potentially using cigarettes to relieve the side effects of these drugs. It is also reported that it is more probable that smoking relieves psychological disturbances produced by smoking withdrawal itself.<sup>(504)</sup> In the US, tobacco industry internal documents were released showing that the industry made several indirect and direct efforts to slow down the reduction of smoking in people with schizophrenia.<sup>(505, 506)</sup>

Eighty percent of people with schizophrenia or schizoaffective disorder are reported to have impairment in their cognitive function.<sup>(507)</sup> This is associated with difficulties in filtering out unnecessary information,<sup>(508)</sup> poor clinical and functional outcomes, and poor community integration.<sup>(509)</sup> These deficits may be associated with a vulnerability factor (termed the addiction vulnerability hypothesis) towards the initiation and maintenance of tobacco use.<sup>(509)</sup> In addition, pre-clinical evidence has shown positive effects of nicotine administration on neurocognition which appear to be more pronounced in smokers with schizophrenia.<sup>(509)</sup> This altered processing may require adaptations from traditional smoking cessation methods.

Other factors reported to play a role in the increased prevalence of smoking and lower smoking cessation rate in mental health populations include: social factors such as unemployment, low educational attainment, peer influence and lack of smoking cessation treatment in mental health systems;<sup>(510)</sup> increased risk-taking behaviour and poor lifestyle choices;<sup>(511)</sup> shared environmental influences;<sup>(512)</sup> and difficulties forming a therapeutic alliance.<sup>(484)</sup> Barriers to cessation include: heavier nicotine dependence;<sup>(513)</sup> lower awareness of the harms of smoking; being unaware or having misconceptions about cessation services; perceived cost and time to access, for example, NRT; financial stress; lack of support for quitting among family and friends; lower levels of confidence in ability to stop smoking; regarding smoking **as their 'only pleasure'**; and relieving boredom.<sup>(513)</sup> A heavier nicotine dependence relates not only to an increased number of cigarettes smoked, but also to the fact that they extract more nicotine from each cigarette which makes it more difficult to quit.<sup>(500, 514, 515)</sup>

### **Why are there are limited studies in this cohort?**

Few studies, in particular few large-scale good-quality studies, have assessed smoking cessation interventions in the mental health population. Recruitment of patients to RCTs from mental health populations is reported as problematic and may be due to concerns about their potential vulnerability and reduced decision-making capacity.<sup>(516)</sup> Patients may distrust the proposed research and the healthcare system in general.<sup>(517)</sup> In addition, responsibilities associated with participation, for example,

more frequent and longer appointments, additional tests or assessments such as expired carbon monoxide testing, may further impact recruitment rates.<sup>(517)</sup> While mental health problems (including mild to moderate depression and anxiety disorder) are very prevalent, the prevalence of serious mental illness is lower. As such, there is a low pool of people to draw from for RCTs. For example, in the Healthy Ireland survey (2015) probable mental health problems are indicated by 9% of the Irish population aged 15 and over.<sup>(518)</sup> Welcome Trust data show that less than one in three trials of the general mental health population successfully achieved their recruitment targets within their predicted time frame.<sup>(519)</sup> This leads to extended recruitment periods and increases in study costs, and may help to explain why there are limited data in these populations for smoking cessation. In addition, the population of users of secondary care mental health services adds further limits.

Most large scale, good trials of interventions in the mental health population focus on assessing adverse effects.<sup>(34)</sup> **Large RCTs of 'unselected' populations do not** typically exclude those with a mental health problem. As such, it may be thought that any evidence of effectiveness in this unselected population may be translated to a mental health population. Some systematic reviews report that, for example, the efficacy of NRT as a smoking cessation intervention in those with depression is comparable to that seen in the general population.<sup>(520)</sup> However, this may be dependent on whether the person is currently experiencing depression or has a past history of depression. Also, previous guidelines noted the paucity of studies in mental health populations and made recommendations based on evidence obtained in an unselected population.<sup>(493)</sup> Available systematic reviews of smoking cessation interventions in those with diagnosed mental health conditions demand further research in this population.<sup>(474-476)</sup>

There are 12 ongoing trials of smoking cessation in mental health populations. Two trials are assessing e-cigarettes in depression and schizophrenia populations, they are due for completion by December 2017 and September 2018, respectively. Eight trials are assessing a form of behavioural therapy with or without additional interventions (for example, web-based intervention plus NRT, individual and group-based behavioural therapy plus pharmacology and text messaging) in a range of mental health populations. These are due for completion from 2017 to 2020. One further trial is assessing provider-led educational interventions in serious mental illness (complete date: June 2020). Finally, one further trial was due for completion **by 2015 but is termed 'ongoing' in the US clinical trials database; it is assessing a** form of behavioural decision support in adults with psychotic disorders.

## Why is there limited evidence of effectiveness?

Our primary outcome of interest was smoking cessation at six months follow-up based on recommendations from the Society for Research on Nicotine and Tobacco.<sup>(521)</sup> Shorter term data are available, but were not included in our assessment. However, it is postulated that risk reduction, through reducing the number of cigarettes smoked per day, as opposed to cessation may be an appropriate outcome to consider in this population. Reduction has been reported as increasing the probability of cessation.<sup>(522)</sup> Since this population are more likely to be heavy smokers, researchers have speculated that focusing on an initial reduction may reduce nicotine levels which may help with future cessation.<sup>(475)</sup> Evidence that combination NRT (such as transdermal patch plus gum) is more effective than monotherapy may also be relevant to the mental health population, particularly given the higher prevalence of heavy smokers in this group.

Low motivation or desire to quit was reported in some studies (for example, one in three were motivated to quit in trials of bupropion as adjunctive therapy) and may be an important factor.<sup>(478, 479)</sup> It has previously been reported that patients with schizophrenia are often in the earlier stages of motivation to quit in comparison to the general population.

## 4.4 Clinical effectiveness in women during pregnancy

### 4.4.1 Search strategy

This systematic review aims to assess the effectiveness of smoking cessation interventions in women during pregnancy.

Searches were carried out for recent systematic reviews of eligible smoking cessation interventions in women during pregnancy. Where high-quality systematic reviews were available for relevant interventions, these were used to identify studies matching the inclusion criteria outlined above. The reviews identified were updated with any additional studies that have emerged since the original review was published. Electronic searches were conducted in Medline, Embase and the Cochrane Register of Clinical Trials to identify randomised controlled trials comparing any eligible smoking cessation intervention in women during pregnancy to another eligible intervention or to no treatment. The results of these searches were combined with each of the individual systematic reviews.

Full details of the search are provided in Appendix 9 of this document. The PICOS (Population, Intervention, Comparator, Outcomes, Study design) analyses used to formulate the search are presented in Table 4.22. Unlike the reviews for unselected

adults and those attending secondary care mental health services, no lower age limit was set for this review.

**Table 4.22 PICOS criteria for study eligibility**

<b>Population</b>	Women who smoke during pregnancy.
<b>Intervention</b>	<ul style="list-style-type: none"> <li>■ nicotine replacement therapy (NRT), such as gum, transdermal patches, nasal and oral spray, inhalers and tablets or lozenges</li> <li>■ electronic cigarettes (e-cigarettes)</li> <li>■ nicotine receptor partial agonists (cytisine or varenicline only)</li> <li>■ antidepressants (bupropion only)</li> <li>■ behavioural or psychosocial interventions; including counselling, health education, financial incentives, feedback and social support.</li> </ul>
<b>Comparator</b>	No treatment (or placebo) or another eligible intervention.
<b>Outcomes</b>	Self-reported abstinence from smoking during pregnancy, measured at the latest point prior to birth (point prevalence abstinence). Continuous abstinence measures timed from the date of randomisation, where available, are used in preference to point prevalence abstinence measures. Biochemically validated abstinence data, where available, are used in preference to self-reported data.
<b>Study design</b>	Randomised controlled trials.

Two systematic reviews relevant to this HTA were identified; both were Cochrane reviews (Table 4.23).<sup>(523, 524)</sup> The first Cochrane review reviewed psychosocial interventions for supporting women to stop smoking in pregnancy and the second reviewed pharmacological interventions for promoting smoking cessation during pregnancy. Updated searches were conducted for additional studies that have emerged since both of these original reviews were published. The searches were restricted to studies published between January 2013 and October 2016 for psychosocial interventions and to studies published between January 2015 and October 2016 for pharmacological interventions.

**Table 4.23 Identified systematic reviews and results of updated search**

Review (year)	Intervention	Primary studies	Updated search
<b>Chamberlain et al. (2013)</b>	Psychosocial	86	5
<b>Coleman et al. (2015)</b>	Pharmacological	9	0

Note: search updated to October 2016

The RCTs included in the systematic review by Coleman et al. met the inclusion criteria for this review.<sup>(524)</sup> The extension of the systematic review from January 2015 to October 2016 did not identify any additional relevant RCTs.

For psychosocial interventions in pregnancy, 59 of the 86 studies in Chamberlain et al. met the inclusion criteria for this review. An updated search (from January 2013 to October 2016) identified five additional studies.<sup>(525-529)</sup> A flow diagram of this search is provided in Appendix 9. Studies that did not meet the eligibility criteria were excluded for the following reasons:

- participants were not adequately randomised,
- population was not pregnant women or the intervention was not primarily aimed at cessation during pregnancy (for example, pre-pregnancy interventions, postpartum interventions, interventions aimed at the partners or families of pregnant women),
- the trial did not study the effectiveness of a behavioural intervention (for example, a trial evaluating the effectiveness of a pharmacological agent whereby a similar behavioural intervention was provided in both arms),
- primary cessation outcomes were not adequately reported, or not reported separately from spontaneous quitters,
- and pregnant women belonged to a specific patient group, for example, studies where only drug or alcohol-dependent women were recruited.

#### 4.4.2 Identification of trials

The primary outcome of interest for this analysis was smoking abstinence in late pregnancy (taking the latest measure prior to birth). Continuous abstinence, where available, was taken in preference to point prevalence. Biochemically validated outcomes were preferred over self-reported outcomes. Secondary outcomes include postnatal abstinence and obstetric and neonatal outcomes. For the purpose of this review, individual psychosocial interventions were categorised into five broad intervention groups:

1. **Counselling:** interventions that provide support to increase problem solving and coping skills and increase motivation to quit. A broad range of interventions may fulfil these goals, including motivational interviewing, cognitive behaviour therapy, psychotherapy and so on. Interventions may be delivered face-to-face, by telephone or by interactive computer programmes. A range of healthcare providers may offer these interventions.
2. **Health education:** interventions involving the provision of information about the risks of smoking and advice to quit. However, further advice or support is not delivered (unlike counselling interventions).
3. **Feedback:** interventions involving the provision of information about the fetal health status or of by-products of tobacco smoking to the mother, such as ultrasound monitoring of the fetus or expiratory carbon monoxide measurement. Measurements in studies taken purely for the purposes of verification of smoking status are not included.
4. **Incentive-based interventions:** interventions involving a financial reward for abstinence, contingent on verification of the smoking cessation. Receipt of money or gift vouchers merely for participation in the trial is not included.
5. **Social support (peer or partner):** these include where the intervention explicitly included provision of support from a peer or partner as a strategy to promote smoking cessation.

A total of 73 relevant studies were identified, published between 1976 and 2016 (Table 4.24). Data were only extracted for study arms relevant to this HTA. The relevant number of trial participants ranged from 17 to 1,885 (mean 364, standard deviation 346). These studies are listed in full in Appendix 10. Appendix 11 lists all the excluded studies.

Studies were also graded on quality, based on assessments using the Cochrane risk of bias tool. Studies at low risk of bias were considered high quality. Overall, 7% of studies (n=5) were considered high quality, all of which were studies of pharmacological interventions.

Studies recorded abstinence either through self-reports or some form of biochemical verification, such as cotinine levels. Biochemical verification is preferred as it is less prone to bias. Across all studies, 81% used biochemical verification, although the percentage varied between studies of pharmacological agents (100%) and behavioural interventions (78.1%). For the purpose of this review, the latest measure of abstinence prior to delivery (late pregnancy) is used. Some trials report on post-partum abstinence, with the longest follow up of 12-months post-partum reported in two trials.

**Table 4.24 Identified primary studies and main characteristics (pregnancy)**

Intervention	Studies n	Participants (n)	High quality n (%)	Biochemically verified n (%)	Continuous abstinence n (%)	Mean (SD) years since publicatio n
Acupuncture	0					
Bupropion	1	11	0 (0)	1 (100.0)	0	1
Combination NRT	0	-	-	-	-	-
Cytisine	0	-	-	-	-	-
Electronic cigarettes	0	-				
NRT	8	2,199	5 (62.5)	8 (100.0)	2 (25)	8.4 (5.3)
NRT + bupropion	0	-	-	-	-	-
NRT + varenicline	0	-	-	-	-	-
Varenicline	0	-	-	-	-	-
Varenicline + bupropion	0	-	-	-	-	-
Counselling	44	18,249	0 (0)	35 (79.6)	3 (6.8)	16.6 (8.2)
Feedback	4	700	0 (0)	3 (75.0)	0 (0.0)	18.8 (11.3)
Health education	6	1,425	0 (0)	3 (50.0)	1 (16.7)	18.2 (12.0)
Financial incentives	3	743	0 (0)	3 (100.0)	1 (33.3)	2.0 (1.7)
Social support	7	800	0 (0)	6 (85.7)	0 (0.0)	11.7 (4.4)

Notes: NRT, nicotine replacement therapy; SD, standard deviation.



Interventions were categorised according to the primary strategy employed. However, many interventions, particularly counselling interventions, incorporate several components. For this reason, further subgroups were created:

- single intervention (whereby only one main strategy was used),
- multiple intervention (whereby several strategies were used),
- and tailored intervention (whereby additional strategies were available which were optional to women).

The care received by the comparator group in these studies varied widely. A distinction was made in this analysis **between 'Usual Care'** – whereby the control group received the routine antenatal care provided to the population, **and 'Less Intensive Intervention'** – whereby the control group received some element of the intervention, albeit at a less intensive level.

Levels of heterogeneity in all pooled analyses were examined using the  $I^2$  statistic along with the Q-statistic. A substantial degree of heterogeneity was expected in the analysis of psychosocial interventions given the breadth and variability in the interventions. In an attempt to minimise heterogeneity, each psychosocial category is reported on separately (counselling, health education, feedback, incentive, and social support). Subgroups are also reported **based on the comparator ('usual care' or 'less intensive intervention')**. Finally, studies were analysed based on intervention components (whether it was provided as a single, tailored or multiple component intervention).

### 4.4.3 Pharmacological interventions for smoking cessation in pregnancy

Nine trials, published between 2000 and 2014, were identified. Eight studied the use of NRT in pregnancy<sup>(530-537)</sup> and one studied the use of bupropion in pregnancy.<sup>(538)</sup> No trials investigating electronic nicotine delivery systems (e-cigarettes) or other smoking cessation pharmacotherapies such as varenicline, in pregnancy, were identified. Details of the study population, treatment regimens and outcomes for all included studies are provided in Appendix 10.

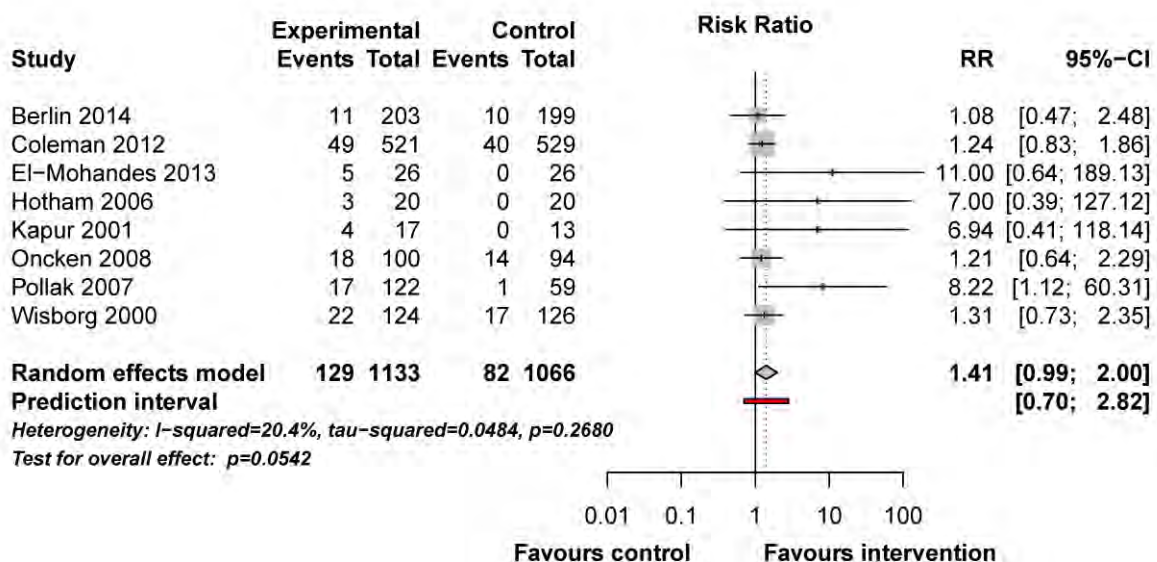
#### 4.4.3.1 NRT in pregnancy

Five of the eight trials compared NRT and behavioural cessation support with placebo patch and behavioural cessation support.<sup>(530-534)</sup> Three trials compared NRT and behavioural cessation support with behavioural cessation support alone.<sup>(535-537)</sup> Intervention was in the form of transdermal patches in six trials, and in the form of 2mg of NRT gum daily in one trial.<sup>(530)</sup> Another trial gave participants a choice of

transdermal patches, lozenges or 2mg of gum.<sup>(536)</sup> Over half (59%) of participants chose transdermal patches. The risk of bias was rated as high in three studies.<sup>(535-537)</sup> Two studies reported continuous abstinence at birth.<sup>(524, 532)</sup> Self-reported abstinence was validated biochemically in all the studies. Six of the eight studies only recruited women in the second trimester of pregnancy. One study recruited women in the first trimester (median 17 weeks' gestation, IQR 15 to 20),<sup>(532)</sup> and another study recruited women up to 30 weeks' gestation.<sup>(537)</sup>

A meta-analysis of the effect of NRT on smoking abstinence in late pregnancy showed a 41% increased likelihood for smoking cessation in late pregnancy (RR 1.41; 95% CI: 0.99 to 2.00;  $p=0.054$ ) (Figure 4.15). The 2015 Cochrane review reported a statistically significant relative risk of 1.41 for smoking cessation in late pregnancy (95% CI: 1.03 to 1.93).<sup>(524)</sup> Continuous abstinence data were reported in two trials, but the Cochrane review only included continuous abstinence data from one trial.<sup>(531)</sup> It included point prevalence abstinence data from the remaining seven trials. In keeping with the review protocol, continuous abstinence data were used in this review which explains the difference between the results of the Cochrane review and this review.

**Figure 4.15 Abstinence in late pregnancy: forest plot of studies comparing NRT versus control**



Low compliance rates substantially limited the assessment of safety.<sup>(531)</sup> Studies were underpowered to detect an effect of NRT on safety including obstetric and or neonatal outcomes. Analyses for obstetric and neonatal outcomes were conducted for singleton births only. Obstetric and neonatal outcomes were considered as secondary outcomes in all but one trial, which included a primary outcome measure for the newborn baby.<sup>(532)</sup> This trial was not sufficiently powered to detect an effect

of NRT on mean birth weight. The mean birth weight was 3065g (standard error 44g) in the NRT group and 3015g (standard error 44g) in the placebo patch group. The clinical significance of a mean difference of 50g in birth weight between the two groups is uncertain. The safety of smoking cessation interventions in pregnancy is discussed in more detail in Chapter 5.

**NRT had no effect on the rate of preterm birth prior to 37 weeks' gestation or on the rate of birth weight less than 2.5kg.**<sup>(530-533, 537) (536)</sup> There was no effect on rates for late miscarriage, stillbirth, admission to the Neonatal Intensive Care Unit or neonatal death.<sup>(530-532) (536)</sup> NRT had no effect on the rate of Caesarean section or the rate of congenital abnormality.<sup>(531, 532)</sup>

Three of the eight studies of NRT reported smoking cessation rates at three months postpartum.<sup>(530, 533, 536)</sup> Two of these reported biochemically validated seven day point prevalence smoking cessation rates.<sup>(530, 536)</sup> Participants in the third study were interviewed by telephone at three months and one year postpartum.<sup>(533)</sup> Self-reported smoking cessation was not confirmed biochemically. Use of NRT during pregnancy had no effect on smoking cessation rates at three months or one year postpartum.

Two studies recorded the rate of partner smoking, both reporting rates of approximately 74%.<sup>(531, 534)</sup> Antenatal support programmes for women and their partners need to focus on the health benefits of life-time abstinence for the woman, her partner and children.<sup>(535)</sup>

#### **4.4.3.2 Bupropion in pregnancy**

One pilot trial (n=11) compared bupropion and behavioural cessation support with placebo and behavioural cessation support.<sup>(538)</sup> The feasibility of the trial was challenging and the risk of bias was unclear. None of the five women randomised to bupropion reported abstinence after eight weeks of treatment (late pregnancy), while two of the six women randomised to placebo reported abstinence. Bupropion had no effect on biochemically validated or self-reported seven day point prevalence smoking abstinence rates in late pregnancy. Obstetric and neonatal outcomes mentioned in the study methods were not reported.

#### **4.4.4 Psychosocial interventions for smoking cessation in pregnancy**

Sixty-four trials, published between 1976 and 2016, were identified.

Psychosocial interventions were classified into five broad categories (counselling, social support, health education, feedback and financial incentives). Counselling was

the most frequently studied psychosocial intervention (68.7%), followed by social support (10.9%), health education (9.4%), feedback (6.3%) and financial incentives (4.7%). Psychosocial interventions, apart from financial incentives (n=3), were categorised into single interventions (n=23), multiple interventions (n=30) or tailored interventions (n=8). Psychosocial interventions, apart from financial incentives (n=3), were compared with usual care (n=32) or less intensive intervention (n=29). Details of the study population, treatment regimens and outcomes for all of the included studies (n=69) are provided in Appendix 10.

Gestation at recruitment to the trials of psychosocial interventions spanned all three trimesters. Six of the 44 counselling trials had a gestational cut-off of less than or **equal to 32 weeks' gestation**,<sup>(539) (539-544)</sup> two had a cut-off of less than or equal to **30 weeks' gestation**,<sup>(545, 546)</sup> and one had a cut-off of **less than or equal to 36 weeks' gestation**.<sup>(547)</sup>

Only one of the six health education trials recruited participants in the first trimester.<sup>(548)</sup> One trial recruited 72.5% (n=145) of participants in the first trimester.<sup>(529)</sup> Three trials recruited participants up to a gestational cut-off of less **than 21 weeks' gestation**,<sup>(549)</sup> less than or equal to **24 weeks' gestation**<sup>(550)</sup> and less **than 28 weeks' gestation**,<sup>(551)</sup> while one trial recruited women at any gestation.<sup>(552)</sup> Ideally, health education interventions should begin before pregnancy or in the first trimester.

#### 4.4.4.1 Health education

Health education (n=6) was an effective intervention for smoking abstinence in late pregnancy, with a risk ratio of 1.43 (95% CI: 1.07 to 1.92).<sup>(529, 548-552)</sup> Subgroup analysis revealed that health education compared with 'less intensive care' (n=3) was effective with a risk ratio of 1.44 (95% CI: 1.04 to 1.99).<sup>(529, 548, 549)</sup> The **effectiveness of health education compared to 'usual care' (n=3)**; however, was not found to be significant (RR 1.51; 95% CI 0.64 to 3.59).<sup>(550-552)</sup> No significant heterogeneity was observed.

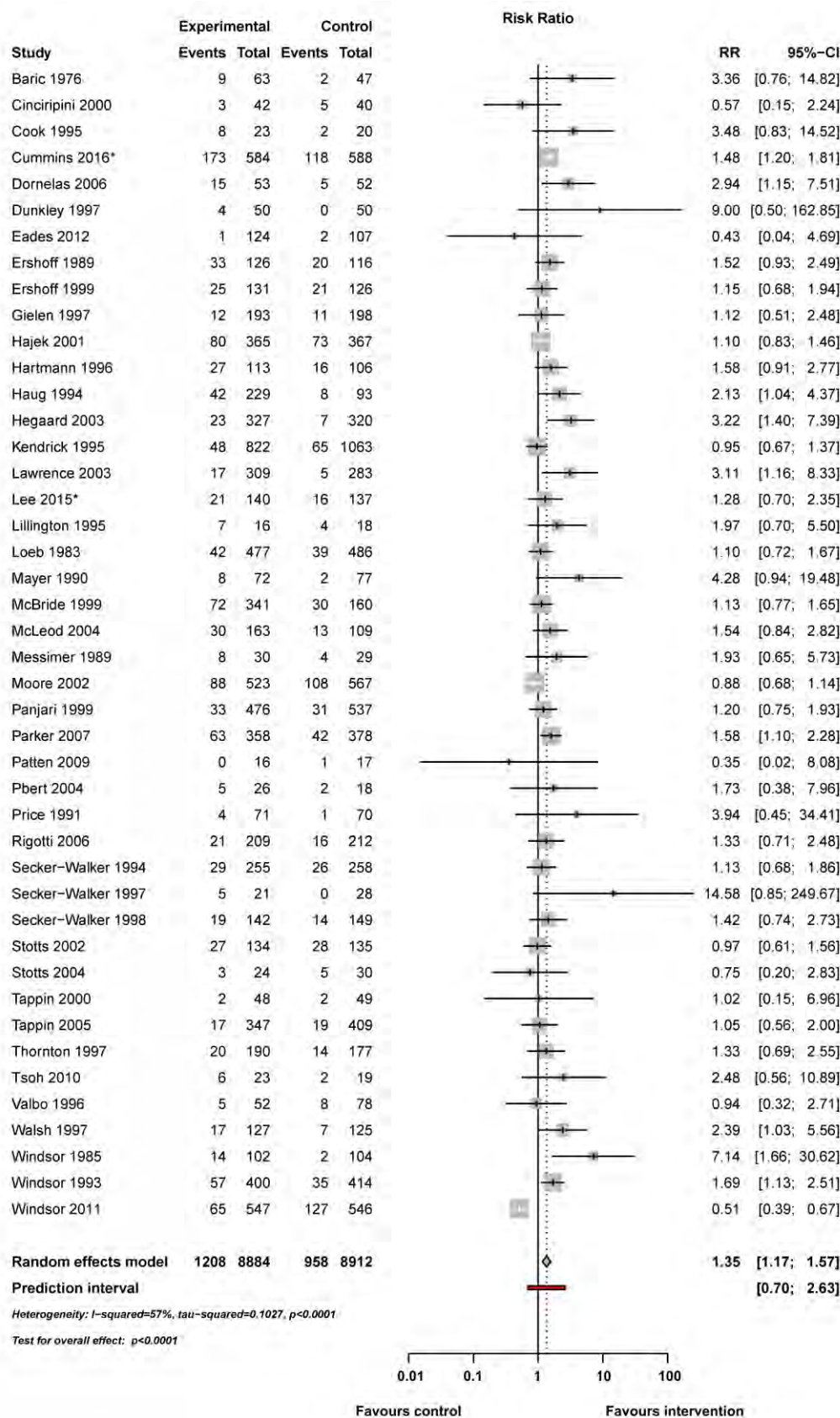
#### 4.4.4.2 Counselling

Counselling was also found to be an effective intervention for smoking abstinence in late pregnancy, with a risk ratio of 1.35 (95% CI: 1.17 to 1.57) (Figure 4.16). Subgroup analysis demonstrated that the effectiveness of counselling was similar **between the 'usual care' comparator group** (RR 1.33; 95% CI 1.12 to 1.58, n=26 studies) and the **'less intensive intervention' group** (RR 1.34; 95% CI 1.04 to 1.72, n=18 studies). Subgroup analysis did not demonstrate a large difference in **effectiveness of counselling grouped by 'single intervention'** (RR 1.27; 95% CI 1.02

to 1.58; n=16 studies), 'tailored intervention' (RR 1.39; 95% CI 0.99 to 1.95, n=6 studies) or 'multiple intervention' (RR 1.39; 95% CI 1.1 to 1.75, n=22 studies).

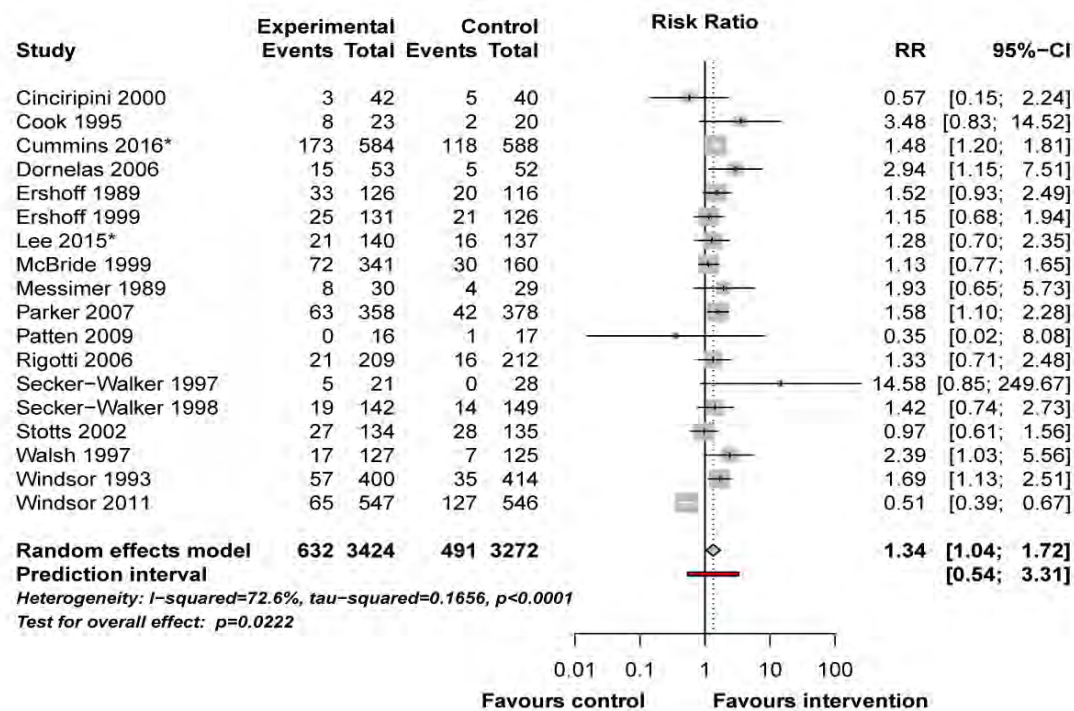
The evidence in many of the comparisons was subject to heterogeneity. The comparisons for which heterogeneity was a concern were counselling **versus 'less intensive'** (n=18,  $I^2=0.73$ ) and counselling (multiple intervention) versus control (n=22,  $I^2=0.7$ ). Figures 4.16, 4.17 and 4.18 demonstrate the forest plots of all studies comparing counselling versus control, subgroup analysis of counselling **versus 'less intensive'**, and subgroup analysis of counselling (multiple intervention) versus control.

**Figure 4.16 Forest plot of studies comparing counselling versus control**

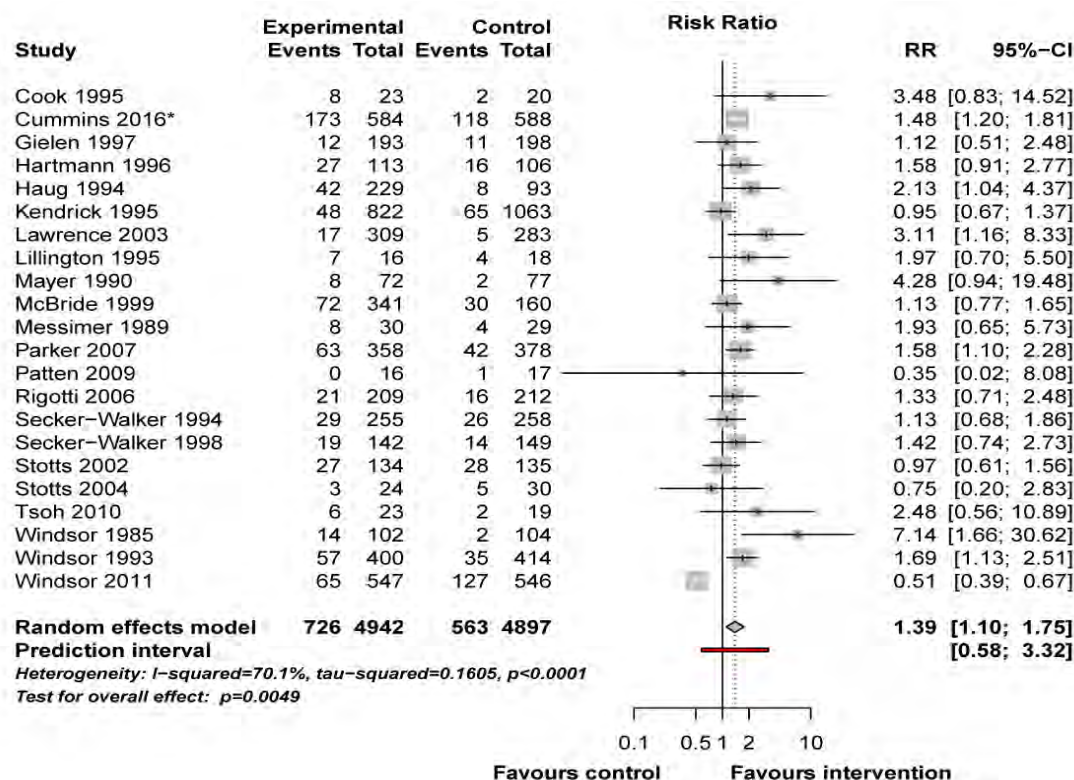




**Figure 4.17 Forest plot of studies comparing counselling versus 'less intensive'**

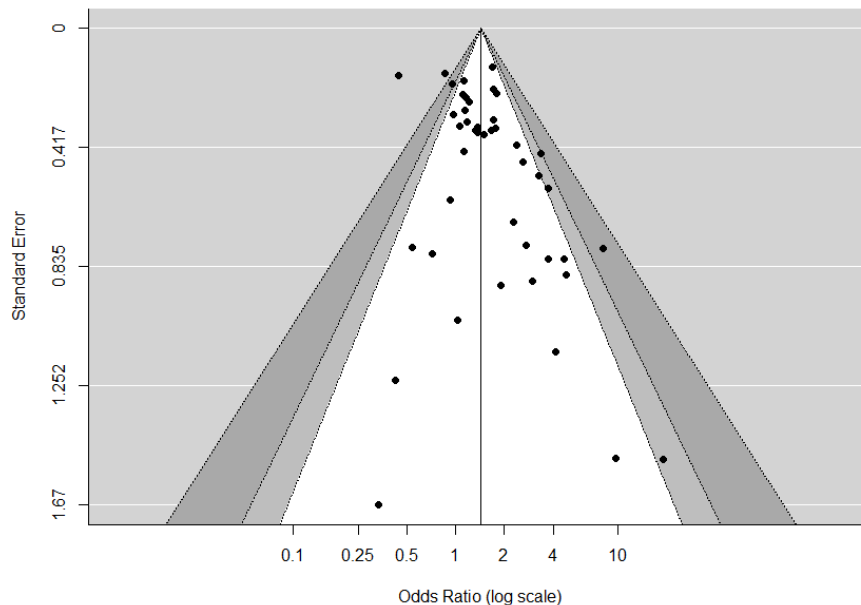


**Figure 4.18 Forest plot of studies comparing counselling (multiple component) versus control**



The possible presence of small study bias was investigated using funnel plots for cases where there were 10 or more studies. Small study bias was detected in the counselling category (Figure 4.19).

**Figure 4.19 Funnel plot for studies comparing counselling with control**



The trim and fill technique was subsequently applied to determine the potential impact of small study bias on the estimated treatment effect. When comparing counselling with control, the risk ratio decreased from 1.35 (95% CI: 1.17 to 1.57) to 1.2 (95% CI: 1.03 to 1.39). While the reduced risk ratio is still superior to control, in two subgroups the treatment effect loses significance. With trim and fill technique, the risk ratio for counselling versus usual care reduces to 1.16 (95% CI: 0.95 to 1.41), and counselling (single intervention) versus control reduces to 1.14 (95% CI: 0.88 to 1.47).

#### 4.4.4.3 Feedback

Feedback (n=4) was not an effective intervention for smoking abstinence in late pregnancy.<sup>(553-556)</sup> However, subgroup analysis by comparator found that feedback versus usual care was effective (RR 4.39, 95% CI: 1.89 to 10.21, n=2 studies). The remaining two studies evaluated feedback compared with less intensive feedback, for which a smaller treatment effect is plausible.

#### 4.4.4.3 Financial incentives

A significant positive effect was found across the three studies investigating financial incentives (RR 2.28, 95% CI: 1.55 to 3.34).<sup>(527, 528, 557)</sup> Inconsistent results were found between trials; however, the study by Tappin (2015) found a significant

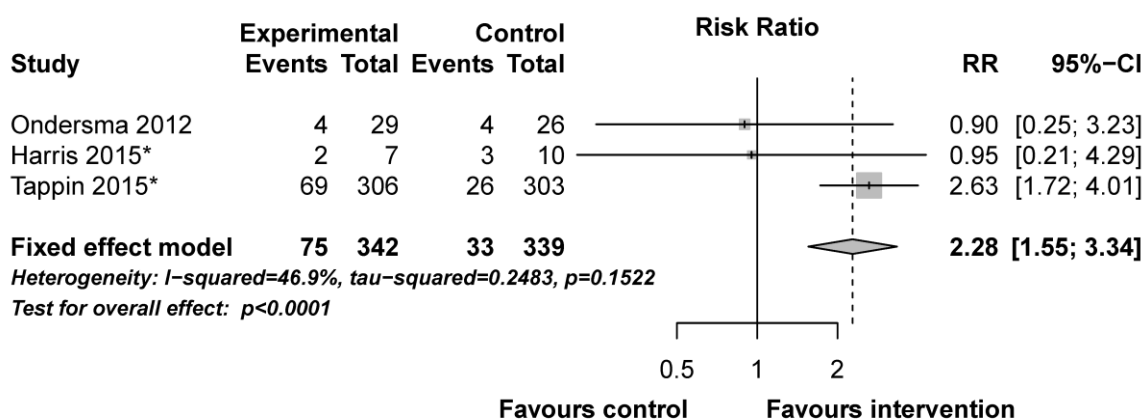


beneficial effect of using financial incentives on cessation rates (RR 2.63; 95% CI 1.72 to 4.01), whereas both other studies failed to demonstrate any effect. See Figure 4.20.

The Tappin (2015)<sup>(528)</sup> study differed from the other two studies with a substantially greater number of participants and higher intensity intervention. In this trial, the intervention group (n=302) received up to £400 worth of shopping vouchers for continued abstinence in late pregnancy in addition to the routine care received by the control group (n=302). The relative risk of not smoking at the end of pregnancy was 2.63 (95% CI 1.73 to 4.01).

Figure 4.20 demonstrates the forest plot of studies which used financial incentives. A fixed effect model was used due to the small number of studies in this category.

**Figure 4.20 Forest plot of studies comparing financial incentives versus control<sup>(558-560)</sup>**



#### 4.4.4.5 Social support

Social support (n=7) was not found to be an effective intervention for cessation (RR 1.25, 95% CI: 0.90 to 1.74).<sup>(91-93)(561-564)</sup> Subgroup analysis by comparator (usual care or 'less intensive') and by intervention type (single, tailored or multiple intervention) did not change the lack of effect.

#### 4.4.5 Discussion and conclusions

The studies reviewed broadly support the view that smoking cessation interventions are effective in pregnancy.

There is some evidence of beneficial effect for NRT as an aid to smoking cessation (RR 1.41; 95% CI 0.99 to 2.0). However, as there was only one trial of bupropion and none investigating varenicline or e-cigarettes, the effectiveness of pharmacological interventions in pregnancy cannot be determined. Neither bupropion nor varenicline is licensed for use during pregnancy in Ireland. Due to the small number of trials and differences in reporting, obstetric and neonatal outcomes are difficult to evaluate. Coleman 2012 was the only trial which reported infant outcomes beyond the neonatal period.<sup>(524)</sup> Significantly better developmental outcomes were observed two years after birth in infants born to women who had been randomised to NRT.<sup>(565)</sup> This supports the use of NRT in pregnancy.<sup>(565)</sup>

Historically, chemicals such as carbon monoxide were considered the most dangerous components of cigarette smoke. More recently, increasing recognition of direct nicotine toxicity to the fetus has generated concerns regarding the safety and efficacy of NRT.<sup>(538)</sup> While acknowledging that the evidence on the effectiveness of NRT in pregnancy is mixed, NRT is still advocated as safe in pregnancy by the National Institute for Health and Care Excellence (NICE) and the Royal College of Obstetricians and Gynaecologists in the UK.<sup>(566, 567)</sup> Current US guidelines recommend using NRT for pregnant smokers only if behavioural therapies fail, and only under close supervision of a healthcare provider. This recommendation is in light of the U.S. Preventive Services Task Force conclusion that NRT in pregnancy has '**not been sufficiently evaluated to determine their efficacy or safety**'.<sup>(568)</sup> Despite these recommendations, however, many obstetricians may still be reluctant to prescribe NRT due to safety concerns.<sup>(569) (570)</sup>

Due to these concerns, smokers should be encouraged to quit prior to conception when more treatment options are available and therapy is more likely to succeed.<sup>(571)</sup> Additional recommendations voiced by researchers include use of intermittent dosage NRT preparations such as gum or nasal spray rather than continuous dose NRT via the transdermal patch, and the removal of the transdermal patch at night to reduce overall nicotine exposure. Pregnant women should also be cautioned against smoking while using the transdermal patch because this can increase nicotine levels in both the mother and the fetus.<sup>(572)</sup> NICE guidelines stipulate that a 2-week course should initially be prescribed, with discontinuation if smoking cessation is not achieved, in addition to removal of transdermal patch at night.<sup>(567)</sup>

Evaluating the effect of psychosocial interventions in pregnancy was complicated by the fact that the definitions of the interventions were very heterogeneous. Clinical heterogeneity also arose from the differences in choice of treatment provider, frequency and intensity of intervention, and participants between studies. Of particular importance relating to the participants involved was the gestational age at

which the intervention was delivered and the age of the mother. Most studies recruited participants over the age of 18, although some specifically recruited adolescents. Albrecht et al. 2006, recruited participants aged between 14 and 19 year of age in their study of peer support as a cessation aid, and Albrecht et al. 1998 recruited participants as young as 12 years of age in their assessment of peer support as an adjunct to health education materials.<sup>(561, 562)</sup>

Financial incentives were the most effective intervention for smoking cessation. Health education was the next most effective intervention; however, on subgroup **analysis this effect was only seen when the comparator was 'less intensive intervention' and not 'usual care'.** Counselling was also effective, and the effect differed little by comparator (usual care and 'less intensive') or by intervention type (single, tailored or multiple interventions). Evidence of small study bias was obtained in these studies, however, indicating that the effect size is potentially overestimated by the available studies. Of note is the lack of a clear difference in effect seen by intervention intensity, challenging the assumption that an ever-increasing level of support increases cessation rates. A significant effect for social support or feedback was not obtained.

No serious adverse events were reported in the trials included in this review. Five NRT trials reported non-serious adverse events.<sup>(530, 531, 533, 535)</sup> The largest trial reported on 535 non-serious adverse events in the NRT group compared with 450 in the placebo group.<sup>(531)</sup> It is worth noting that adherence to NRT across trials was generally low, with limited adherence to the placebo patches also noted. Analysis is complicated by differences in the definition of adherence and persistence between studies. Adverse events in trials of psychosocial interventions were primarily focused on an increase in smoking behaviour among participants. Only one trial reported an increase in smoking among women who were unsuccessful in quitting.<sup>(573)</sup>

Furthermore, the studies identified span more than 40 years, with the earliest trial published in 1976.<sup>(574)</sup> Since then, a wide range of professionals were involved in the implementation of the interventions, including midwives,<sup>(540)</sup> doctors,<sup>(556) (575)</sup> and routine clinic staff.<sup>(539)</sup> Difficulties in implementing these types of interventions are reported in trials and these are relevant to the implementation of any individual psychosocial intervention in the Irish healthcare setting. It is reported in the literature that heavy workloads lead to inadequate time to complete the intervention.<sup>(576-579)</sup> In addition, provider pessimism may also be a problem for implementing any smoking cessation intervention.<sup>(540)</sup>

Overcoming the barriers of insufficient time in a busy clinic setting may include increasing the use of referral services. In recent years, use of telephone-based, quitline referral services<sup>(580)</sup> and technology-based interventions have gained

popularity.<sup>(581)</sup> <sup>(549)</sup> <sup>(557)</sup> In the UK, most services reported use of a quitline referral.<sup>(580)</sup>

## 4.5 Discussion

The review of clinical effectiveness considered studies evaluating smoking cessation interventions in three distinct population groups: unselected adults; people attending secondary mental health services; and pregnant women. The primary outcome of interest was long-term (six months or more) cessation, and abstinence in late pregnancy in pregnant women. Sixteen systematic reviews were identified for inclusion in this HTA. Searches were updated to capture any primary studies published since the original systematic reviews were undertaken. A large volume of data was retrieved regarding smoking cessation interventions among unselected adults. By comparison, there was a lack of data for mental health populations and a moderate number of studies evaluating smoking cessation interventions in pregnancy.

Pharmacological and behavioural interventions have demonstrated effectiveness in unselected adult smokers and this is well documented in numerous systematic reviews on the topic. However, among pregnant women and patients with mental health disorders, the beneficial effect of smoking cessation interventions is less pronounced.

A total of 313 trials investigating smoking cessation interventions among unselected adult smokers were identified for inclusion in this review. All pharmacological interventions were more effective than control. Varenicline was the most effective monotherapy (RR=2.57, 95% CI: 2.32 – 2.85). Varenicline with NRT was the most effective dual therapy (RR=3.54, 95% CI: 2.57 – 4.61). There was considerable heterogeneity in how behavioural interventions were defined. All evaluated behavioural therapies were more effective than an **alternative of 'do nothing'**. When compared with control (defined as brief advice or written materials), group behaviour therapy was the most effective behavioural intervention (RR=1.85, 95% CI: 1.53 – 2.23). Control in the form of brief advice or written materials was **50% more likely to lead to quitting than the alternative of 'do nothing'**.

The studies reviewed broadly support the view that smoking cessation interventions are effective in pregnancy. Due to the fact that bupropion and varenicline are not indicated in pregnancy, NRT is the only pharmacotherapy licensed for use to pregnant smokers who wish to quit, and its efficacy appears to be lower than in non-pregnant smokers. An analysis of eight studies showed a 41% increased likelihood for cessation associated with NRT use in pregnancy, but this did not reach statistical significance (RR 1.41; 95% CI: 0.99 to 2.00). A range of behavioural interventions in

pregnancy were reviewed, and there is evidence of a small, but statistically significant effect of counselling, health education and financial incentives on cessation rates. Due to the limited effectiveness of interventions in pregnancy, smokers should be encouraged to quit prior to conception when more treatment options are available and therapy is more likely to succeed.

Due to the fact that many smokers spontaneously quit in the early stages of pregnancy, it is possible that interventions in pregnancy (particularly in later pregnancy) are focused on more heavily dependent women and those with greater barriers to successful cessation. This may partly explain the lower efficacy compared with non-pregnant populations. In addition, the modest impact of NRT may be due to inadequate dosing of NRT in pregnancy. It has been demonstrated that nicotine clearance is increased by 60% in pregnancy.<sup>129</sup> In an attempt to limit the fetal exposure to nicotine, prescribers may also under-dose NRT, administering a lower concentration and less frequent dosing than is necessary to avert withdrawal symptoms. Finally, it is worth noting that compliance and persistence with NRT is low during pregnancy. Only 7.2% of participants in the active nicotine patch arm of the 2012 study by Coleman et al. persisted with treatment beyond one month.

Very limited evidence was retrieved for smokers attending secondary care mental health services. The majority of evidence relates to small trials with small participant numbers. Absolute cessation rates were lower in this population compared with that in the unselected adult population, with average quit rates in the control arms of approximately 7% compared with 11% for the unselected population. The combination of low control arm cessation rates and small numbers of participants resulted in some large, but not statistically significant treatment effects. Relevant data were only identified for patients with the diagnoses of schizophrenia, schizoaffective disorder and bipolar disorder. For smokers with schizophrenia or schizoaffective disorder, the addition of bupropion to behavioural interventions plus NRT significantly increased cessation rates compared with behavioural interventions plus NRT alone. Based on one placebo-controlled study, there is evidence that varenicline increases abstinence rates at six months when used as an adjunct to behavioural therapy in the schizophrenia population, although this was not statistically significant. No trial was identified specifically investigating the efficacy of NRT in this population; however, both NRT monotherapy and dual therapy were used as an adjunct to behavioural therapy in trials investigating the efficacy of bupropion.

The lack of evidence for effectiveness in the mental health population is due to the fact that few studies, in particular large-scale, high-quality studies, have been conducted to date. Recruitment of patients to RCTs from mental health populations is reported as problematic, and the focus of many trials related to the adverse event

profile rather than efficacy of the intervention. Studies excluded from this review included studies that report shorter cessation outcomes and smoking reduction rate. Researchers have speculated that risk reduction may be a better initial focus for this population due to the higher nicotine dependence and greater burden of disease compared to the general population. Motivation to quit is important in this population. Two trials comparing bupropion to placebo found only one in three participants were motivated to quit, lowering the likelihood of successful cessation.

It is important to note, however, that this review excluded the EAGLES 2016 trial; the largest trial to date to have been conducted comparing varenicline, bupropion, NRT and placebo. Individuals were stratified by the presence ( $n=4,074$ ) or absence ( $n = 3,984$ ) of a history of psychiatric disorders.<sup>36</sup> This trial was not included as it did not meet the inclusion criteria for participants to be attending secondary care mental health services. All of the first-line medications (varenicline, bupropion, and NRT) were more effective than placebo, with varenicline the most effective single agent. One limitation of the EAGLES trial, however, was that only smokers with psychiatric disorders who were stable and treated or who had previous psychiatric conditions that were in remission were included. Therefore, it may not be possible to generalise the findings to patients who are untreated or whose symptoms are unstable.

The effect sizes for many interventions were clinically significant. For example, with a risk ratio of 3.54 associated with dual therapy with Varenicline and NRT, an adult smoker is over three-and-a-half times more likely to achieve successful cessation with this intervention. Effect sizes were smaller in pregnant populations, but not clinically insignificant. For example, a significant positive effect was found across the three studies investigating financial incentives, with a RR of 2.28 (95% CI: 1.55 to 3.34).

The studies included in this HTA were intended to be representative of the three populations of interest. In terms of age, gender, and level of dependency, the study populations would appear to be broadly applicable to the Irish setting. In the mental health population group, data were only retrieved on patients with schizophrenia, schizoaffective disorder and bipolar disorder. As these diagnoses constitute a large proportion of individuals attending secondary mental health services in Ireland, the findings should be applicable to an Irish setting, if it is acknowledged that trial eligibility was often restricted to those with clinically stable disease.

## 4.6 Key points

### Overview

- The review of clinical effectiveness considered studies evaluating smoking cessation interventions in three distinct population groups: unselected adults; people attending secondary mental health services; and pregnant women. The primary outcome of interest was long-term (six months or more) cessation, and abstinence in late pregnancy in pregnant women.
- Sixteen systematic reviews relevant to this HTA were updated to capture any primary studies published since the original systematic reviews were undertaken.

### Findings

- For unselected adults:
  - 313 studies were identified, evaluating either pharmacological or behavioural interventions.
  - For pharmacological interventions, all were more effective than control. Varenicline was the most effective monotherapy (RR 2.57, 95% CI: 2.32 – 2.85). Varenicline with NRT was the most effective dual therapy (RR 3.54, 95% CI: 2.57 – 4.61).
  - Quit attempts made with brief advice or written materials are 50% more likely to result in a successful quit attempt than quitting with no form of support
  - In terms of behavioural therapies, all evaluated therapies were more **effective than an alternative of 'do nothing'.** When compared with control (defined as brief advice or written materials) group behaviour therapy was the most effective behavioural intervention (RR 1.85, 95% CI: 1.53 – 2.23). There was considerable heterogeneity in how behavioural interventions were defined.
- For people attending secondary mental health services:
  - We identified 10 studies relevant to the target population. The studies were generally small in terms of the number of participants. Absolute quit rates in the control arms tended to be low relative to those observed for unselected adults.
  - The only statistically significant evidence of a beneficial treatment was for bupropion when used as an adjunct to behavioural therapy and NRT in a population with schizophrenia or schizoaffective disorder (RR 3.86, 95% CI: 1.01 – 14.80).
- For pregnant women:
  - 73 studies were identified evaluating either pharmacological or



behavioural interventions.

- Eight trials were identified investigating NRT use as a smoking cessation aid in pregnancy, and they were deemed of high quality. Some evidence of a beneficial effect was found for NRT in this group with a 41% increase in cessation rates, but this did not reach statistical significance (RR 1.41; 95% CI: 0.99 to 2.00).
- 64 studies were identified evaluating psychosocial interventions for smoking cessation in pregnancy. The studies were rated as being of a low quality.
- There was evidence to suggest counselling, health education and financial incentives increase cessation rates in pregnant smokers.
- Pregnant women who smoke should be offered a psychosocial intervention in the first instance. The psychosocial intervention with the largest body of evidence to support its effectiveness is counselling.

#### Points to consider

- There was substantial variation in how behavioural interventions were defined and delivered, often resulting in heterogeneity in observed treatment effects. Variability was seen in the frequency and intensity of interventions.
- The studies included were intended to be representative of the three populations of interest. In terms of age, gender, and level of dependency, the study populations would appear to be broadly applicable to the Irish setting.
- In the mental health population group, data were only retrieved on patients with schizophrenia, schizoaffective disorder and bipolar disorder. These diagnoses constitute a large proportion of individuals attending mental health services in Ireland and our findings should be applicable, albeit recognising that trial eligibility was typically restricted to those with clinically stable disease.
- The evidence base for e-cigarettes is likely to evolve as further trials complete. The effectiveness of e-cigarettes for smoking cessation should be re-evaluated as new evidence becomes available.
- The effectiveness of pharmacological interventions is improved by an average of 18% by the provision of adjunct behavioural therapy.
- There are limited observational data against which to compare the trial data to determine applicability in the real world setting.



## 5 Safety

### 5.1 Introduction

This chapter will provide an overview of the current evidence in relation to the safety of pharmacological smoking cessation interventions and e-cigarettes. No substantive adverse effects were identified following review of the efficacy literature associated with behavioural interventions. For this reason, this chapter will focus on the safety of the pharmacological agents (nicotine replacement therapy (NRT), varenicline and bupropion) and e-cigarettes. The safety of these agents in pregnancy, people with mental health disorders and adolescents is also presented.

A comprehensive review of the literature was performed. Firstly, a review of the adverse event profile from efficacy trials (identified in Chapter 4) was conducted. Following this, data from observational studies, surveillance reports and company submissions were reviewed in order to summarise the evidence on long-term safety (including rare events).

### 5.2 Nicotine replacement therapy (NRT)

#### 5.2.1 Health effects of nicotine

Nicotine itself is not considered a carcinogen<sup>(582)</sup>, but in vitro and animal studies have suggested that nicotine may play a role in tumour promotion.<sup>(583, 584)</sup> This risk has not been documented in humans, and nicotine supplementation is clearly safer than the continuation of smoking. Tobacco smoke contains thousands of compounds, including over 60 known carcinogens separate to nicotine. In addition, smoking produces a higher peak and average dose of nicotine than nicotine replacement therapy (NRT).<sup>(585)</sup> This suggests that smoking would lead to greater nicotine-related risk than using NRT.

Nicotine produces haemodynamic effects (such as increased heart rate, increased systolic blood pressure and decreased digital blood flow) regardless of whether administered by cigarette smoking or NRT.<sup>(586)</sup> Studies suggest that nicotine may play a role in smoking-related cardiovascular disease through haemodynamic effects,<sup>(587-589)</sup> and possibly through the acceleration of atherosclerosis.<sup>(583, 590)</sup> However, tobacco smoke contains many harmful chemical components other than nicotine that can harm the cardiovascular system, including combustion products such as carbon monoxide and nitrogen oxides.<sup>(591)</sup> It is not clear what fraction of cardiovascular morbidity can be attributed to nicotine intake. It is generally believed that the benefits of nicotine pharmacotherapy for smoking cessation far outweigh the risks among smokers with stable heart disease.<sup>(587, 592)</sup>

While nicotine is a highly addictive drug,<sup>(582)</sup> the addiction risk of nicotine in medications has proven to be very low compared to the risk posed by tobacco products. This is in part because of lower doses and slower absorption of nicotine obtained from NRT products compared with nicotine obtained from tobacco smoke inhalation.<sup>(593, 594)</sup> Studies have demonstrated that only a minority of long-term NRT use can be attributed to dependence; most long-term use represents the extension of the therapeutic efficacy.<sup>(595, 596)</sup>

### **5.2.2 Common adverse events**

Most adverse events associated with NRT are mild and temporary in nature. A large meta-analysis of adverse events associated with nicotine patch use reports mild skin sensitivity as the most common adverse event, rarely leading to withdrawal of patch use, as well as sleep disturbance for some smokers using the 24-hour patch.<sup>(597)</sup> The major side effects usually reported with nicotine gum include hiccoughs, gastrointestinal disturbances, jaw pain and orodental problems. The major side effects reported with the nicotine inhaler and nasal spray relate to local irritation at the site of administration; the mouth and nose, respectively. Nicotine sublingual tablets have been reported to cause hiccoughs, burning sensation in the mouth, sore throat, coughing, dry lips and mouth ulcers.<sup>(598)</sup>

### **5.2.3 Adverse events identified in systematic review**

Due to the varied way adverse events were reported across the studies included in their assessment, the Cochrane review of NRT did not conduct a quantitative analysis of each of the reported side effects of NRT use.<sup>(7)</sup> However, the review does provide a broad overview of the safety profile of this treatment, along with a meta-analysis of the most clinically significant adverse event associated with its use – chest pain and heart palpitations. The most common adverse events for each type of NRT therapy are shown in Table 5.1. None of these adverse events were reported as severe. Studies identified following this Cochrane review did not differ in terms of the adverse event profile.

**Table 5.1 Most common side effects associated with NRT use**

<b>Type of NRT</b>	<b>Most common side effects</b>
<b>Gum</b>	Hiccoughs Gastrointestinal disturbance Jaw pain Oro dental problems
<b>Patch</b>	Skin sensitivity and irritation
<b>Inhaler, intranasal and oral spray</b>	Nose, mouth or throat irritation Coughing Hiccoughs
<b>Tablets</b>	Mouth irritation Hiccoughs Sore throat Dry lips Mouth ulcers

#### **5.2.4 Chest pain and heart palpitations**

A recent systematic review and meta-analysis of adverse events associated with NRT has been carried out.<sup>(599)</sup> The review included 120 studies involving 177,390 individuals and considered a possible excess of chest pains and heart palpitations among users of NRT compared with placebo groups.<sup>(599)</sup> The authors reported an odds ratio (OR) of 2.06 (95% CI 1.51 to 2.82) across 12 studies that documented these events.

The Cochrane review replicated this data collection exercise and analysis where data were available across all 260 randomised controlled trials in their review. The event rate for chest pain and palpitations was 2.5% in the NRT groups compared with 1.4% in the control groups in the 15 trials in which it was reported (OR 1.88; 95% CI 1.37 to 2.57).<sup>(7)</sup> The review reports that this is potentially the only clinically significant serious adverse event to emerge from the trials, and its occurrence is infrequent.

### 5.2.5 Cardiovascular adverse events

The benefits of quitting smoking far outweigh any risks associated with correctly administered NRT. However, there is concern that some of the cardiotoxic effects of smoking may be attributable to nicotine. Nicotine, as a stimulant, increases sympathetic activity. This leads to an increase in heart rate, vasoconstriction, and a resulting increase in systolic blood pressure. It is also suggested that nicotine may contribute to endothelial dysfunction and to developing resistance to insulin.<sup>(600)</sup> Insulin resistance results in glucose intolerance, which may precipitate or aggravate diabetes, worsening cardiovascular risk.<sup>(600)</sup>

Carbon monoxide exposure and hyperlipidaemia contribute to increased cardiovascular risk in smokers through increased thrombogenesis, oxidative damage, and reduced oxygen availability. These effects are not due to nicotine, and studies have demonstrated that smoking cessation using NRT has favourable effects on these factors.<sup>(601)</sup> Furthermore, nicotine levels achieved with replacement therapy are much lower than those found with smoking. Two coronary perfusion studies, one using quantitative thallium tests and the other using coronary angiography, suggest no increase in cardiac ischaemia in subjects using nicotine.<sup>(602, 603)</sup>

When first licensed, concern was expressed about the cardiovascular effects associated with NRT use, leading to many clinical trials to investigate this effect.<sup>(604)</sup> However, a large meta-analysis that included 35 trials with over 9,000 participants did not find evidence of excess adverse cardiovascular events among those using a nicotine patch, and the total number of such events was low.<sup>(597)</sup> A more recent meta-analysis of 120 studies, for a total of 177,390 individuals, found no increased risk of myocardial infarction or death associated with the use of NRT.<sup>(599)</sup> However, patients with pre-existing cardiac disease were specifically excluded from the majority of these studies.

Studies involving cardiac patients have also failed to find any evidence of an increased risk of cardiovascular effects or mortality associated with NRT use.<sup>(416, 605)</sup> One trial of nicotine patches, which recruited smokers aged over 45 with at least one diagnosis of cardiovascular disease, found no evidence that serious adverse events were more common in smokers in the nicotine patch group.<sup>(416)</sup> Events related to cardiovascular disease such as increase in angina severity occurred in approximately 16% of patients, but did not differ according to whether or not patients were receiving NRT. The authors concluded that NRT should not be contraindicated in patients with cardiovascular or cerebrovascular disease.

Similarly, a secondary analysis of subjects in the Lung Health Study (a randomised controlled trial for the prevention of chronic obstructive pulmonary disease), demonstrated that cardiovascular deaths were associated with continued smoking,

but not with those who used nicotine gum for up to five years. Increased cardiovascular morbidity or mortality was not observed regardless of the duration or dose of nicotine gum administered.<sup>(582)</sup>

Regulatory authorities in Europe have taken action to support the use of NRT in patients with cardiovascular disease. In 2003, the AFSSAPS (French regulatory agency for medicines) recommended the changes to the Summary of Product Characteristics of NRT, removing all contraindications relating to cardiovascular and cerebrovascular disease.<sup>(606)</sup> In 2005, the **UK's** Committee on Safety of Medicines of the Medicines and Healthcare Products Regulatory Agency (MHRA) brought in similar changes.<sup>(607)</sup> In Ireland, the Summary of Product Characteristics for licensed NRT products recommends a risk-benefit assessment be made in smokers with certain cardiovascular conditions, including recent myocardial infarction, unstable or worsening angina, severe cardiac arrhythmias and recent cerebrovascular accident.<sup>(13, 608, 609)</sup>

### 5.2.6 Safety in adolescents

There is little reason to believe that NRT poses a significantly greater risk to adolescent smokers compared to adult smokers. NRT is licensed in individuals over the age of 12 under the recommendation of a healthcare professional. See section 5.8 for a detailed discussion on the safety of NRT in adolescents.

### 5.2.7 Safety in pregnancy

NRT may be safely administered in pregnancy under the supervision of a medical professional, particularly when behavioural therapies have failed.<sup>(564, 610, 611)</sup> See section 5.6 for a detailed discussion on the safety of NRT in pregnancy.

### 5.2.8 Neuropsychiatric safety of NRT

NRT is not associated with an increased risk of neuropsychiatric adverse events in those with or without pre-existing psychiatric disease.<sup>(34)</sup> See section 5.7 for a detailed review of the safety of NRT and other smoking cessation medications in mental health populations.

## 5.3 E-cigarettes

### 5.3.1 General points

Recently, studies on the safety of e-cigarettes have emerged. However, this research **must be considered a 'work in progress' given that the safety of any product reflects** an evolving body of knowledge and as the product itself is undergoing constant development.

Existing studies exploring the safety of e-cigarettes can be divided into chemical, or toxicological, and clinical studies. Clinical studies are the most informative, but also the most demanding. In particular, the safety profile of the product must be explored in cohorts of well-characterised users in the long-term in order to address the potential of future disease development. This would require following a large cohort for a substantial number of years before any firm conclusions on product safety can be made.

### **5.3.2 Common adverse events**

The most commonly observed side effects of e-cigarette use in clinical trials and surveys are that of temporary throat and respiratory irritation and dry cough.<sup>(612-615)</sup> This is consistent with most in vitro studies demonstrating the non-specific irritant effect from e-cigarette vapour.<sup>(17)</sup> While symptoms of irritation occur most frequently in e-cigarette users, hypersensitivity to propylene glycol present in the e-cigarette vapour, and the possibility of unknown contaminants or byproducts contained in the vapour causing similar irritant effects cannot be discounted.<sup>(17)</sup> However, it remains unclear whether such an irritation could translate into clinically meaningful lung disease.

### **5.3.3 Adverse events identified in the systematic review**

Two randomised controlled trials (RCTs) were identified in the systematic review of the effectiveness of e-cigarettes for smoking cessation. Neither trial reported any serious adverse events linked to their use. There was no significant difference between the adverse event rates at six-month follow up in the trial comparing nicotine e-cigarettes to placebo e-cigarettes and NRT patches, or at three- and 12-month follow up in the trial comparing nicotine e-cigarettes to placebo e-cigarettes.<sup>(472, 473)</sup> The most frequently reported adverse events were cough (26%), dry mouth (22%), shortness of breath (20%), throat irritation (17%) and headache (17%).<sup>(473)</sup> With the exception of throat irritation, the frequency of all of these adverse events decreased over time. The Cochrane review also included cohort studies in their analysis of adverse events associated with e-cigarette use.<sup>(25)</sup> Similar to that of the included RCTs, the main adverse events consisted of mouth and throat irritation which dissipated over time.

### **5.3.4 Nicotine poisoning**

Unintended fatal nicotine poisoning is extremely rare. Self-experiments in the 1890s suggested that ingestion of 30-60mg of nicotine is fatal, and while this figure is often quoted, the results are dubious.<sup>(616)</sup> Case reports of nicotine poisoning from accidental e-liquid ingestion by children indicate nausea, vomiting and ataxia to be common symptoms, usually resulting in spontaneous recovery.<sup>(617, 618)</sup> One fatality associated with nicotine exposure in children has been recorded.<sup>(619)</sup>

There has been an increase in calls to poison centres in recent years in Ireland following accidental nicotine ingestion. The National Poisons Information Centre lists nicotine as one of the most common agents involved in the enquiries they receive.<sup>(620)</sup> There has also been a spike in the number of e-cigarette fluid poisonings presenting to the Poisons Centre in Beaumont Hospital in recent years.<sup>(620)</sup> It would seem imperative that the **e-liquid refill bottles should be in 'childproof' packaging** to prevent small children, who may find the flavouring appealing, from drinking it.

Nicotine has also been used in suicide attempts. One fatality has been documented where the subject drank three nicotine vials totalling over 10,000mg nicotine, and another whereby intravenous injection of nicotine occurred.<sup>(619, 621)</sup>

### 5.3.5 Device explosion and fires

Case reports of lithium battery explosions and thermal injuries have started to emerge. While rare events, such injuries may incur significant tissue damage requiring extensive treatment.<sup>(622)</sup>

Concerns have also been voiced by researchers regarding the potential dangers of e-cigarettes in the presence of home oxygen therapy. The heating element reaches a high temperature in order to aerosolise the e-liquid to be inhaled. Consequently, it is possible that it could ignite in the presence of oxygen.<sup>(623)</sup>

### 5.3.6 Chemical and toxicological studies

Chemical and toxicological studies indicate that the use of e-cigarettes may be less harmful than smoking.<sup>(624)</sup> There is no tobacco and no combustion involved in e-cigarettes use; therefore, regular users may avoid several harmful toxic chemicals that are typically present in the smoke of tobacco cigarettes. However, studies have demonstrated that trace amounts of potentially harmful chemicals may be released, such as formaldehyde and acetaldehyde and tobacco-specific nitrosamines (TSNAs).<sup>(18)</sup> It is worth noting, however, that levels of these compounds are substantially lower than found in tobacco smoke, and in some cases (such as nitrosamines), are comparable to the amounts found in pharmaceutical nicotine products.<sup>(625)</sup>

Goniewicz et al. (2014) performed toxicity testing to evaluate the nature of vapour generated from e-cigarettes, and to compare it to cigarette smoke and the reference product – the medicinal nicotine inhaler.<sup>(18)</sup> A comparison of six potentially toxic and carcinogenic compounds is given in Table 5.2. Toxic substances were found in e-cigarettes; however, they were nine to 450 times lower than in cigarette smoke and were, in many cases, comparable with trace amounts found in the nicotine inhaler.

Potentially toxic carbonyls, such as formaldehyde, can form when e-liquids are heated to high temperatures. In early models of e-cigarettes, the temperature of the heating element was not sufficient to create these compounds. However, some **newer 'variable voltage' models allow users to increase the temperature of the heating element to deliver more nicotine, also generating carbonyls.**<sup>(626)</sup> One study demonstrated that high levels of aldehyde only form in 'dry puff' conditions however; this occurs when the liquid overheats causing a strong unpleasant taste, which users recognise and avoid.<sup>(627)</sup> Under normal conditions aldehyde emissions are very small, even in new-generation high-power e-cigarettes.

Other investigators are interested in the flavourings and preservatives used in e-liquids. A few studies have identified various nicotine-related degradation products and other impurities in e-liquids and vapours,<sup>(628, 629)</sup> although some researchers have concluded these impurities occur at levels unlikely to cause harm.<sup>(630)</sup>

**Table 5.2 Comparison of sample toxicants emitted by tobacco cigarettes and e-cigarettes. Adapted from Goniewicz et al. (2014)**

<b>Toxic compound</b>	<b>Tobacco cigarette (mcg in mainstream smoke)</b>	<b>E-cigarette (mcg per 15 puffs)</b>	<b>Average ratio (conventional versus electronic cigarette)</b>
<b>Formaldehyde</b>	1.6–52	0.20–5.61	9
<b>Acetaldehyde</b>	52–140	0.11–1.36	450
<b>Acrolein</b>	2.4–62	0.07–4.19	15
<b>Toluene</b>	8.3–70	0.02–0.63	120
<b>Tobacco-specific nitrosamine (NNN)</b>	0.005–0.19	0.00008–0.00043	380
<b>Tobacco-specific nitrosamine (NNK)</b>	0.012–0.11	0.00011–0.00283	40

Two studies directly examined aldehyde levels in e-cigarette users. One cross-sectional study reported that e-cigarette users had much lower levels of acrolein and crotonaldehyde in urine than smokers.<sup>(631)</sup> Another study, funded by the Medicines and Healthcare Products Regulatory Agency (MHRA), examined changes in acrolein



levels in smokers who switched to e-cigarette use.<sup>(16)</sup> Users who exclusively switched to e-**cigarettes and those who became 'dual users' of cigarettes and e-cigarettes** significantly reduced their acrolein intake.

A cross-sectional study published in February 2017 investigated nicotine, carcinogen and toxin exposure in long-term e-cigarette and NRT users in the UK.<sup>(632)</sup> Five groups were recruited: cigarette-only users, former smokers with long-term ( $\geq 6$  months) e-cigarette-only or NRT-only use, and long-term dual cigarette-e-cigarette or cigarette-NRT users. No clear between-group differences in salivary or urinary biomarkers of nicotine intake were found. The e-cigarette-only and NRT-only users had significantly lower metabolite levels for tobacco-specific N-nitrosamines and volatile organic compounds (including metabolites of the toxins acrolein, acrylamide, acrylonitrile, 1,3-butadiene and ethylene oxide) than cigarette-only, dual cigarette-e-cigarette, or dual cigarette-NRT users. The authors concluded that long-term NRT-only and e-cigarette-only use, but not dual use of NRTs or e-cigarettes with cigarettes, is associated with substantially reduced levels of measured carcinogens and toxins relative to smoking.

### 5.3.7 Direct toxicity to the lung

Animal studies raise questions regarding a direct toxic effect of e-cigarette vapour in the lungs. One study subjected mice to e-cigarette vapour over a two-week period, prior to infecting them with streptococcus pneumonia or influenza virus and killing them.<sup>(633)</sup> Relative to the control group, mice exposed to e-cigarette vapour demonstrated negative indicators such as an increase in pro-inflammatory cytokines, diminished lung glutathione and higher viral titre.

A similar study exposed mice, human airway epithelial cells and human lung fibroblasts to e-cigarette vapour with flavourings.<sup>(634)</sup> Human airway epithelial and lung fibroblasts demonstrated an increase in secretion of inflammatory cytokines, and exposed mice demonstrated an increase in proinflammatory cytokines and reduction in lung glutathione levels.

Another study investigated the effects of nicotine in e-cigarette fluid, by exposing mouse lungs and normal human airway epithelial cells to aerosolised nicotine-free and nicotine-containing e-cigarette fluid.<sup>(635)</sup> Exposure to inhaled nicotine-containing e-cigarette fluids triggered effects normally associated with the development of chronic obstructive pulmonary disease (COPD), including cytokine expression, airway hyper-reactivity and lung tissue destruction. These effects were nicotine-dependent, suggesting that inhaled nicotine contributes to lung disease in animal models.

A meaningful interpretation of these studies is difficult, as in each case e-cigarette vapour was not compared to cigarette smoke. Human studies have not corroborated

the findings of lung toxicity. A case study involving lipoid pneumonia, possibly caused by flavouring of e-cigarette vapour, was reported in 2012.<sup>(636)</sup> However, no further cases of this have since been reported. A study that monitored asthma patients who switched from smoking to vaping e-cigarettes found significant improvements in symptoms and in respiratory function.<sup>(21)</sup>

### **5.3.8 Clinical studies**

There is no evidence from clinical studies that long-term e-cigarette use leads to reductions in smoking-related diseases, and it would take a few decades before a beneficial effect could be established. Nonetheless, it is feasible to detect early changes in airway function and respiratory symptoms in smokers switching to e-cigarettes. Initial findings are supportive of an improvement in respiratory outcomes in those who switch.<sup>(21)</sup>

#### **5.3.9 Acute pulmonary effects**

Vardavas et al. (2012) examined the short-term pulmonary effects of using an e-cigarette, including the impact on respiratory flow resistance, impedance, and exhaled nitric oxide.<sup>(637)</sup> E-cigarettes were found to have immediate adverse physiological effects after short-term use that are similar to some of the effects seen with tobacco smoking. However, it must be noted that the reported 16% decrease in exhaled nitric oxide levels and 11% increase in peripheral flow resistance by impulse oscillometry from baseline after using an e-cigarette for five minutes were so small and well within test variability, that it is unlikely to have any clinical relevance.

On the other hand, Flouris et al. (2013) did not elucidate a significant effect on pulmonary function (as measured by FEV1, FVC, FEV% and PEF) following acute active or passive e-cigarette use.<sup>(20)</sup>

#### **5.3.10 Long-term pulmonary effects**

Asthma and chronic obstructive pulmonary disease (COPD) are progressive diseases characterised by persistent inflammatory and remodelling responses of the airways causing progressive decline in lung function.<sup>(638)</sup> It has been well established that the inflammatory response to cigarette smoke plays a key role in COPD pathogenesis, and an increased morbidity and mortality have been reported in asthmatic individuals who smoke.

A study of one group of smokers without COPD who switched to using e-cigarettes, and gave up tobacco smoking completely, found significant early positive changes from baseline at three months of a sensitive measure of obstruction in the more peripheral airways (that is to say, forced expiratory flow measured between 25% and 75% of FVC).<sup>(21)</sup> Steady progressive improvements were also observed at six and 12 months.<sup>(21)</sup> In a clinical study conducted to determine effect and safety of e-

cigarette use with asthma, substantial improvements in respiratory physiology and subjective asthma outcomes were reported.<sup>(639)</sup> Exposure to e-vapour in this vulnerable population did not trigger any asthma attacks.

#### 5.3.11 Cardiovascular effects

The acute increase in heart rate and blood pressure that occurs after tobacco use is greater than that found following e-cigarette use.<sup>(624)</sup> In addition, the acute negative effects of smoking on coronary blood flow have not been elucidated by e-cigarette use.<sup>(624)</sup>

#### 5.3.12 Risks of passive e-cigarette vaping

The risk to bystanders of e-cigarette users appears to be very low. One study showed that the nicotine content of exhaled e-cigarette vapours is eight times lower than exhaled cigarette smoke.<sup>(640)</sup> Another study demonstrated that while nicotine from e-cigarette vapour is deposited on surfaces, the levels are very low.<sup>(641)</sup>

In addition, in estimating environmental nicotine exposure, side-stream smoke (that is, the smoke from the lighted end of the cigarette, produced regardless of whether the smoker is puffing or not) accounts for 85% of passive smoking. There is no side-stream vapour released from e-cigarettes.<sup>(19)</sup>

#### 5.3.13 E-cigarette use in youth and initiation of smoking

The World Health Organization (WHO) commissioned a review of the data on the prevalence and trends of e-cigarette use among people aged 20 or less.<sup>(642, 643)</sup> Trend data was available of adolescent e-cigarette use from probability sample surveys from three countries; the USA, Poland and Italy. In Italy, current use of e-cigarettes among smokers and non-smokers is very low and is not increasing. A similar situation is noted in England, although trend data is not based on probability samples. Conversely, USA and Poland both show a rapid increase in the current use of e-cigarettes.

A cross-sectional study investigating e-cigarette use in Irish youths (aged 16-17 years) was conducted in 2014. A total of 23.8% of respondents had used e-cigarettes at least once, however current e-cigarette use (once a month or more) was low (3.2%).<sup>(644)</sup> Concurrent or experimental use of e-cigarettes and tobacco was found to be more common than sole use. These figures are comparable to international data. According to the 2015 National Youth Tobacco Survey in the US, an estimated 27.1% of adolescents had used e-cigarettes at least once, and 5.3% were current users of e-cigarettes.<sup>(645)</sup>

Considerable debate exists about whether e-cigarette use among non-smokers is a **precursor or 'gateway' to smoking**. Existing longitudinal studies indicate that e-cigarette use by minors, who have never smoked, at least doubles their chance of future smoking initiation.<sup>(646-649)</sup> It is not clear if it is the experimentation with e-cigarettes that leads to smoking, or if individual characteristics predict both e-cigarette use and future smoking.

### 5.3.14 Conclusions

Based mostly on the levels and number of toxicants produced during the typical use of e-cigarettes, it is likely that e-cigarettes are less toxic than cigarette smoke.<sup>(650)</sup> However, e-cigarettes are unlikely to be harmless, and long-term use may increase the risk of chronic obstructive pulmonary disease, lung cancer, and possibly cardiovascular disease as well as some other diseases also associated with smoking.<sup>(651)</sup> The magnitude of these risks is likely to be smaller than from tobacco smoke, with Public Health England estimating e-cigarettes to be 95% safer than smoking.<sup>(19, 650, 652)</sup> Nevertheless, some parties have called for the prohibition and or further regulation of e-cigarette products, as was discussed at the WHO Conference of the Parties to the WHO Framework Convention on Tobacco Control in November 2016.<sup>(643)</sup>

## 5.4 Varenicline

### 5.4.1 Common adverse events

Varenicline is a nicotine receptor partial agonist, with nausea consistently the most commonly reported adverse event associated with its use in clinical trials.<sup>(318, 319, 450-452)</sup> A meta-analysis that included 2,045 individuals cited nausea (29%), insomnia (14%) and headache (14%) as the most commonly reported adverse events.<sup>(653)</sup> In addition to insomnia, abnormal dreams are associated with varenicline use.<sup>(295, 654)</sup> **Abnormal dreams are listed as 'very common' ( $\geq 1/10$ ) adverse events in the product safety data for Champix®.**<sup>(655)</sup>

Nausea is most frequently mild to moderate and transient in nature, leading to a discontinuation rate of 3% due to symptoms. Symptoms of nausea may be reduced when varenicline is administered following food.<sup>(656)</sup> Patients should be advised to take varenicline with food or at least water to minimise symptoms of nausea.

### 5.4.2 Adverse events identified in systematic review

The Cochrane review of nicotine receptor partial agonists for smoking cessation includes an analysis of the incidence of adverse events associated with varenicline and cytisine.<sup>(38)</sup> They reported that the main side effect of varenicline was mild to moderate nausea (RR 3.27, 95%CI 3.00 to 3.55 compared with placebo), which

decreased over time and did not result in high drop-out rates. With the exception of headache, these adverse events appear to be related to dosage, and in the case of nausea, can be reduced by dose-titration.<sup>(451)</sup>

Meta-analyses of the other main adverse events demonstrated an increased rate of insomnia (RR 1.49, 95% CI 1.35 to 1.65), abnormal dreams (RR 2.12, 95% CI 1.88 to 2.38) and headaches (RR 1.17, 95% CI 1.07 to 1.29) when compared with placebo.

An analysis of the incidence of serious adverse events is also reported. The authors defined this as those that result in death, are life-threatening, require hospitalisation or prolong an existing hospital stay, lead to significant disability, or result in a congenital anomaly or birth defect.<sup>(38)</sup> There was a high degree of variability in the numbers of serious adverse events reported in the cytisine trials. One study comparing cytisine to placebo did not report any information; another reported no events; and the final study reported seven serious adverse events, none of which were deemed to be treatment related. In contrast, the study comparing cytisine to NRT reported 56 serious adverse events in 45 participants in the cytisine group, and 45 events in 39 people taking NRT.

In the varenicline trials, there were no treatment-related deaths in the varenicline group during treatment or follow up. Non-fatal serious adverse events occurred in 29 trials. A meta-analysis of all varenicline versus placebo studies in the Cochrane review, which included the recently completed EAGLES study, found that those receiving the treatment had an increased risk of experiencing a serious adverse event (RR 1.25, 95%CI 1.04 to 1.49). A subgroup analysis carried out for neuropsychiatric serious adverse events and cardiac serious adverse events found no statistically significant effect of varenicline treatment for either of these types of event compared with placebo (RR 0.82, 95%CI 0.57 to 1.19; and RR 1.36, 95%CI 0.91 to 2.04, respectively).

### **5.4.3 Cardiovascular adverse events**

The US Food and Drug Administration (FDA) approved varenicline in May 2006. The priority safety review published in 2006 found that varenicline-treated patients experienced serious cardiovascular adverse events more commonly than those treated with placebo.<sup>(657)</sup> In 2010, a post-marketing experience report published by the FDA highlighted the case reports of myocardial infarctions and cerebrovascular accidents that occurred in patients treated with varenicline; however, the role of smoking itself contributing to these events in smokers could not be ruled out.<sup>(38)</sup> In 2011 and 2013, further revisions to the marketing label highlighted results of individual studies and reviews that studied cardiovascular events in patients using varenicline.<sup>(658, 659)</sup>

Three independent systematic reviews conducted around this time echoed these concerns; serious cardiovascular adverse events occurred more frequently in the varenicline treated group compared with placebo in each review.<sup>(660-662)</sup> Certain studies were included in more than one review; the trial by Rigotti and colleagues<sup>(663)</sup> that contributed most in terms of weight to the meta-analyses was included in all three reviews.

Similarly, a large observational prospective cohort study of dispensed prescriptions for varenicline in New Zealand between April 2007 and November 2010, conducted by the Intensive Medicines Monitoring Programme, voiced concerns over the cardiovascular safety of varenicline.<sup>(664)</sup> In total, 172 cardiovascular adverse events were observed within the cohort. The investigators considered that two cases may have been triggered by the use of varenicline.

On the other hand, a 2016 systematic review and meta-analysis of varenicline and cardiovascular serious adverse events, including 38 randomised controlled trials (RCTs) with 12,706 participants, found no evidence of an association in people with (RR 1.04, 95% CI 0.57 to 1.89) or without (RR 1.03, 95%CI 0.64 to 1.64) cardiovascular illness.<sup>(665)</sup> The study also analysed all-cause mortality, and found no difference between the varenicline and placebo groups (RR 0.88, 95% CI 0.50 to 1.52).

Recent large observational studies from Denmark<sup>(666)</sup> and the UK<sup>(667)</sup> did not find a clear association with increased risk of cardiovascular events. The Danish study compared cohorts of people prescribed varenicline or bupropion (17,926 in each group) from 2007 to 2010 for rates of acute coronary syndrome, ischaemic stroke, and cardiovascular death six months from the start of treatment. The study found no excess of events in the varenicline group (6.9 cases per 1000 person-years) compared with the bupropion group (7.1 cases per 1000 person-years).<sup>(666)</sup> In the UK study, data from 753 National Health Service (NHS) general practices were reviewed to compare recipients of NRT (n=106,759; the reference group) with users of varenicline (n=51,450) and bupropion (n=6,557), for the incidence of neuropsychiatric and cardiovascular events.<sup>(667)</sup> Reduced risks of ischaemic heart disease (HR 0.80, 95% CI 0.72 to 0.87), cerebral infarction (HR 0.62, 95% CI 0.52 to 0.73), heart failure (HR 0.61, 95% CI 0.45 to 0.83) and arrhythmia (HR 0.73, 95% CI 0.60 to 0.88) was observed in varenicline compared with NRT users.

It is clear from these studies that there is conflicting evidence regarding cardiac adverse events with varenicline. The CATS study, conducted among participants in the EAGLES 2016 study, was designed to monitor the incidence of major cardiovascular events for 28 weeks after the completion of the EAGLES (Evaluating Adverse Events in a Global Smoking Cessation Study) 2016 trial.<sup>(668)</sup> The results had not yet been published at the time of finalising this assessment.

#### **5.4.4 Abuse potential**

Varenicline appears to have little, if any, abuse potential.<sup>(669)</sup>

#### **5.4.5 Neuropsychiatric adverse events**

Due to an initial concern of clinically significant neuropsychiatric events associated with varenicline administration, both the European Medicines Agency (EMA) and the FDA issued a warning for its use in patients with pre-existing psychiatric conditions. However, the EMA removed the black triangle warning in May 2016. This occurred following publication of safety and efficacy data from the EAGLES trial in April 2016. The EAGLES trial found no increased incidence of adverse neuropsychiatric effects in patients with or without pre-existing psychiatric disorder.<sup>(34)</sup> See section 5.7 for a detailed discussion of the safety of varenicline in mental health populations.

#### **5.4.6 Varenicline in pregnancy**

See section 5.7.4 for a detailed discussion on the safety of varenicline in pregnancy. There are few studies demonstrating the safety and efficacy of varenicline in a pregnant population. Varenicline is currently not recommended during pregnancy or lactation in Ireland. NICE clinical guidelines in the UK<sup>(610)</sup> and the American College of Obstetricians and Gynecologists in the US<sup>(611)</sup> similarly caution against varenicline in pregnancy due to a lack of data.

### **5.5 Bupropion**

#### **5.5.1 Common adverse events**

The most common adverse events associated with the use of bupropion are insomnia, occurring in 30% to 40% of patients, dry mouth (10%) and nausea.<sup>(670)</sup> Allergic reactions, including pruritus, hives, angioedema and dyspnoea have also been reported with the use of bupropion. Allergic and hypersensitivity reactions requiring medical treatment, however, are rare; occurring at a rate of 1:1000 to 3:1000 in national surveillance schemes and clinical trials.<sup>(28, 671)</sup>

#### **5.5.2 Adverse events identified in systematic review**

The Cochrane review of antidepressants for smoking cessation carried out a detailed review of adverse events associated with bupropion.<sup>(28)</sup> Consistent with product safety data, the most common side effects were insomnia, dry mouth and nausea, with sleep disturbance occurring in up to half (30-50%) of patients. Allergic reactions were also reported.

A meta-analysis of 33 trials comparing bupropion with placebo, carried out for the Cochrane review, showed that bupropion was associated with a marginal and



statistically non-significant increase in the rate of serious adverse events (RR 1.30, 95% CI 1.00 to 1.69).<sup>(28)</sup> Subgroup analysis of cardiovascular events also detected no difference between the two groups (RR 1.16, 95% CI 0.65 to 2.06, 25 trials).

### 5.5.3 Seizures

Bupropion was first used for the treatment of depression in the late 1980s and at this time was only available in an immediate release form.<sup>(672)</sup> In an open label trial of 3,341 patients using up to 450mg per day of this formulation, the risk of seizure during the first eight weeks of treatment was 0.36%.<sup>(673)</sup> In 1996 a sustained release formulation was introduced. Following this, a large, open, uncontrolled observational safety surveillance study was conducted by the manufacturers which examined 3,100 adult patients using slow release bupropion for eight weeks for treatment of depression.<sup>(30)</sup> Three participants (0.1%) had a seizure considered to be related to the therapeutic use of bupropion. This gave rise to the figure of 1:1,000 as the seizure rate given in the product safety data.

The evidence for seizure risk from trials is consistent with findings from large observational studies of the use of bupropion SR (slow release formulation) for smoking cessation. A post-marketing observational cohort study reported on 11,753 English patients who had been dispensed bupropion.<sup>(29)</sup> Eleven seizures were reported for a rate of one in 1,000. However, four of these were associated with a past history of seizure.

Another observational study used a UK general practice database to estimate the relative incidence of seizure or sudden death in a large sample of 9,329 individuals.<sup>(674)</sup> This is the largest safety study of first-time users of bupropion reported to date. An equivalent of one additional seizure per 6,219 first time bupropion users was found during the first 28 days of treatment, suggesting that bupropion has a better safety profile in relation to seizure than previously reported. They found no evidence of an increased risk of sudden death.

Nonetheless, bupropion is contraindicated in patients with a current or past history of seizures, and the following predisposing conditions for seizures:

- patients with a known central nervous system (CNS) tumour
- patients undergoing abrupt withdrawal from alcohol or any medicinal product known to be associated with risk of seizures on withdrawal (in particular benzodiazepines and benzodiazepine-like agents)
- patients with a current or previous diagnosis of bulimia or anorexia nervosa
- patients also taking any other medicinal products known to lower the seizure threshold.



### 5.5.4 Overdose

Bupropion may cause adverse effects in overdose. Seizures occur in one in three cases of intentional overdose of the immediate release form.<sup>(675)</sup> There is a close relationship between seizures and dose. Those who take more than 30 tablets are more prone to seizures and almost every patient who takes more than 60 tablets has a seizure.<sup>(676)</sup>

A review of bupropion-only, non-therapeutic exposures reported to the US Toxic Exposure Surveillance System for 1998-1999 identified 3,755 exposures to Wellbutrin<sup>®</sup> slow release, 2,184 to Wellbutrin<sup>®</sup>, and 1,409 to Zyban<sup>®</sup> (bupropion is marketed as both Wellbutrin<sup>®</sup> and Zyban<sup>®</sup>).<sup>(677)</sup> Non-therapeutic exposures included intentional overdose and unintentional ingestion, as well as reports of adverse reactions. Of those exposed to Zyban<sup>®</sup> who showed any symptoms, 13% developed a seizure. There were no deaths associated with Zyban<sup>®</sup>. To date, no patient is reported to have died while taking bupropion in trials for smoking cessation.

### 5.5.5 Cardiac adverse events

Bupropion has sympathomimetic effects, evidenced by the fact that in overdose, tachycardia, hypertension and seizures may occur. However, in clinical trials of bupropion in smokers with pre-existing cardiovascular disease, including hypertension, no significant adverse cardiovascular side effects were observed.<sup>(678-680)</sup> It is recommended that blood pressure is monitored in hypertensive patients if bupropion is co-administered with NRT.

### 5.5.6 Abuse potential

While bupropion is structurally similar to certain stimulants, clinical studies in healthy subjects and substance abusers suggest it has a low abuse potential.<sup>(681-684)</sup> Bupropion is not regulated as a controlled substance by the European Medicines Agency or by the US Drug Enforcement Administration under the International Conventions that regulate drugs with significant abuse potential.

### 5.5.7 Precipitation of mania

Bupropion is contraindicated in patients with a history of bipolar disorder as it may cause a manic episode during the depressed phase of their illness, according to product safety data. See section 5.7.8 for further discussion of administering bupropion in this group.

The possibility of mood destabilisation has been observed only in a small number of individuals with bipolar disorder, however, these patients were taking the medication as an antidepressant as opposed to smoking cessation.<sup>(685, 686)</sup> There is no strong

evidence to suggest that bupropion induces mania in stably-treated bipolar disorder when used as a smoking cessation aid.<sup>(687)</sup>

### 5.5.8 Neuropsychiatric adverse events

Subgroup analysis of neuropsychiatric serious adverse events in the Cochrane review detected no difference between the bupropion and placebo groups, with a RR of 0.60 (95% CI 0.28 to 1.28, 19 trials).<sup>(28)</sup> The event rates were 0.4% and 0.7%, respectively.

As discussed previously, the 2016 EAGLES trial sought to evaluate the neuropsychiatric safety of bupropion, varenicline and nicotine patch in smokers with and without psychiatric disorders.<sup>(34)</sup> The study found a significant increase in neuropsychiatric adverse events could not be attributed to varenicline or bupropion when compared to nicotine patch or placebo in patients with or without pre-existing psychiatric disorders.

Prior to this, recommendations were conflicting regarding the risk of adverse neuropsychiatric events. In 2009, the US Food and Drug Administration (FDA) added additional language to their existing boxed warning about the risk of serious mental health events, including depressed mood, hostility, and suicidal ideation associated with bupropion use for smoking cessations, based upon post-marketing surveillance data. This was in contradiction to the position taken by the European Agency for the **Evaluation of Medicines, which had stated there was 'no pharmacodynamic nor clinical reason for suspecting bupropion to be causally associated with depression or suicide'**.

Observational data was similarly inconsistent before publication of the EAGLES trial. In an analysis of five years of data from general practices in the UK, no differences in rates of depression, suicide and non-fatal self-harm were detected between people prescribed varenicline, bupropion or NRT for smoking cessation.<sup>(688)</sup> Similarly, a registry-based cohort study in Denmark evaluated risk of psychiatric adverse events in people prescribed bupropion or varenicline over a three-year period.<sup>(689)</sup> They found no significant difference in psychiatric events between the bupropion and varenicline cohorts.<sup>(689)</sup> However, an analysis based on US data comparing suicidal behaviour and depression in people prescribed bupropion, varenicline or NRT for smoking cessation did detect significant group differences; both bupropion and varenicline demonstrated an increased risk of suicidality and depression compared to NRT.<sup>(690)</sup>

See section 5.7.4 for a further discussion of the safety profile of bupropion in mental health populations.

### 5.5.9 Bupropion in pregnancy

There does not appear to be an increased risk of major congenital malformations associated with prenatal exposure to bupropion. There is insufficient evidence, however, regarding the risk of spontaneous abortion.<sup>(691)</sup> The use of bupropion is not currently recommended in pregnant women in Ireland. Similarly, NICE clinical guidelines in the UK<sup>(610)</sup> and the American College of Obstetricians and Gynecologists in the US<sup>(611)</sup> do not recommend the use of bupropion during pregnancy or breastfeeding for the purpose of smoking cessation. See section 5.6.3 for a detailed discussion on the safety of bupropion in pregnancy.

## 5.6 Safety in pregnancy

### 5.6.1 Nicotine replacement therapy

The risks of smoking during pregnancy are well known. The use of tobacco products is associated with premature rupture of the membranes, preterm birth, intrauterine growth restriction, placenta praevia, abruption of the placenta and sudden infant death syndrome.<sup>(692)</sup> Nicotine easily crosses the placenta. In nicotine patch users, amniotic fluid nicotine levels are 88% higher than in maternal plasma, and nicotine levels in the fetal circulation are 15% above maternal levels. Nicotine affects fetal respiratory movements and circulation in a dose-dependent manner.<sup>(693)</sup> This raises the possibility of fetal toxicity.

The long-term fetal and neonatal effects of NRT in humans are unclear. However, epidemiological studies have linked prenatal tobacco exposure to the following neurobehavioural effects:<sup>(693)</sup>

- attention-deficit hyperactivity disorder
- learning disabilities
- behavioural problems
- increased risk of nicotine addiction.

Whether NRT, at the usually prescribed doses, has the same neurobehavioural effects is unknown. The clear benefit of NRT use during pregnancy is that NRT delivers nicotine without delivering the additional reproductive toxins present in tobacco smoke. Additionally, NRT exposes the mother to continuous low doses of nicotine, avoiding the peak levels associated with cigarette smoking. Women should receive as low a dose of NRT as possible to maintain smoking abstinence and to control cravings. See Chapter 3: Epidemiology for a further discussion on the burden of disease attributable to smoking in pregnancy.

A retrospective study using the Danish National Birth Cohort (1996 to 2002) did not demonstrate a significant association between birth weight and duration of NRT use (difference in birth weight of 0.25g for each week of NRT use; 95% CI, 2.31 to 2.81) or type of NRT product (patch, gum, inhaler).<sup>(694)</sup> Another study using the Danish National Birth Cohort (1997 to 2003) reported no increased risk of major malformation the offspring (RR: 1.13; 95% CI, 0.62 to 2.07).<sup>(695)</sup>

A meta-analysis of six trials of NRT use in pregnancy (n = 1,745) was inconclusive with regard to its safety and effectiveness in pregnancy.<sup>(696)</sup> There were no statistically significant differences between treated and untreated women in rates of miscarriage, premature birth, low birth weight, stillbirth, admission to the Neonatal Intensive Care Unit (NICU), or neonatal death. It was uncertain whether the lack of statistically significant differences was a true effect of NRT or if it was due to **patients' poor adherence. Reported compliance rates for either NRT or placebo in the studies included ranged from 7% to 29%.**

The Smoking, Nicotine and Pregnancy (SNAP) trial was a randomised controlled trial (RCT) involving 1,050 women with pregnancies of between 12 and 24 weeks' gestation who smoked five or more cigarettes daily.<sup>(531)</sup> All participants received behavioural counselling and were randomised to receive either NRT (nicotine patch) or a transdermal placebo. There were no significant differences in mean birth weight (difference -0.05; 95% CI -0.17 to 0.08), rates of preterm birth (OR 0.90; 95% CI 0.58 to 1.41), low birth weight (OR 1.38; 95% CI 0.90 to 2.09), or congenital abnormalities (OR 0.70; 95% CI 0.30 to 1.66). However, as the rates of compliance were low, it is difficult to draw conclusions.

A follow-up to this study analysing the long-term outcomes of NRT use found that more infants of mothers who were in the NRT group had no impairment compared with those in the placebo group (OR 1.40; 95% CI 1.05 to 1.86).<sup>(565)</sup> Although this was the first study to report outcomes beyond two years, the initial compliance rates were low and rates of abstinence were self-reported.

In another RCT studying smoking abstinence rates and fetal effects of nicotine gum use for smoking cessation during pregnancy, 194 women were randomised to receive behavioural counselling and six weeks of treatment with either 2mg of nicotine gum or placebo.<sup>(530)</sup> Interestingly, birth weights were found to be significantly higher in the NRT group (3,287g ± 566 versus 2,950g ± 653,  $p < 0.001$ ). Gestational age at delivery was also greater with NRT use (38.9 ± 1.7 weeks vs. 38.0 ± 3.3 weeks,  $p = 0.014$ ). Compliance was low but similar in each group, ranging from 90% at the first visit to 30% at the fifth visit. It is worth noting that the study population comprised women with comorbid substance-use disorder and mental health issues, which may have affected the external validity of the results.

Two systematic reviews of NRT use during pregnancy concluded that behavioural support should be offered to pregnant women before NRT (including cognitive-behavioural therapy and counselling).<sup>(697, 698)</sup> Both reviews recommended NRT administration under supervision where behavioural therapy fails or in the case of higher (more than 5 cigarettes per day) addiction, to decrease the risk for low birth weight and preterm delivery associated with continued smoking.

The Cochrane review (Coleman, 2015) reported on safety outcomes from six trials assessing NRT use in pregnant women. Significant increases in serious adverse events were not found among the treatment groups.<sup>(527, 531-533, 535, 536)</sup>

NRT is advocated as safe in pregnancy by NICE and the Royal College of Obstetricians & Gynaecologists in the UK.<sup>(610, 699)</sup> Current U.S. guidelines recommend considering NRT for pregnant smokers only if behavioural therapies fail, and only under close supervision of a treatment provider.<sup>(569)</sup> This recommendation is in light of the U.S. Preventive Services Task Force conclusion that NRT in pregnancy has 'not been sufficiently evaluated to determine their efficacy or safety'.<sup>(700)</sup> The Society of Obstetricians and Gynaecologists of Canada's Guidelines on Substance Use in Pregnancy and the CAN-ADAPTT guidelines similarly recommend behavioural therapy and or counselling before considering NRT.<sup>(701)</sup> Despite these recommendations, however, many obstetricians may still be reluctant to prescribe NRT due to safety concerns.<sup>(569, 702)</sup>

Additional recommendations voiced by researchers include intermittent dosage NRT preparations such as gum or nasal spray rather than continuous dose NRT via the nicotine patch, and the removal of the nicotine patch at night to reduce overall nicotine exposure. NRT should be discontinued if there has been no associated reduction in smoking. Pregnant women should also be cautioned against smoking while using the nicotine patch because this can increase nicotine levels in both the mother and the fetus.<sup>(572)</sup>

### 5.6.2 Varenicline

There are few studies demonstrating the safety and efficacy of varenicline in a pregnant population. Preclinical animal studies have demonstrated placental transfer of varenicline, however, they report conflicting evidence regarding adverse events.<sup>(703)</sup>

A prospective cohort study using prescription event monitoring identified 6,882 women of reproductive age over a four-year period who were prescribed varenicline.<sup>(704)</sup> For the 23 reports of pregnancy identified (0.84% of all cases), exposure to varenicline was from the time of conception for 19 cases. Duration of exposure during pregnancy ranged from one day to 16 weeks. Adverse outcomes

were identified in five of 17 live births: one baby had birth asphyxia and recurrent chest infections, one had gastro-oesophageal reflux, one was diagnosed with ankyloglossia and two had feeding difficulties. This study suggests that approximately 1% of women of reproductive age prescribed varenicline may be exposed to this medicine during pregnancy, resulting in significant fetal exposure. Given the small study population, it is not possible to draw conclusions about the safety and efficacy of varenicline in pregnancy.

An industry-sponsored, prospective, population-based cohort study analysing the effects of varenicline use during pregnancy on major congenital malformations and other abnormal pregnancy outcomes was completed by the manufacturer (*the Pfizer Varenicline Pregnancy Cohort Study*) in May 2016.<sup>(705)</sup> The results of this study are awaited at the time of publishing this HTA.

Varenicline is currently not recommended during pregnancy in Ireland. NICE clinical guidelines in the UK<sup>(610)</sup> and the American College of Obstetricians and Gynecologists in the US<sup>(611)</sup> similarly do not recommend varenicline use during pregnancy or breastfeeding.

### 5.6.3 Bupropion

Bupropion and its active metabolites cross the placenta to the fetal circulation.<sup>(706)</sup> Neither bupropion nor its metabolite appear to affect placental tissue viability or functional parameters.<sup>(707)</sup>

Initial reports from the GlaxoSmithKline Bupropion Pregnancy Registry suggested a possible increase in cardiovascular defects following exposure to bupropion during pregnancy.<sup>(708)</sup> **Further analysis of data from the manufacturer's pregnancy registry,** which reported on prospectively enrolled pregnancies with 1,005 outcomes, however, observed no increased rate of major malformations compared with the general population.<sup>(708)</sup>

Nonetheless, the effect on the fetus remains unclear, especially with first trimester exposure. Chun-Fai-Chan et al. (2005) found no increase in the rate of major congenital malformations compared with controls in 136 women exposed to bupropion in the first trimester.<sup>(37)</sup> In addition, there was no significant change observed in rates of live birth, stillbirth, therapeutic abortion, mean birth weight, or gestational age at birth. However, there were significantly more spontaneous abortions in the treatment group (14.7% vs. 4.5%,  $p = 0.009$ ). The sample size in this study was small, and it is therefore difficult to draw conclusions about the safety of the drug.

In a prospective observational matched control study of 44 pregnant women, the smoking cessation rate was 45% in women who received 150mg to 300mg of

bupropion daily, compared with 13.6% in controls ( $p = 0.047$ ), and there was no difference in pregnancy outcomes.<sup>(709)</sup>

Another study of 1,213 women with first trimester exposure demonstrated no increase in malformations compared with those using bupropion after the first trimester, or using other antidepressants.<sup>(710)</sup> Some participants in this study were also on other antidepressants besides bupropion. A limitation of the study was that the authors were unable to confirm exposure to bupropion as information was obtained from dispensing data.

In contrast, a retrospective case–control study of 6,853 infants with major heart defects and 5,869 control infants showed an association between bupropion exposure in early pregnancy and left outflow tract heart defects (OR 2.6; 95% CI 1.2 to 5.7,  $p = 0.01$ ).<sup>(711)</sup> Bupropion exposure was defined as any reported use between one month pre-conception and three months post-conception. This finding, however, may have been confounded by a concurrent diagnosis of depression or recall bias regarding exposure to bupropion.

Most studies have concluded that there does not appear to be an increased risk of major congenital malformations associated with prenatal exposure to bupropion. There is insufficient evidence, however, regarding the risk of spontaneous abortion.<sup>(691)</sup> The use of bupropion is currently not recommended in pregnant women in Ireland. NICE clinical guidelines in the UK<sup>(610)</sup> and the American College of Obstetricians and Gynecologists in the US<sup>(611)</sup> similarly do not recommend the use of bupropion during pregnancy or breastfeeding for the purpose of smoking cessation.

## **5.7 Safety in mental health populations**

### **5.7.1 Significance of smoking in psychiatric settings**

The burden of disease attributable to smoking in psychiatric populations is substantial. Patients diagnosed with severe mental illness are up to three times more likely to be smokers than the general population. Smoking prevalence reaches figures of up to 70% for certain sub groups, such as in-patients and patients with schizophrenia.<sup>(482, 712)</sup> Mental illness is associated with higher levels of nicotine dependence, intensity of smoking, and smoking severity.<sup>(500, 713)</sup> Smoking is believed to account for the majority of excess mortality among individuals with serious mental illness.<sup>(87)</sup> Life expectancy among people with severe mental illness is 10 to 25 years less than that among the general population.<sup>(714, 715)</sup>

The underlying reasons for the strong relationship between smoking and psychiatric disorders are complex and vary by diagnosis. Genetic, neurological and psychosocial factors are proposed to contribute to the increased smoking prevalence in this



group.<sup>(716, 717)</sup> The interaction of nicotine with neurotransmitter systems in the brain mediates the release of neurotransmitters such as dopamine, serotonin and noradrenaline; affecting mood, attention, cognitive functioning and memory. Self-medication of symptoms may serve as a potential explanation for the increased rates of smoking in individuals with mental illness.<sup>(718)</sup>

Also of clinical relevance are the interactions caused by polycyclic aromatic hydrocarbons of tobacco smoke that induce liver enzymes and reduce the clearance of psychotropic medications. For example, when a patient stops smoking, clozapine and olanzapine dosages may need to be reduced by 30 to 40% to avoid toxicity.<sup>(719)</sup> Nicotine does not create this effect, and therefore NRT will not affect changes in medication levels following smoking cessation.

### **5.7.2 Systemic Issues**

Between 2004 and 2011 the decline in smoking among individuals with mental illness was significantly less than among those without mental illness.<sup>(720)</sup> It appears that tobacco control policies for the general population were not as effective in mental health populations. It is widely believed that tobacco dependence has been a largely neglected issue in mental health settings.

While a societal change towards reducing smoking and the exposure to tobacco smoke in public and work places has taken place in Ireland over recent years, smoking is still largely condoned across psychiatric settings. Many mental health professionals inappropriately perceive it as an important coping mechanism for patients.<sup>(721)</sup> Smoking may also be perceived as constituting a means of reward or punishment in achieving compliance with treatment, and may play an important part in the context of social interaction between patients and staff.<sup>(722)</sup>

### **5.7.3 Smoking cessation interventions**

In general, smoking cessation treatment in mental health populations follows similar principals to smoking cessation in other populations.<sup>(723)</sup> Contrary to common belief, smokers within mental health populations are frequently equally as willing to quit as those in the general population, and may do so without aggravating psychiatric symptoms if provided with appropriate support.<sup>(720)</sup> Unfortunately, success in quitting appears to be only half of that as in the general population, and relapse rates within mental health populations are higher.<sup>(724)</sup>

Nicotine replacement therapy (NRT) is generally well-tolerated in psychiatric populations. In addition, behavioural interventions with proven effectiveness in the general population, including group support, have been successfully integrated into tailored behavioural programmes for patients with serious mental illness.<sup>(725)</sup> It has



been noted that mental health populations may need a higher level of support to quit, especially one-to-one support.

It has been demonstrated that NRT may be required at higher doses than in the general population, and a combination of patch and a faster-acting form (such as gum or inhaler) is preferable. It has also been demonstrated that a longer duration of NRT may be required for prolonged abstinence.<sup>(726, 727)</sup>

#### **5.7.4 Neuropsychiatric safety of varenicline, bupropion and NRT**

Concerns about the neuropsychiatric safety of varenicline and bupropion arose from sporadic case reports<sup>(728)</sup> and post-marketing surveillance analyses (see below).

Observational studies have demonstrated inconsistent results. RCTs (including the EAGLES trial) and meta-analyses of varenicline and bupropion in smokers with various psychiatric disorders identified no neuropsychiatric safety issues and no worsening of the underlying psychiatric condition.<sup>(28, 729-733)</sup> These results need to be viewed with caution, however, in view of the difficulties in disentangling treatment-related events with other potential confounding factors (for example, psychiatric effects of nicotine withdrawal, and increased suicide rates among smokers).<sup>(475)</sup>

#### **5.7.5 Post-marketing surveillance**

In May 2007, the European Medicines Agency informed the FDA that they were investigating a signal of suicidality-related adverse events with varenicline. Later in 2007, a fatal case involving bizarre and aggressive behaviour by a varenicline-treated patient became highly-publicised. The European Medicines Agency subsequently issued a black triangle warning for its use in patients with pre-existing psychiatric conditions.

The FDA undertook evaluations of the post-marketing data regarding cases of suicide and cases of bizarre and aggressive behaviour associated with varenicline, bupropion and NRT.<sup>(33, 734)</sup> Varenicline had the largest proportion of reports (24%) in which it was explicitly stated that the suicidal events were a first-time significant behaviour change from the past, followed by bupropion (15%) and nicotine (none). Varenicline cases had the most reports that described worsening of pre-existing psychiatric disease (17%) compared to nicotine (12%) and bupropion (8%); depression was the most common pre-existing psychiatric condition that worsened for all three drugs. The study concluded there was a possible association between suicidal events and the use of varenicline and bupropion. A new product warning section was added to highlight the risk of serious neuropsychiatric adverse events associated with varenicline, especially in patients with pre-existing psychiatric disorders.

For bupropion, there was a similar recommendation to add language to the already existing product warning about the risk of suicidality in those using bupropion for smoking cessation in 2009. This was in contradiction to the position taken by the European Agency for the Evaluation of Medicines, which had stated there was **'neither a pharmacodynamic nor clinical reason for suspecting bupropion to be causally associated with depression or suicide'**.<sup>(735)</sup>

The black triangle warning issued by the European Medicines Agency for varenicline was removed in May 2016 following publication of safety and efficacy data from the EAGLES (Evaluating Adverse Events in a Global Smoking Cessation Study) trial.<sup>(44)</sup> The EAGLES trial, published April 2016, found no increased incidence of adverse neuropsychiatric effects in patients with or without pre-existing psychiatric disorders (this is further discussed below). Similarly, in September 2016, advisors **to the FDA's** Psychopharmacologic Drugs Advisory Committee and Drug Safety Risk Management Advisory Committee voted to have the boxed warning removed following a review of data from the EAGLES trial. Pfizer announced in December 2016 that removal of the boxed warning for Chantix® has been approved.<sup>(736)</sup>

Evaluating the risk of suicidal ideation and behaviour is complicated by the fact that people who smoke have a two-to-three-fold increased risk of suicide.<sup>(737, 738)</sup> The **UK-based Drug Safety Research Unit's report of their cohort study of prescription event** monitoring found no evidence of an excess of suicidal thoughts or behaviours with varenicline; both of the reported suicide attempts (out of 2,682 patients) occurred in the context of precipitating factors for the event and with a previous history of psychiatric illness.<sup>(739)</sup> A similar study conducted in New Zealand by the Intensive Medicines Monitoring Programme identified one suicide in a cohort of 3,415 recipients of dispensed varenicline prescriptions.<sup>(740)</sup>

### 5.7.6 Observational studies

**A recent systematic review (June 17, 2016) was carried out by the FDA's Division of Epidemiology** to ascertain the neuropsychiatric risk of NRT, varenicline and bupropion based on all available observational studies.<sup>(33)</sup> Studies were selected for review if they reported the relative risk of neuropsychiatric events, used an adequate design to differentiate temporal relationship between drug exposure and outcomes, and attempted to account for baseline group differences because of the observational design. A literature review identified a total of six observational studies for in-depth review.<sup>(667, 688, 689, 741-743)</sup> All reviewed studies were retrospective, population-based studies. See Table 5.3 for a summary of the studies.

Of the six studies reviewed, five included assessment of the risk of neuropsychiatric medical encounters associated with smoking cessation products<sup>(667, 689, 741-743)</sup> and

three evaluated the association between smoking cessation products and the risk of suicide or non-fatal self-harm.<sup>(667, 688, 741)</sup>

The findings of the six reviewed epidemiological studies showed inconsistent results. Four of the studies did not observe a statistically significant difference in the risk of neuropsychiatric adverse events between varenicline versus NRT, varenicline versus bupropion, or bupropion versus NRT.<sup>(688, 689, 742, 743)</sup> The point estimates did not suggest a consistent trend of association.

One study found a significant reduction in neuropsychiatric risk among varenicline users (34% reduction in risk of outpatient depression visit and 44% reduction in the risk of outpatient visit for suicide or non-fatal self-harm) and a 25% reduction in risk of depression visit in bupropion users, comparing to NRT users.<sup>(667)</sup> Yet, another study observed that while varenicline use was not associated with significant risk of suicide-related behaviours, the risk of neuropsychiatric in- or out-patient visits significantly increased by 18% during varenicline-exposed time compared to unexposed time in varenicline users.<sup>(741)</sup>

Each of the reviewed studies had limited study designs. The most important limitations were:

- 1) use of outcome measures with suboptimal sensitivity and specificity,
- 2) residual confounding,
- 3) use of bupropion (another smoking cessation drug with neuropsychiatric risk) as the reference group against which the neuropsychiatric risk of varenicline was examined,
- 4) inability to assess the influence of pre-existing psychiatric illness on the association between smoking cessation treatments and neuropsychiatric outcomes.

All studies relied on diagnostic codes to capture neuropsychiatric adverse outcomes, which likely underestimated the absolute risk of events. It is difficult to estimate how many outcome events were missed in each study or to know whether or not the proportion of outcome under-ascertainment varied among study drugs, which resulted in decreased precision of estimates and unpredictable direction of bias.

**Table 5.3 Observational studies evaluating neuropsychiatric safety of smoking cessation agents**

<b><u>Study</u></b>	<b><u>Setting</u></b>	<b><u>Exposure</u></b>	<b><u>Reference</u></b>	<b><u>Stratified by Psych History</u></b>	<b><u>Main Outcome</u></b>	<b><u>Findings</u></b>
<b>Molero et al. 2015</b>	Sweden (Nationwide linked healthcare data)	Varenicline during exposed period	Unexposed period	Yes	New psychiatric diagnoses or suicidal behaviour	No increased risk of suicidality during varenicline-exposed time  Increased risk of neuropsychiatric outpatient visits during varenicline-exposed time
<b>Kotz et al. 2015</b>	England (Database of NHS records from GP practices)	Varenicline, bupropion, or NRT	NRT	No	Six-month GP visits for depression or self-harm	Significant reduction in neuropsychiatric risk among varenicline users vs NRT (34% reduction in outpatient depression visit and 44% reduction in outpatient visit for suicide or non-fatal self-harm)  Significant reduction in risk of depression visit in bupropion users compared to NRT
<b>Meyers et al.</b>	USA	Varenicline or NRT	NRT	Yes	30-day neuropsychiatric hospitalisations	No statistically significant difference in the risk of neuropsychiatric adverse events
<b>Cunningham et al. 2016</b>	USA	Varenicline or NRT	NRT	Yes	30-day neuropsychiatric hospitalisations	No statistically significant difference in the risk of neuropsychiatric adverse events
<b>Pasternak et al. 2013</b>	Denmark (Nationwide linked	Varenicline or bupropion	Bupropion	Yes	30-day neuropsychiatric emergency department visits or	No statistically significant difference in the risk of neuropsychiatric adverse events

	healthcare data)				hospitalisations	
<b>Thomas et al. 2013</b>	UK	Varenicline, bupropion, or NRT	NRT	No	90-day suicide, nonfatal self-harm, depression, all-cause mortality	No statistically significant difference in the risk of neuropsychiatric adverse events

Key: NRT – nicotine replacement therapy; NHS – National Health Service (UK); GP – general practitioners

Another major concern of the existing observational data is residual confounding and channelling bias, especially among the three studies that included data received after the publicity of the neuropsychiatric safety concern associated with varenicline and bupropion.<sup>(667, 688, 741)</sup> Adverse publicity may have resulted in patients with a history of neuropsychiatric illness being preferentially prescribed NRT, and healthier patients or patients at lower risk of neuropsychiatric events being preferentially prescribed the other two drugs (that is to say, channelling bias).

### **5.7.7 EAGLES 2016 trial**

EAGLES 2016, a double-blind triple-dummy randomised controlled trial (RCT), is the largest trial to date to have been conducted comparing varenicline, bupropion, NRT and placebo. Individuals were stratified by the presence (n=4,074) or absence (n=3,984) of a history of psychiatric disorders.<sup>(34)</sup> The primary safety endpoint was a composite measure of 16 neuropsychiatric adverse events. Rates of neuropsychiatric adverse events were similar across all four treatment groups, with more adverse events in the psychiatric cohort.

Event rates in the psychiatric cohort during treatment and up to 30 days after were varenicline 6.5%, bupropion 6.7%, NRT 5.2% and placebo 4.9%. The corresponding rates in the non-psychiatric cohort were 1.3%, 2.2%, 2.5% and 2.4%, respectively. The risk difference between groups was significantly lower for the varenicline group compared with placebo in the non-psychiatric cohort (RD -1.28, 95% CI -2.40 to -0.15); all other differences in the remaining comparisons (varenicline, bupropion, NRT, all versus placebo) in both cohorts were statistically non-significant.

The authors interpreted this as indicating that none of the first-line smoking cessation treatments significantly increases the risk of neuropsychiatric adverse events when compared with placebo in smokers with or without psychiatric disorders. This large, multinational trial provides further evidence that varenicline and bupropion can be used safely by psychiatrically stable smokers.

However, the EAGLES trial was not without its limitations. The trial only included smokers with psychiatric disorders who were stable and treated, or who had previous psychiatric conditions that were in remission. It may not be possible to generalise this to all patients accessing secondary mental health services, particularly those who are untreated or symptomatically unstable. In addition, they restricted the scope of the psychiatric cohort to smokers in four major disease categories (mood, anxiety, psychotic, and borderline personality disorders) and excluded participants with other current substance use disorders or who were at risk of suicide or self-harm. Finally, despite the fact that this was the largest trial of its kind, some sub-cohorts in the psychiatric cohort were smaller than others, and

subsequently were not sufficiently powered to capture rare adverse events (such as completed suicide).

Nevertheless, EAGLES provided additional evidence that varenicline and bupropion can be used safely by psychiatrically stable smokers, reflected in changes in safety warnings issued by the FDA and European Medicines Agency. In addition, it provided valuable information on efficacy in this cohort. The first-line medications (varenicline, bupropion, and NRT) were more effective compared to placebo, with varenicline the most effective single agent.

### **5.7.8 Additional safety considerations with bupropion**

In addition to safety concerns regarding neuropsychiatric adverse events discussed previously, additional care must be taken when prescribing bupropion to specific patient groups. For these patients, NRT or varenicline should be considered.

#### **Bipolar affective disorder**

Bupropion is currently contraindicated in patients with bipolar affective disorder as it may precipitate manic symptoms during the depressed phase of the illness. This potential for mood destabilisation, however, has been observed only in a small proportion of individuals who were taking the medication as an antidepressant,<sup>(685, 686)</sup> and there is no strong evidence to suggest that bupropion induces mania when used as a smoking cessation agent in stable bipolar affective disorder. Nevertheless, bipolar patients who are taking bupropion as a smoking cessation aid should be closely monitored for signs of accelerated mood cycling, and this medication should only be used in conjunction with a mood stabilising agent. Prescribers must also be aware of the potential for drug interactions with other mood stabilisers (for example, carbamazepine, which induces metabolism of bupropion and decreases plasma levels substantially).<sup>(744)</sup>

#### **Schizophrenia**

There is a theoretical concern about the safety of using bupropion in patients with schizophrenia, as bupropion may precipitate or exacerbate psychosis.<sup>(745)</sup> This is thought to be due, in part, to its dopaminergic action.<sup>(672)</sup> In addition, bupropion and its metabolite inhibit the cytochrome P450 CYP2D6 isoenzyme.<sup>(746)</sup> Therefore the use of bupropion alongside many of the drugs used in the treatment of schizophrenia that are metabolised by this isoenzyme (including antipsychotic medications such as risperidone and haloperidol) may cause significant drug interactions.<sup>(31)</sup>

## Conditions that lower seizure threshold

Due to the risk of seizures, bupropion is contraindicated in certain conditions that lower the seizure threshold. Many patients with such conditions access secondary mental health services, including those with eating disorders (such as anorexia and bulimia nervosa),<sup>(747)</sup> withdrawal from benzodiazepines and alcohol<sup>(748)</sup> and certain antipsychotics.<sup>(687)</sup>

## Concurrent psychotropic medications

Concomitant use of monoamine oxidase inhibitors (MAOIs) and bupropion is contraindicated.<sup>(35)</sup> MAOIs, used in the treatment of depression (including atypical depression), may result in hypertensive crises.<sup>(749)</sup> Bupropion inhibits the reuptake of dopamine and norepinephrine and can increase the risk of hypertensive reactions when used together with drugs that also inhibit the reuptake of dopamine or norepinephrine, including MAOIs. The potential for drug interactions with mood stabilisers such as carbamazepine<sup>(744)</sup> and antipsychotics metabolised by cytochrome P450 CYP2D6 isoenzyme<sup>(750)</sup> **must also be taken into consideration.**

## Recommendations

Key recommendations for the administration of bupropion in psychiatric populations include the following:<sup>(751)</sup>

- cautious treatment initiation
- close monitoring for mood and behaviour changes during therapy
- patient and provider education
- regular follow-up
- regular plasma monitoring of therapeutic drugs.

## 5.8 Safety in adolescents

### 5.8.1 Nicotine replacement therapy

There is little reason to believe that nicotine replacement therapy (NRT) poses a significantly greater risk to adolescent smokers compared to adult smokers. NRT is licensed in individuals over the age of 12 under the recommendation of a healthcare professional.<sup>(13)</sup>

Several clinical trials of NRT in adolescents have been published.<sup>(752-755)</sup> In general, these studies tend to report low quit rates, with no significant difference between active and placebo treatments, and low adherence to therapy. However, the studies note no serious adverse events associated with NRT use in this group.



### 5.8.2 Bupropion

Bupropion has been widely used for psychiatric disorders in children and adolescents with few significant adverse events. Trials of smoking cessation with bupropion in adolescents with and without psychiatric disorders have proven safe, however efficacy is generally lower than the adult population.<sup>(756, 757)</sup>

Zyban<sup>®</sup> is not currently recommended in Ireland for those under 18 years.<sup>(35)</sup>

### 5.8.3 Varenicline

The safety of varenicline has not been adequately evaluated in adolescents.<sup>(758)</sup> Champix<sup>®</sup> is not licensed for use in the adolescent population in Ireland.<sup>(655)</sup>

## 5.9 Discussion

Pharmacological interventions for smoking cessation are generally safe and well-tolerated. In the absence of contraindications, these agents are undoubtedly safer than the continuation of smoking.

Unfortunately, there are limited options available for certain patient groups, including pregnant women and mental health populations, due to contraindications and relative contraindications to the use of selected pharmacological interventions. The safety of e-cigarettes is an evolving area of research. While believed to be safer than smoking, evidence on long-term safety of e-cigarettes has yet to be established. No substantive evidence of adverse events was identified associated with behavioural interventions for smoking cessation.

### 5.10 Key points

#### Nicotine replacement therapy (NRT)

- Most adverse events associated with NRT are mild and temporary in nature.
- Commonly reported side effects include mild skin sensitivity (patch), hiccoughs and gastrointestinal disturbance (gum), local irritation of mouth, nose and throat (inhaler, spray and sublingual tablets).
- Chest pain and heart palpitations are potentially the only clinically significant serious adverse events to emerge from the trials.
- NRT does not appear to be associated with an increase in serious cardiovascular adverse events, in those with and without pre-existing cardiac disease.

#### E-cigarettes

- Safety data on e-cigarettes is limited to two small short-term clinical trials. Mild, temporary adverse drug reactions were found, such as throat and respiratory

irritation and dry cough.

- Toxicological studies have demonstrated that while toxic chemicals may be present in e-cigarette vapour, they are observed at lower concentrations than in cigarette smoke. Data on long-term toxicity from e-cigarette use is not yet available.
- While believed to be safer than smoking, direct confirmation from clinical studies that long-term e-cigarette use leads to reductions in smoking-related diseases is not available. Therefore, the clinical effect of long-term e-cigarette use is unknown.
- **The risk to bystanders from 'passive vaping' appears to be very low.**

#### Varenicline

- Nausea is the most commonly reported adverse event associated with varenicline use. Other common adverse events include insomnia, abnormal dreams and headache.
- There is conflicting evidence regarding cardiac adverse events associated with varenicline. A systematic review and meta-analysis from 2016 did not find evidence of an association, in people with or without cardiovascular illness.

#### Bupropion

- The most common adverse events associated with the use of bupropion are insomnia, dry mouth and nausea.
- Allergic reactions requiring medical treatment are rare.
- Bupropion increases the risk for seizures; a seizure rate of one in 1000 is given in the product safety data. Bupropion is contraindicated in patients with an increased risk of seizures.
- Bupropion is contraindicated in patients with a history of bipolar disorder as it may precipitate a manic episode.

#### Pregnancy

- Nicotine easily crosses the placenta. The long-term fetal and neonatal effects of NRT in humans are unclear; however, it is safer than continued smoking.
- Major congenital malformations have not been observed in randomised controlled trials (RCT) and observational studies associated with NRT use. NRT is recommended during pregnancy, particularly when behavioural therapy fails.
- The use of bupropion and varenicline is not recommended during pregnancy or breastfeeding in Ireland.

#### Mental health populations

- Observational and post-marketing surveillance data have shown inconsistent findings relating to neuropsychiatric adverse events for bupropion and varenicline.
- The EAGLES 2016 (Evaluating Adverse Events in a Global Smoking Cessation Study) trial, however, did not show a significant increase in neuropsychiatric adverse events attributable to varenicline or bupropion relative to nicotine patch or placebo in patients with or without pre-existing psychiatric disorders.

## 6 Economic analysis

This chapter reviews previously published cost-effectiveness analyses of smoking cessation interventions. It also outlines the methods used in the economic evaluation carried out as part of this HTA, including the results of a cost-effectiveness and budget impact analysis within the Irish health and social care setting.

### 6.1 Review of cost-effectiveness studies

A review of previous cost-effectiveness studies was carried out in order to summarise the cost-effectiveness estimates, and to examine the approaches taken to modelling the expected costs and benefits of smoking cessation interventions.

#### 6.1.1 Details of the search

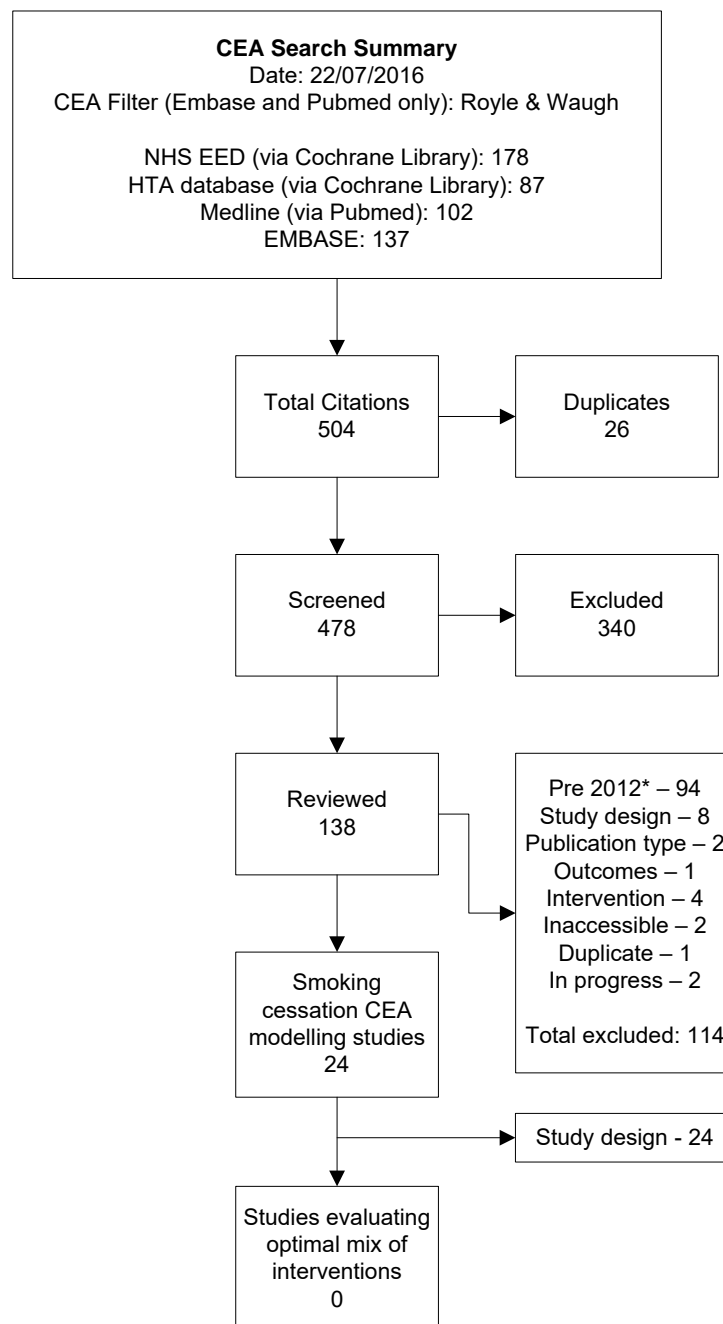
A search was conducted in Medline, Embase, the HTA database (via the Cochrane Library) and the NHS Economic Evaluation Database (NHS EED, also via the Cochrane Library) for cost-effectiveness modelling studies that estimated the long-term costs and benefits of smoking cessation therapies. The inclusion criteria used for the review are shown in Table 6.1.

**Table 6.1 Inclusion criteria for review of cost-effectiveness studies**

<b>Population</b>	Unselected adult smokers
<b>Intervention</b>	Interventions designed to optimise the mix of smoking cessation treatments provided by quit services at a population level that include some or all of the following:  Pharmacotherapy interventions involving: <ul style="list-style-type: none"> <li>• nicotine replacement therapy (NRT)</li> <li>• varenicline</li> <li>• bupropion</li> <li>• e-cigarettes</li> <li>• cytisine</li> </ul> Behavioural interventions involving: <ul style="list-style-type: none"> <li>• counselling</li> <li>• brief advice</li> <li>• telephone, text or Internet support</li> </ul>
<b>Comparator</b>	Current standard of care
<b>Outcome</b>	Incremental cost per additional quality-adjusted life year (QALY) or successful quitter
<b>Study Design</b>	Cost-effectiveness modelling study

Details of the search and the number of studies identified are shown in Figure 6.1.

**Figure 6.1 Flowchart of studies identified in the systematic review of cost-effectiveness analyses (CEA)**



\* Summary of relevant CEA studies to 2011 taken from systematic reviews by Bolin 2012<sup>(759)</sup> and Ruger 2012<sup>(760)</sup>

The search identified two systematic reviews of cost-effectiveness analyses published in 2012.<sup>(759, 760)</sup> The results of these reviews were combined with an updated search to July 2016, which identified 24 additional studies of potential relevance (Figure 6.1).<sup>(761-773)</sup> However, no prior studies that examined optimising the mix of interventions provided at a population level were identified.

### 6.1.2 Summary of cost-effectiveness results

This HTA aims to identify the optimal mix of interventions that can be provided by the health service to reduce the overall prevalence of smoking in the population. The search found that no cost-effectiveness modelling studies have been published to date that examine this issue. Rather than comparing alternative mixtures of interventions with the current standard of care, most of the studies examined the cost-effectiveness of one type of intervention (pharmacotherapy, counselling, Internet support, and so on) compared with placebo or with another type of intervention. The results of these studies are of limited relevance as they assume that all smokers in the modelled cohort will use their allocated intervention. This does not reflect that smokers can choose to use many different types of interventions in their quit attempt, and that the majority of smokers who want to quit will try to do so unassisted.<sup>(774)</sup>

A narrative summary of the most important findings of the modelling studies that compare individual interventions to each other is provided in this section, to highlight some of the major methodological issues to be considered when estimating the cost-effectiveness of smoking cessation interventions. As they do not address the research question under investigation in this assessment, the relevance and applicability of all of these studies is rated as low.

**A 2016 study of smoking cessation in Japan compared the current 'market mix' of interventions in that country (73% unassisted, 21% NRT, 5% varenicline, 2% behavioural therapy) to comparators in which all members of the cohort started their first quit attempt using a given treatment.<sup>(766)</sup>** In this model, smokers were allowed to have multiple quit attempts and the choice of interventions was informed by survey data. The results indicated that varenicline dominated the existing standard of care, being more effective and less costly on average. At a willingness-to-pay threshold of zero, the probability that varenicline was more cost-effective than the existing standard of care was 38%. The degree of uncertainty in the incremental cost-effectiveness ratios (ICERs) was high, however, with ICER estimates obtained from Monte Carlo simulation being scattered across all four quadrants of the cost-effectiveness plane.<sup>(766)</sup>

Another study in the Netherlands estimated the overall cost-effectiveness of the health system reimbursing any smoking cessation intervention compared with not funding these types of interventions.<sup>(775)</sup> This study found that reimbursement of these interventions was **cost-effective with an ICER of €3,939 per** quality-adjusted life year (QALY). This was due to higher uptake rates of smoking cessation treatments and a greater number of quit attempts as a result of the free provision of these interventions.

Other relevant research in this area was the development of the NICE return-on-investment tool, which is designed to allow commissioning groups and local **healthcare providers in the UK's National Health Service (NHS) to estimate the costs and benefits of changing the package of services offered.**<sup>(776)</sup> The output of this project was an Excel-based programme that decision-makers can customise via a graphical user interface to estimate the effect of changing the overall package of interventions provided. While not a tool for cost-effectiveness analysis, it does estimate the difference in costs and QALYs for a given set of interventions over a specified time frame. Selection of the proportion of smokers receiving each type of intervention is at the discretion of the person using the programme, so it is unclear on what basis plausible estimates of the achievable increases in the uptake of various interventions are arrived at.

A previous modelling study on the combined effect of all smoking cessation measures (including taxation and increased regulation) on smoking prevalence and mortality in Ireland estimated that changes in cessation treatment policy was associated with a 39% increase in cessation rates.<sup>(777)</sup> These changes mainly involved a greater level of reimbursement of pharmacotherapy interventions and behavioural treatments, as well as the establishment of a national QUITline service.

Although almost all of the existing literature deals with the cost-effectiveness of individual interventions as opposed to the overall mix of therapies provided at a population level. The results of these analyses are still useful insofar as they provide information on the relative cost-effectiveness of different treatments when compared directly. Table 6.2 summarises the results of previous economic studies, modelling a cohort of smokers in a real life setting, that reported life years gained (LYG) or QALY outcomes for a range of pharmacological and behavioural interventions. All results are converted to 2016 Euro. The relevance and credibility of the results reported in these studies as they relate to the decision question being examined in this HTA was assessed using the ISPOR checklist.<sup>(778)</sup> All were rated as being of low relevance as none of the studies included all of the interventions of interest to this HTA, and no previous study used cost data that could reasonably be considered applicable to Ireland.

**Table 6.2 Summary of previous cost-effectiveness studies**

Study	Comparison	Perspective (Country)	Time horizon (Discount rate)	Results
Fiscella 1996 <sup>(779)*</sup>	Physician counselling plus NRT patch versus physician counselling alone	Payer (USA)	Lifetime (3%)	Cost per QALY ranged from <b>€5,942</b> to <b>€14,812</b> in men, and from <b>€6,707</b> to <b>€9,452</b> in women
Wasley 1997 <sup>(780)*</sup>	NRT plus brief physician advice versus brief advice alone	Payer (USA)	Lifetime (5%)	Cost per LYG ranged from <b>€2,377</b> to <b>€3,902</b> for men and <b>€4,023</b> to <b>€5,810</b> for women
Song 2002 <sup>(781)*</sup>	Counselling alone, counselling plus NRT or bupropion, counselling plus NRT and bupropion	Payer (UK)	Lifetime (0%)	Cost per LYG vs counselling alone ranged from <b>€1,701</b> to <b>€4,079</b> for NRT, <b>€1,086</b> to <b>€2,538</b> for bupropion and from <b>€1,513</b> to <b>€3,348</b> for NRT plus bupropion
Antonanzas 2003 <sup>(782)*</sup>	Bupropion or NRT versus nothing	Payer (Spain)	20 years (NA)	Cost per LYG of <b>€2,165</b> for bupropion and <b>€5,524</b> for NRT
Gilbert 2004 <sup>(783)*</sup>	Physician counselling plus NRT or bupropion versus physician counselling	Payer (Seychelles)	Lifetime (3%)	Cost per LYG ranged from <b>€1,489</b> to <b>€5,168</b>
Feenstra 2005 <sup>(784)*</sup>	Minimal GP counselling with or without NRT versus intensive counselling with NRT or bupropion	Societal (Netherlands)	Up to 75 years (4%)	Cost per QALY ranged from <b>€1,206</b> to <b>€5,371</b>
Bolin 2006 <sup>(785)*</sup>	Bupropion versus NRT	Societal (Sweden)	20 years (3%)	Cost per QALY for bupropion of <b>€740</b> for men, and <b>€549</b> for women, versus NRT
Cornuz 2006 <sup>(786)*</sup>	Brief physician advice plus NRT or bupropion versus brief advice alone	Payer (USA & Europe)	Lifetime (3%)	Cost per LYG ranged from <b>€834</b> to <b>€3,666</b> for men and from <b>€3,078</b> to <b>€9,165</b> in women
Bolin 2008 <sup>(787)**</sup>	Varenicline versus bupropion	Societal (Sweden)	Lifetime (3%)	Varenicline dominated bupropion
Hoogendoorn 2008 <sup>(788)*</sup>	Varenicline versus unassisted quitting or NRT	Payer (Netherlands)	Lifetime (4% on costs, 1.5% on effects)	Cost per QALY <b>€281</b> versus unaided, <b>€907</b> vs NRT



Study	Comparison	Perspective (Country)	Time horizon (Discount rate)	Results
Howard 2008 <sup>(789)*</sup>	Varenicline versus bupropion, NRT and unaided quitting	Payer (USA)	Lifetime (3%)	Varenicline dominated all comparators
Thavorn 2008 <sup>(790)*</sup>	Pharmacy-based intervention versus routine care	Payer (Thailand)	Lifetime (3%)	Intervention dominated usual care (cost saving and generated LYG)
Annemans 2009 <sup>(791)*</sup>	Varenicline versus brief counselling, unassisted quitting or bupropion	Payer (Belgium)	Lifetime (3% on costs, 1.5% on effects)	<b>Cost per QALY of €336 versus brief counselling, €2,315 versus unassisted quitting and cost saving versus bupropion</b>
Bae 2009 <sup>(792)**</sup>	Varenicline versus bupropion and NRT	Payer (South Korea)	Lifetime (5%)	ICER of <b>€4,761</b> compared with bupropion and NRT
Bolin 2009 <sup>(793)*</sup>	Varenicline versus NRT in Belgium, UK, Sweden and France	Payer (Europe)	Lifetime (3.5%)	Varenicline was cost saving in all countries except France, <b>where the cost per QALY was €3,917</b>
Bolin 2009 <sup>(794)*</sup>	Extended varenicline versus placebo	Societal (Sweden)	50 years (3%)	Cost per QALY <b>€7,345</b> for men and <b>€7,389</b> for women
Igarashi 2009 <sup>(795)*</sup>	Physician counselling versus physician counselling plus varenicline	Payer (Japan)	Lifetime (3%)	Addition of varenicline dominated in men, and had a cost per QALY of <b>€2,980</b> in women
Knight 2010 <sup>(796)*</sup>	Extended varenicline versus varenicline, bupropion, NRT or unassisted quitting	Payer (USA)	Lifetime (3%)	Extended varenicline dominated all comparators except for normal duration varenicline, where the <b>cost per QALY was €971</b>
Linden 2010 <sup>(797)**</sup>	Varenicline versus bupropion and unaided quitting	Payer (Finland)	20 years (5%)	<b>ICER of €9,466/QALY and €8,389/QALY</b> compared with bupropion and unaided cessation, respectively
Athanasakis 2012 <sup>(761)</sup>	Varenicline versus bupropion, NRT and unaided cessation	Payer (Greece)	Lifetime (3%)	Varenicline dominates all comparators
Guerriero 2013 <sup>(765)</sup>	Text message bases smoking cessation support versus usual care	Payer (UK)	Lifetime (3.5%)	Text message support dominated
Leaviss 2014 <sup>(768)</sup>	Cytisine versus varenicline	Payer (UK)	Lifetime (3.5%)	Cytisine dominated varenicline, being more effective and less costly

Study	Comparison	Perspective (Country)	Time horizon (Discount rate)	Results
VonWartburg 2014 <sup>(772)</sup>	Standard and extended-use varenicline versus bupropion, NRT and unassisted quitting	Payer (Canada)	Lifetime (3%)	Both varenicline regimens dominate comparators. ICER for extended varenicline versus standard course was <b>€3,602/QALY</b>
Cantor 2015 <sup>(762)</sup>	Physician and or pharmacist training versus no training	Payer (USA)	Lifetime (3%)	No training dominated either physician only, or pharmacist only, training. Training for both was associated with an ICER of <b>€2,784/QALY</b> compared with no training.

\* Identified in systematic review by Ruger; \*\* Identified in systematic review by Bolin; ICER – incremental cost-effectiveness ratio; LYG – life year gained; NRT – nicotine replacement therapy; QALY – quality-adjusted life year.

The existing literature in this area has consistently found that practically all smoking cessation interventions are associated with very low ICERs, which would make them appear extremely cost-effective using conventional willingness-to-pay thresholds in Ireland and elsewhere. In many cases, varenicline was found to dominate bupropion, NRT and unassisted quitting, by both improving outcomes and reducing the overall costs to the health service. However, there are aspects of these analyses that limit their applicability to the policy question examined in this HTA, which is interested in the overall mix of treatments provided. These issues are described in the next section which examines relevant methodological aspects of the economic evaluation of smoking cessation services.

### **6.1.3 Methodological issues in economic evaluations of smoking cessation**

Previously published studies differ from this HTA in how the comparators included in the economic models were defined. In the majority of these analyses, all smokers in the modelled cohort were assumed to receive the same treatment, and were compared with a cohort that all received either a different treatment or no intervention. While this is useful to directly compare two or more therapies, it does not provide information on the effect of policy decisions that aim to optimise the overall mix of interventions being funded in an effort to reduce the prevalence of smoking nationally. Taking this broader view has a number of implications. The first is that one needs to reliably estimate preferences in relation to cessation options for smokers attempting to quit. This can pose difficulties if national survey data on quit methods are unavailable, or fail to provide enough detail to estimate what proportion of quitters use each type of intervention (alone or in combination) or no support at all. Once the current standard of care has been sufficiently described, it is necessary to define alternative states of affairs based on plausible changes in the proportion of patients receiving each type of intervention. Estimating what can realistically be achieved in this context is challenging. For instance, evidence from Chapter 4 indicates that varenicline is associated with better long-term cessation outcomes than NRT, but 2015 Healthy Ireland survey data shows far fewer Irish smokers making a supported quit attempt use varenicline compared with NRT (<4% versus 24%). It is unclear what effect any prospective policy change designed to increase varenicline use would have on these figures.

Similar uncertainty surrounds the use of e-cigarettes, which are now the second most popular option (after unassisted quitting) in Ireland for those attempting to quit (29%).<sup>(61)</sup> Given the uncertainty in relation to defining what effect a given policy will have on the overall proportion of people availing of each cessation intervention, the comparators in this analysis can more usefully be chosen with the aim of evaluating what changes are likely to efficiently reduce the overall smoking prevalence, and then trying to develop policies that help effect these changes. This

involves taking a more exploratory approach, similar to a scenario analysis, of the effect of altering the current mix of interventions, rather than evaluating the effect of a specific a priori policy decision. While this information is essential for designing policy that will bring about worthwhile changes in smoking cessation preferences among those attempting to quit, specification of particular policy measures that could be employed in the pursuit of a target mix of interventions is beyond the scope of this HTA. Instead, it focuses on the first step of identifying objectives that smoking cessation services could work towards, and considering the desirability or otherwise of expected changes that are likely to occur given current trends in the uptake of smoking cessation interventions.

The way in which the clinical effectiveness of each of the smoking cessation interventions is estimated is obviously of crucial importance in the analysis. The findings of the review of published cost-effectiveness studies indicate that there is a high degree of heterogeneity in the estimates of absolute quit rates among groups using each type of cessation aid. These differences arise primarily due to two issues:

1. the diversity of estimates of the quit rate for unassisted smoking cessation attempts, and
2. the difficulty in estimating the combined effect of pharmacotherapy and behavioural support interventions for those whose quit attempt involves both.

Unassisted quit rates used in recent economic analyses have ranged from 2% to 9%.<sup>(762, 765)</sup> If the absolute quit rates for each of the intervention groups are calculated with reference to the unassisted quit rate (by applying the relative effect for each type of intervention), then any differences are propagated through the model. This potentially has significant implications for the overall results.

Difficulties in estimating the combined effect of pharmacological and behavioural support interventions arise from the fact that the majority of the trials in this area have sought to isolate the relative effect of a single intervention (be it a drug or a form of counselling), rather than the combined effect of specified drug and behavioural support interventions when used together. While this makes sense when attempting to establish the efficacy of a particular treatment, it poses problems when modelling routine clinical practice that usually involves some form of input from a healthcare professional in addition to pharmacotherapy. The inconsistency in the evidence for the effect of behavioural therapies adds further complexity. Even among studies that can be broadly classified under one heading, there can be a high level of heterogeneity in the support provided, and in many cases there is also a lack of a consistent dose-response when comparing interventions that differ in intensity or duration of contact.

One option for estimating the combined effect of pharmacological and behavioural support interventions is to assume that the treatment effects can be considered either multiplicative or additive. This risks the combined effect being overestimated since it assumes that the full benefit of each treatment modality is achieved, when in fact the additional benefit of behavioural support as an adjunct to pharmacotherapy is less than when it is used as the sole intervention. An alternative is to examine the evidence from studies where behavioural therapy was used as an adjunct to pharmacotherapy.<sup>(471)</sup> A meta-analysis of these studies in an unselected adult population found that the addition of any type of behavioural support increased cessation rate by an average of 18% (RR 1.18, 95% CI 1.09 to 1.28, see chapter 4). However, there was no consistent evidence of a dose-response, as the effect estimate did not increase linearly with increasing levels of behavioural support.

Previous economic analyses have also differed in the way the long-term clinical implications of smoking cessation were quantified. Smoking-related diseases typically included in the analyses were restricted to lung cancer, myocardial infarction (MI), stroke, coronary heart disease (CHD), chronic obstructive pulmonary disease (COPD) and asthma, although some studies omitted asthma due to a lack of evidence.<sup>(759, 761)</sup> A recent Japanese study that included stomach and hepatic cancers is also of note.<sup>(766)</sup> Increases in the prevalence of smoking-related illnesses are calculated using the population-attributable fraction for each disease. However, while this is likely to provide the correct population prevalence for each disease, it does not take into account the issue of comorbidity and any implications this might have for either costs or benefits.

Adverse events beyond the incidence of smoking-related illness, such as those associated with the cessation interventions themselves, harm to others through passive smoking, or the risks associated with any increase in the risk of obesity as a result of smoking cessation, were not considered in any of the studies identified in the review. The issue of obesity related to smoking cessation was examined in a recent modelling study to evaluate whether savings in health costs deriving from smoking prevention and its related diseases are greater than the costs associated with increased obesity. This estimated that body mass index (BMI) increased by 0.26kg/m<sup>2</sup> for quitters compared with those who continued to smoke, but that the cost saving from quitting smoking far outweighed the additional costs associated with weight gain.<sup>(798)</sup>

Most of the previously published cost-effectiveness analyses were based on a limited number of economic models that were repopulated with setting-specific clinical and cost data.<sup>(759)</sup> The most widely used of these was the BENESCO model, which was originally developed in 2008 to assess the cost-effectiveness of varenicline.<sup>(789)</sup> This is a Markov model with a cycle length of one year that follows a closed longitudinal

cohort of smokers making a single quit attempt to death or until they reach 100 years. Smokers who successfully quit can relapse, but smokers who fail on the first quit attempt cannot ever make a second quit attempt. The model estimates clinical outcomes and costs for men and women separately, and distinguishes between three age groups (18-34, 35-64 and 65-100). Outcomes for males and females are modelled separately because of gender differences in smoking prevalence, as well as smoking-related mortality and morbidity. Disease states included in the model are lung cancer, COPD, ischemic heart disease (IHD), stroke and asthma exacerbation. No treatment-related adverse events are considered.

Analyses using this model have tended to find that varenicline is the dominant comparator, being associated with greater health gain and reduced costs compared with other interventions. However, as pointed out by Leaviss et al., the assumption that smokers can only quit after receiving treatment during the first cycle is likely to favour interventions with greater efficacy, such as varenicline, since it perpetuates the differences in smoking cessation at one year, rather than allowing this to diminish over time as smokers quit unaided or after multiple quit attempts using cessation interventions of lower efficacy.<sup>(768)</sup>

Among the other challenges that are presented by the economic evaluation of smoking cessation interventions is the issue of dealing adequately with the temporal effects of smoking on individuals and on smoking prevalence in society. There is a great deal of uncertainty about the impact of quitting history on what support smokers choose to use in any given quit attempt, and their chances of successful quitting, even though it is known that most smokers quit after a considerable number of failed attempts.<sup>(129, 799)</sup> In the absence of sufficient data to characterise this complex sequence of events, one option is to assume that each quit attempt is independent, and so has the same probability of success each time. This would appear to be an adequate approach when considering the populations involved in the smoking cessation trials upon which these estimates of effect are based, which included smokers drawn from an unselected adult population that would have had a diverse range of quitting histories prior to enrolment.

Other potential temporal changes that may affect the cost-effectiveness of smoking cessation interventions delivered at the level of the individual include the continuing decrease in the prevalence of smoking as a result of population-level interventions such as mass media campaigns, price increases, plain packaging initiatives and changes in societal attitudes to smoking. Finally, there is the problem of modelling the long-term health consequences of smoking, which may take decades to manifest. The most common approach is to apply the relative risk of developing each of these diseases to people who are current or former smokers. While this provides a means of calculating the overall average burden of disease at a

population level, it does not take into account differences in the duration or intensity of smoking history prior to quitting, or differences in the length of time that people in this Markov state have abstained from smoking, which would affect their risk of developing a smoking-related illness within a particular age group.

#### **6.1.4 Summary of the review of cost-effectiveness studies**

No studies that examined the specific research question of interest in this HTA were identified in a review of previous economic evaluations of smoking cessation. While many have compared different smoking cessation interventions to each other, there is a lack of studies examining how to optimise the mix of smoking cessation interventions currently available compared with the existing standard of care. However, the existing literature does indicate that compared with other types of healthcare interventions, smoking cessation interventions are among the most cost-effective use of resources, with ICERs far below conventional willingness-to-pay thresholds in Ireland and elsewhere. Challenges in relation to modelling the expected costs and consequences of changing the way smoking cessation services are provided in Ireland include:

- adequately defining comparators,
- estimating absolute quit rates for each intervention and for unassisted quitting,
- and taking account of societal level interventions such as increased regulation and taxation on the long-term cost-effectiveness of smoking cessation services provided at the level of the individual.

## **6.2 Economic analysis methods**

An analysis of the cost-effectiveness and budget impact of smoking cessation services in Ireland was carried out using an original decision analysis model developed for this HTA. This section reports the methods used in this analysis and the findings of the research.

### **6.2.1 Type of economic evaluation**

A cost-effectiveness analysis was carried out to estimate the incremental cost per additional smoker achieving long-term cessation (six months or more) for a range of different comparators. These were defined in terms of the proportion of smokers using each type of cessation intervention, including unaided quitting, in their attempt to stop smoking.

A cost-utility analysis was also carried out to estimate the incremental cost per quality-adjusted life year (QALY) gained for each comparator, taking into account the long-term costs and consequences associated with smoking-related illness.

Separate economic evaluations of smoking cessation interventions were not carried out for the two sub-groups identified in this assessment (pregnant women and people attending secondary mental health services). For pregnant women there was evidence of short-term benefits in terms of cessation during pregnancy, but not in terms of longer term cessation. The included studies were not designed to detect changes to obstetric and neonatal outcomes. Due to the lack of data on longer term outcomes, a full economic evaluation was not justified. In relation to people attending secondary mental health services, evidence of effectiveness was only found for a limited number of interventions and thus there was insufficient evidence of long-term outcomes to justify an economic evaluation.

### **6.2.2 Target population and setting**

The primary population of interest was unselected adult smokers aged 18 years or over making a quit attempt in Ireland. The population includes those with and those without a Medical Card. The model examined differences in the rates of the following four smoking-related illnesses in each of the modelled comparators: lung cancer, stroke, ischaemic heart disease (IHD) and chronic obstructive pulmonary disease (COPD).

### **6.2.3 Base case and comparators**

The base case comparator was the current mix of interventions used (current practice) in Ireland, which was characterised by the proportion of current smokers using each type of smoking cessation method in their quit attempt. This was informed by data from the Healthy Ireland survey 2015, details of which are described in Figure 6.16. These data indicate that e-cigarettes are widely used as a cessation aid by Irish smokers seeking to quit, even though, unlike other smoking cessation therapies, e-cigarettes are not currently advocated by smoking cessation services or reimbursed through the Health Service Executive (HSE). Given their widespread use, and based on the availability of randomised controlled trial (RCT) data on their relative effectiveness as a smoking cessation option (Section 4.2.5), they are included in the analysis as part of the mix of interventions comprising current practice and in each of the comparator strategies.

Interventions were initially compared directly to each other through a cost-effectiveness analysis which assumed that 100% of smokers made one quit attempt per year, all using a given intervention, in order to estimate the relative cost-effectiveness of each intervention on its own, compared to each other intervention on its own (for example, 100% of those attempting to quit using varenicline versus 100% using NRT and so on).

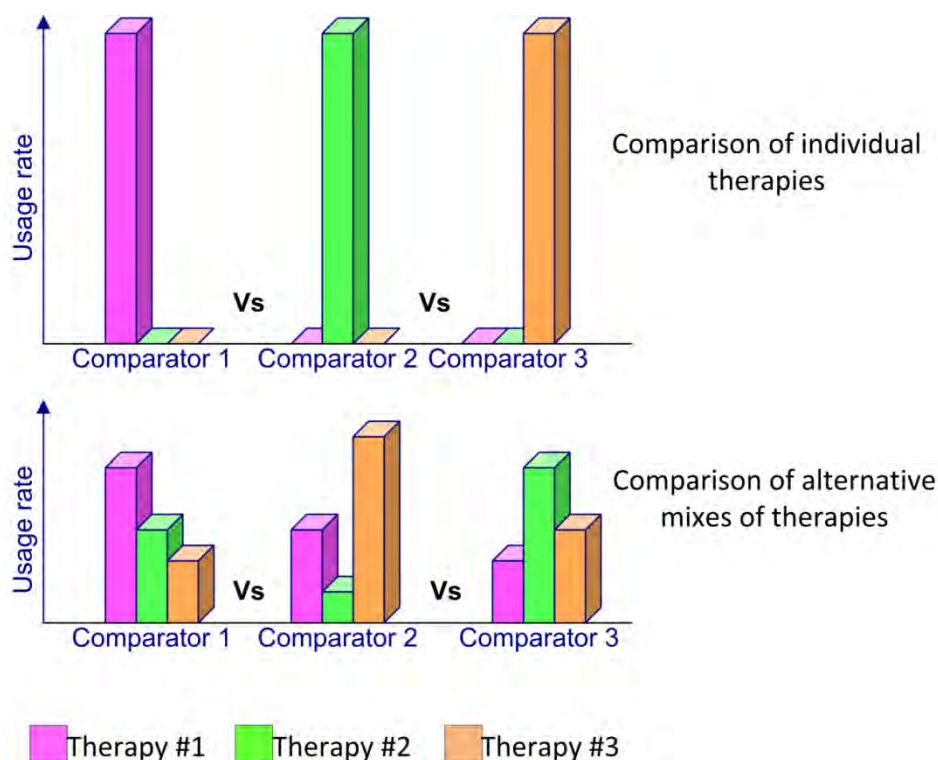
Comparator strategies were then chosen based on plausible changes in the proportion of smokers willing to use each individual type of cessation intervention as



a result of policies to promote evidence-based decision-making by smokers who wish to increase their chances of quitting. In formulating the strategies, consideration was given to the likely influence of patient preferences, economic incentives, and societal trends in smoking cessation. Strategies were also informed by international data on the proportion of quit attempts made using each type of intervention in other countries.

For clarity, the difference between these two types of analysis is illustrated in Figure 6.2.

**Figure 6.2 Illustration of the difference between the comparison of different intervention mixes and the comparison of individual therapies**



#### 6.2.4 Perspective, time horizon and discount rate

The analysis of the incremental cost per person quitting was carried out from a quasi-societal perspective, which took into account all direct costs of smoking cessation interventions, whether they fell on the individual or the publicly funded health and social care services. The analysis of the long-term QALY outcomes associated with smoking cessation (cost-utility analysis) included all costs included in the primary analysis, as well as the direct costs to the HSE for treatment of smoking-related illness. The cost of cigarettes was excluded, so savings to individuals who successfully quit, or any associated decrease in tax revenue accruing to the State, were not factored into the cost-effectiveness analysis.

This analysis does not involve modelling the natural history of smoking at the level of the individual, as this would require detailed knowledge of the relationship between duration and intensity of smoking and the subsequent incidence of smoking-related morbidity and mortality decades later. Rather, the analysis models the effects of smoking at a population-level using data on the percentage of cases of a particular group of diseases that are attributable to smoking (the population attributable fraction [PAF]). Therefore, the important consideration when choosing the appropriate time horizon for the analysis is not the delay between exposure to tobacco smoke and the development of smoking-related illness, but rather the changes over time in the overall prevalence of smoking that could render individual-level smoking cessation services more or less cost-effective over time. The uncertainty involved in estimating any future changes in smoking behaviour at a population-level means that the external validity of using an extended time horizon is questionable. For this reason, the time horizon used in this analysis was 20 years. A discount rate of 5% was applied to both costs and benefits, in line with national HTA guidelines.<sup>(153)</sup>

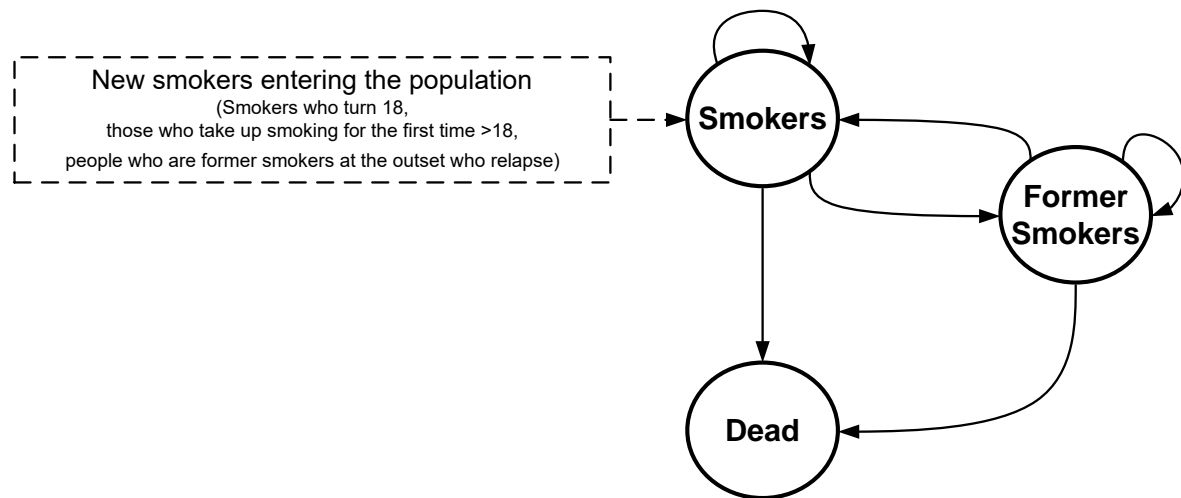
### **6.2.5 Model structure**

An original state transition Markov model was developed to compare the costs and consequences of changing the proportion of smokers using each type of cessation intervention in their quit attempt. The model is an open cross-sectional population model that tracks the population of smokers at the outset of the simulation (2016) and allows new smokers to enter the model over the 20-year time horizon. The basic model structure is shown in Figure 6.3.

### **6.2.6 Sensitivity Analysis**

Monte Carlo simulation was carried out, with each parameter being defined as a distribution based on the plausible range of values, which were then sampled over the course of 10,000 replications to take account of the uncertainty associated with the model outputs. Deterministic univariate sensitivity analysis was carried out to estimate the effect of uncertainty pertaining to individual parameter estimates.

**Figure 6.3 Basic Markov model structure for each comparator**



At the outset, the smoking state is populated with the total number of smokers in Ireland at present (2016). There is nobody in either the former smoker or dead state at the outset. New smokers enter each year, representing those who are smoking when they turn 18, those who take up smoking for the first time aged over 18, and those who were former smokers in 2016 who later relapse. The cycle length is one year and transitions between the states are as follows:

- Smokers can either stay smoking, successfully quit to become former smokers, or die.
- Former smokers can either remain abstinent, relapse to become current smokers, or die.

The mortality rate and prevalence of smoking-related illness are age and sex-dependent, and the age and sex structure of the entire cohort changes over the time horizon of the analysis in line with Irish demographic projections. The mortality differential (difference in life years gained [LYG]) between comparators is based on differences in the absolute numbers of people in the smoker and former smoker states, since the mortality rate for current smokers is greater than that of former-smokers of the same age.

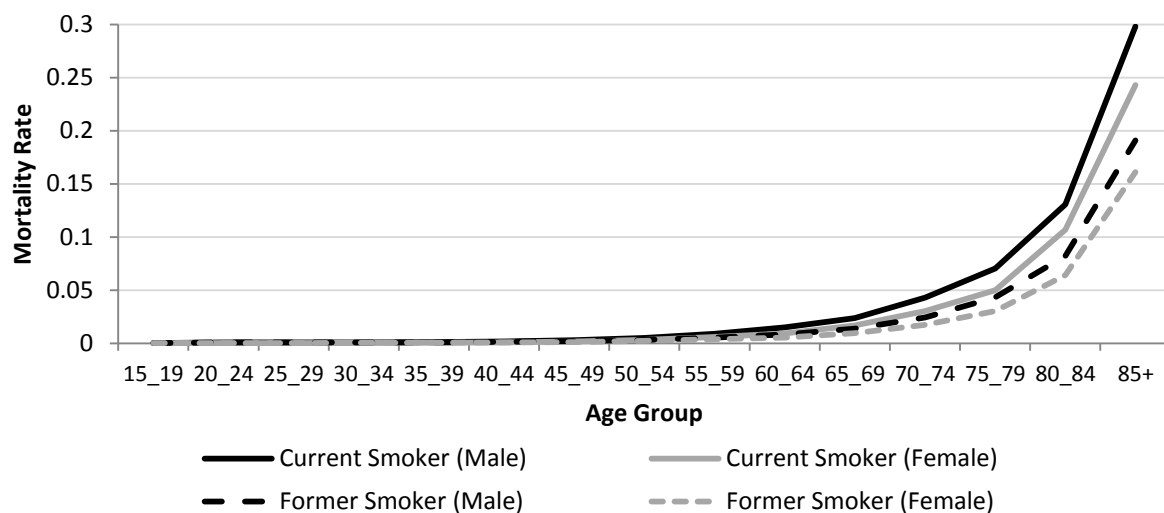
Utility differences stem from the higher mortality rate and increased prevalence of the four smoking-related illnesses included in the analysis (lung cancer, stroke, IHD, COPD) in comparators with greater numbers of current versus former smokers, as these conditions are associated with reduced quality of life. Differences in costs between comparators are affected by any changes in the cost of providing cessation services, combined with differences in treatment costs associated with increased or decreased incidence of smoking-related illness between comparators.

All transition probabilities, utility weights and cost parameters used in the model are described in greater detail in the following sections.

### 6.2.7 Clinical and epidemiological parameter estimates

The overall mortality rate by five-year age group and gender for smokers and former smokers **was calculated using data from the US Surgeon General's report on the relative risk of all-cause mortality by age group.** This was combined with three years of Irish population mortality data from the Central Statistics Office (CSO), and the results of the Healthy Ireland survey 2015 on smoking rates for men and women in each five-year age band.<sup>(61, 102, 800)</sup> Figure 6.4 shows the all-cause mortality rates for current and former smokers, by age group and gender.

**Figure 6.4 All-cause mortality rates by smoking status, age and gender**



Irish data on overall lung cancer prevalence by age and gender were obtained from the National Cancer Registry Ireland (NCRI, ICD code C34) for the years 1994 to 2014 (giving 21 years follow-up prevalence).<sup>(801)</sup> Prevalence rates for current, former and never smokers were calculated using the relative risk of lung cancer in each of these groups from the Health and Social Care Information Centre (HSCIC) report on smoking statistics in England 2015 (as reported in Chapter 3).<sup>(802)</sup> Prevalence rates within the population of smokers, former smokers and never smokers were calculated for all four diseases included in this analysis as shown in Figure 6.5.

**Figure 6.5 Method for calculating disease prevalence rates in current, former and never smokers**

Total disease prevalence ( $P_T$ ) within the overall population is the weighted sum of the prevalence within the three subgroups (current smokers [ $P_{CS}$ ], former smokers [ $P_{FS}$ ] and never smokers [ $P_{NS}$ ], with the weights being the proportion of people in each group (current smokers [% $_{CS}$ ], former smokers [% $_{FS}$ ] or never smokers [% $_{NS}$ ], Equation 1).

$$P_T = P_{NS} \cdot \%_{NS} + P_{FS} \cdot \%_{FS} + P_{CS} \cdot \%_{CS} \quad (1)$$

Disease prevalence within the group of current and former smokers can be expressed in terms of the prevalence among never smokers using the relative risk of the disease in current and former smokers ( $RR_{CS}$  and  $RR_{FS}$ , respectively).

$$P_{FS} = P_{NS} \cdot RR_{FS} \quad (2)$$

$$P_{CS} = P_{NS} \cdot RR_{CS} \quad (3)$$

Substituting these into Equation 1 allows the disease prevalence among never smokers ( $P_{NS}$ ) to be expressed in terms of the total population prevalence ( $P_T$ ), the proportion of people who are current smokers (% $_{CS}$ ), former smokers (% $_{FS}$ ) or never smokers (% $_{NS}$ ), and the relative risk associated with being a current or former smoker ( $RR_{CS}$ ,  $RR_{FS}$ ), all of which are known (Equation 8):

$$P_T = P_{NS} \cdot \%_{NS} + P_{NS} \cdot RR_{FS} \cdot \%_{FS} + P_{NS} \cdot RR_{CS} \cdot \%_{CS} \quad (4)$$

$$P_T = P_{NS} (\%_{NS} + RR_{FS} \cdot \%_{FS} + RR_{CS} \cdot \%_{CS}) \quad (5)$$

$$\frac{P_T}{P_{NS}} = (\%_{NS} + RR_{FS} \cdot \%_{FS} + RR_{CS} \cdot \%_{CS}) \quad (6)$$

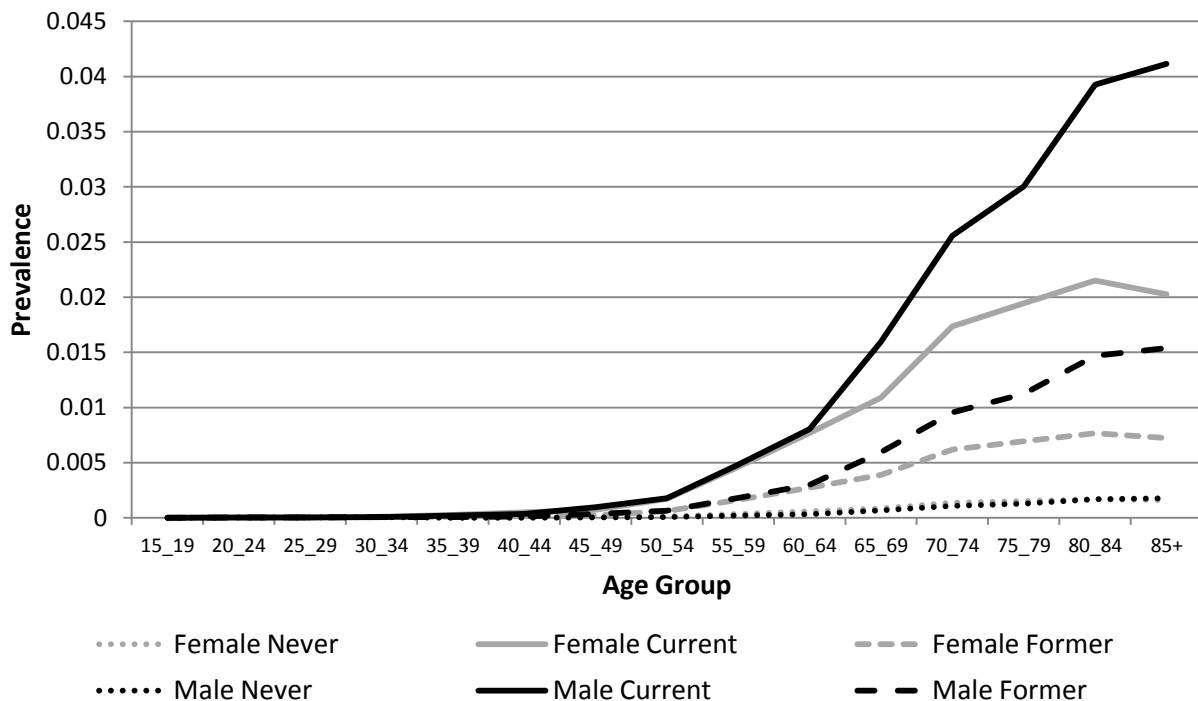
$$\frac{P_{NS}}{P_T} = \frac{1}{(\%_{NS} + RR_{FS} \cdot \%_{FS} + RR_{CS} \cdot \%_{CS})} \quad (7)$$

$$P_{NS} = \frac{P_T}{(\%_{NS} + RR_{FS} \cdot \%_{FS} + RR_{CS} \cdot \%_{CS})} \quad (8)$$

Solving for  $P_{NS}$  then allows us to calculate  $P_{FS}$  (prevalence rate in former smokers) and  $P_{CS}$  (prevalence rate in current smokers) using Equations 2 and 3, above.

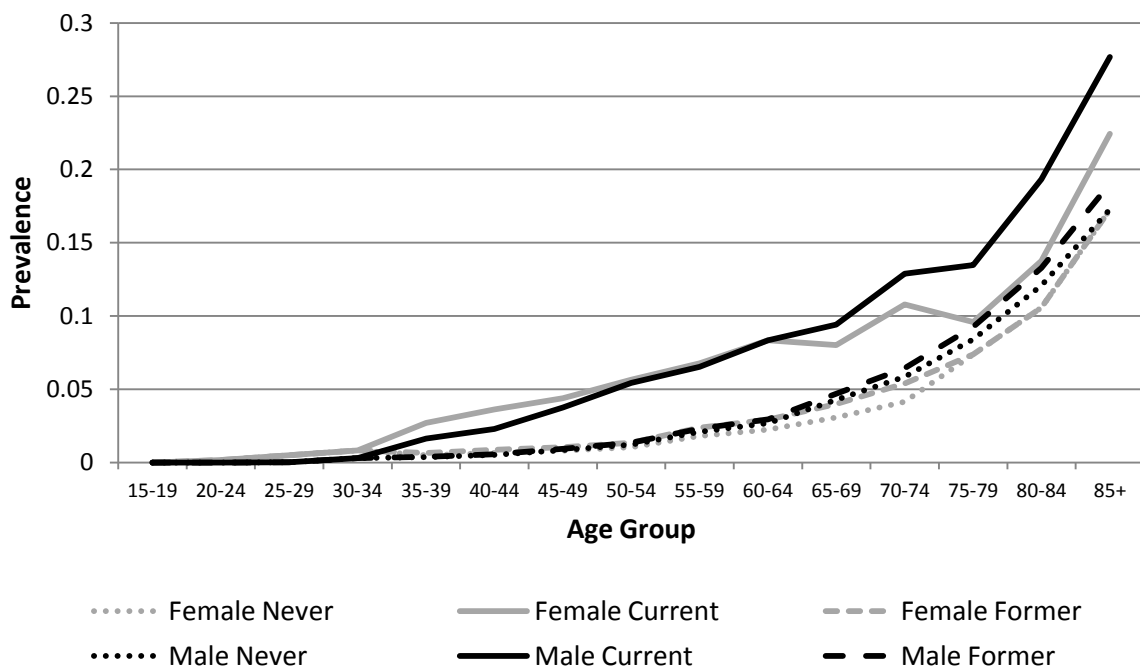
Prevalence rates of lung cancer in never, former and current smokers, by age and gender, are shown in Figure 6.6.

**Figure 6.6 Prevalence of lung cancer (ICD C34) by smoking status, age and gender**

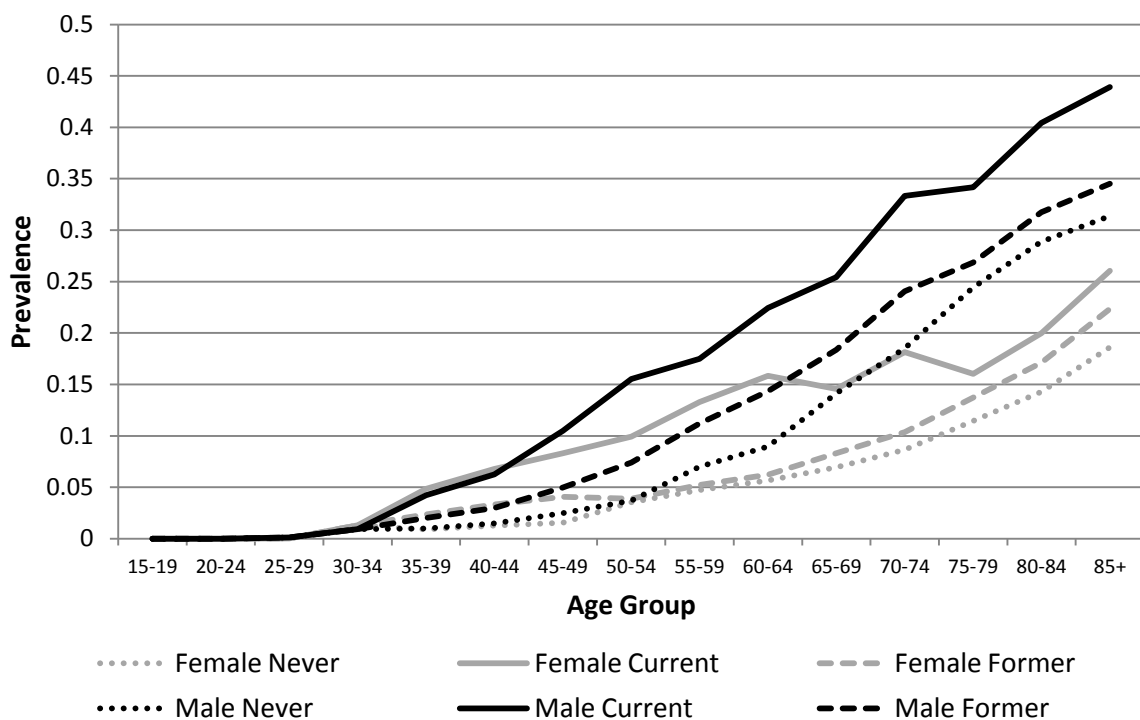


In the absence of validated Irish data on the prevalence of stroke and cerebrovascular disease (ICD codes I60-I69), ischaemic heart disease ([IHD], ICD codes I20-I25) and COPD (ICD codes I41-I44) by age and gender, prevalence estimates were obtained from the international literature. For cerebrovascular disease and IHD, population prevalence estimates were based on US data from 2015.<sup>(50)</sup> COPD population prevalence rates were taken from a 2011 study from the Netherlands.<sup>(803, 804)</sup> Prevalence among smokers and former smokers was calculated as described in Table 6.3 and applied to Irish population data for 2015 obtained from the CSO, using relative risks from the HSCIC report.<sup>(102, 802)</sup> The prevalence estimates for stroke, IHD and COPD used in the model are shown in Figures 6.7, 6.8 and 6.9, respectively. The applicability of international data to Ireland is uncertain, given differences that may exist among populations in the distribution of risk factors for each disease. To capture this uncertainty surrounding the prevalence data, and to examine its potential impact on the results of the analysis, prevalence rates for each disease were varied  $\pm 20\%$  in the model.

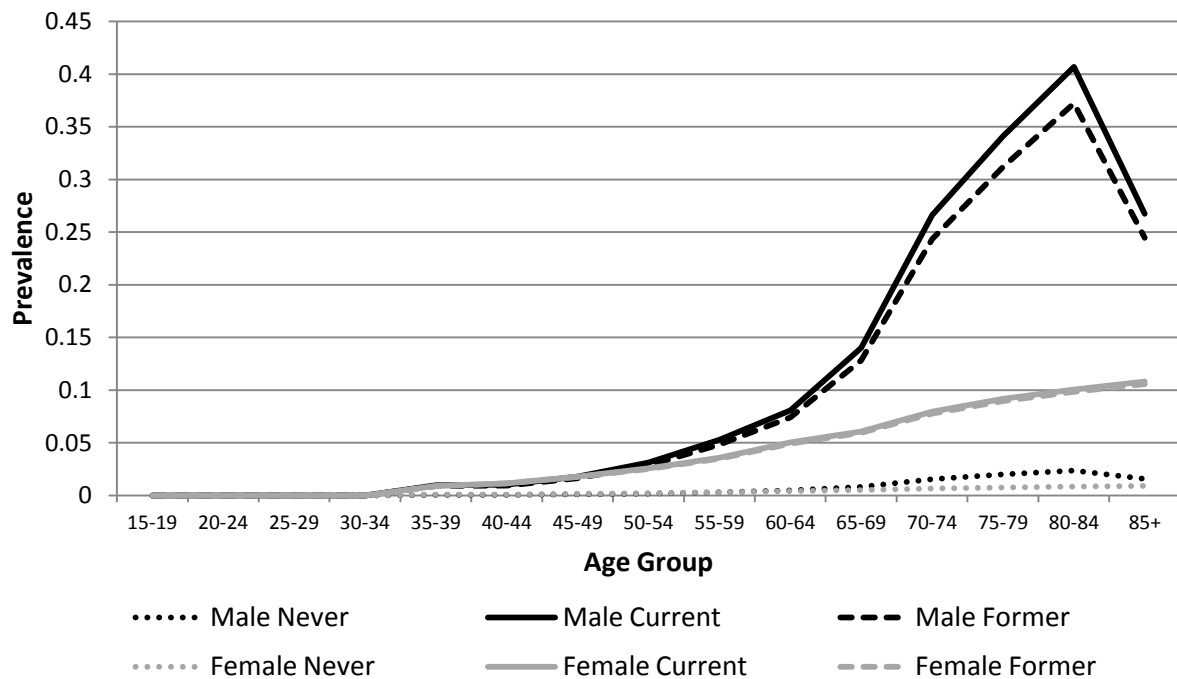
**Figure 6.7 Prevalence rates for cerebrovascular disease (ICD I60-I69) by smoking status, age and gender**



**Figure 6.8 Prevalence rates for ischaemic heart disease (IHD) (ICD I20-I25) by smoking status, age and gender**



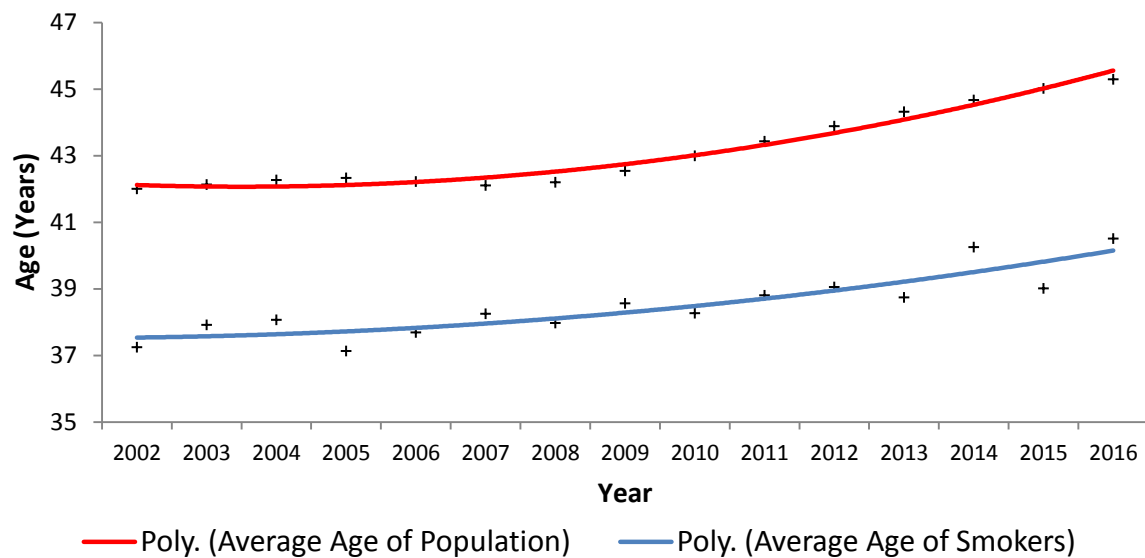
**Figure 6.9 Prevalence rates for chronic obstructive pulmonary disease (COPD) (ICD I41-I44) by smoking status, age and gender**



In order to apply these data to calculate all-cause mortality and disease prevalence rates within the economic model, it is necessary to estimate the age and gender structure of the current population of smokers in Ireland, and how this will change over the 20-year time horizon. In this analysis it was assumed that changing trends in the age structure of smokers follow those of the general population. This would mean that if, say, the percentage of the population that was aged between 18 to 25 years was growing over time, then 18 to 25 years olds would tend to account for an increasing percentage of all smokers, as the absolute numbers within this age group would rise. Comparison of longitudinal data on the average age of the Irish smoking population from the Smoking Tracker Survey run by the Office of Tobacco Control (OTC) in the HSE and CSO data on the overall population structure over the same time period would appear to have comparable trends over time (Figure 6.10).<sup>(805)</sup>

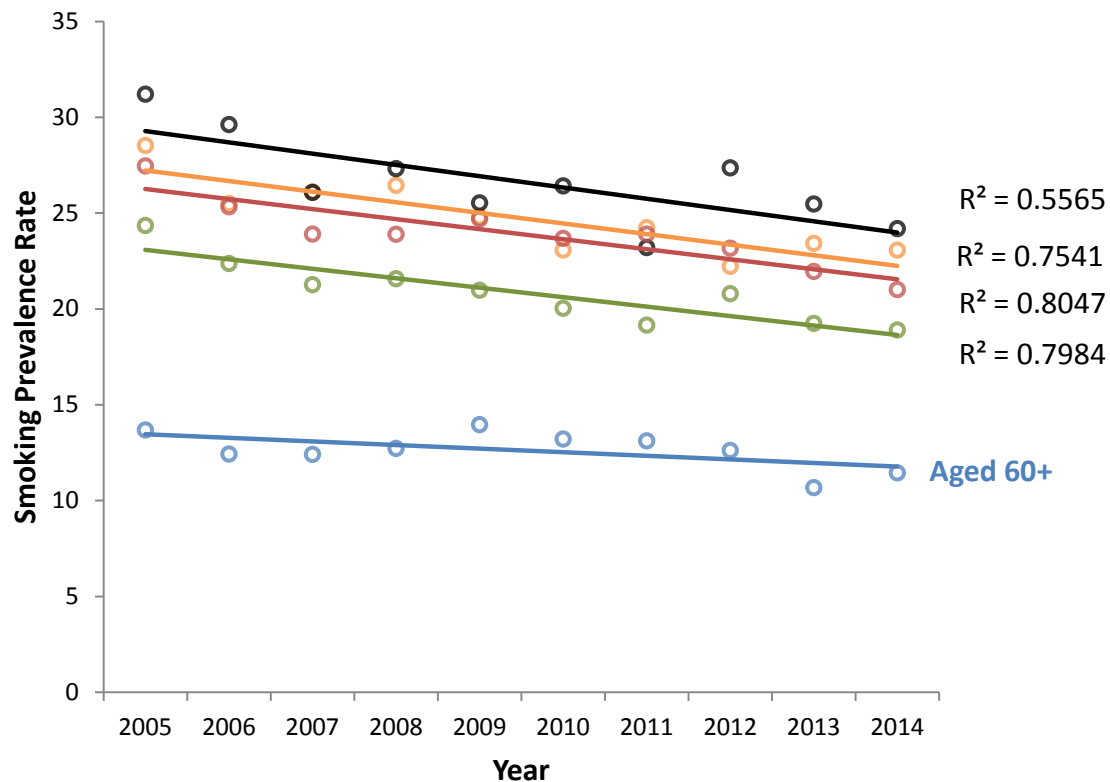


**Figure 6.10 Trends in the average age of smokers and the general population 2002 to 2015**

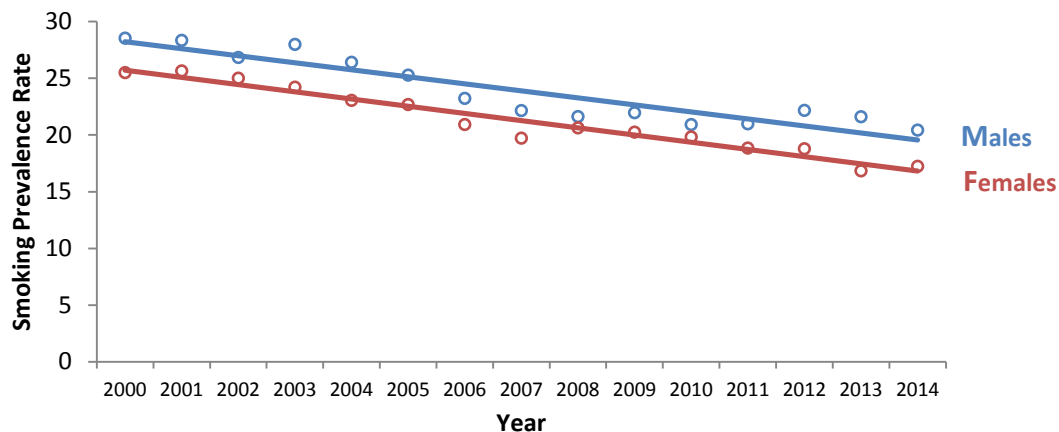


If, for the purpose of modelling, it is assumed that changes in the age structure of smokers tend to follow changes in the overall population over the given time horizon, it implies that quit rates within each age group remain fairly stable relative to each other. If this were not the case, and smokers in some age groups were quitting at a much faster rate than others, then one would expect to see smoking prevalence within that age group decrease more rapidly than in other age groups. To test this, age-specific prevalence rates over the last decade (2005 to 2014) from the UK HSCIC smoking statistics dataset were examined (see Figure 6.11). These show that although there is a degree of overlap for certain years, when a linear regression is performed, smoking prevalence trends over time within each group remain stable relative to each other. A possible exception to this trend is in those aged 60 and over, although smoking prevalence in this group is also declining. Similarly, when a linear regression is carried out on historical UK data on smoking rates in males and females, the rate of decline in both appears to be comparable (Figure 6.12). This suggests that for the modelling exercise it is reasonable to assume that an average quit rate can be applied to the population to estimate the change in the overall size of the smoking population over time. Changes in the age structure of the overall population can then be used to estimate the age structure of the population of smokers over the given time horizon.

**Figure 6.11 Trends in smoking prevalence by age group (UK data)**



**Figure 6.12 Trends in smoking prevalence by gender (UK data)**



Based on this assumption, the expected changes in the percentage of male and female smokers in each five-year age group over the time horizon of the model (2016 to 2036) was calculated based on the age/gender structure of the current smoking population taken from the Healthy Ireland survey, and Irish population projections from the CSO (M1F1 population variant).<sup>(61, 102)</sup>

As the analysis uses an open Markov cohort, new smokers enter the model each year. The total number of annual entrants reflects those that are already smoking

when they turn 18 years, those who take up smoking for the first time after age 18, and those who were former smokers at the outset, but relapse over the course of the time horizon of interest. While it would be possible to use a closed model to compare the cost-effectiveness of different strategies, an open model that takes account of these additional smokers provides results that are more indicative of the actual scale of smoking cessation activity projected to occur over the time horizon, as well as allowing changes in overall smoking prevalence to be estimated into the future.

However, there are a number of caveats associated with any estimate of smoking prevalence derived from this analysis. For example, it may overestimate future prevalence by not taking into account wider societal interventions (increased taxation, introduction of plain packaging, changing attitudes and behaviours, and so on) that may have a significant impact on smoking rates. It also assumes that the success rate for unassisted quitting observed in clinical trials applies to all smokers choosing this option in Ireland. However, this does not take into account that fact that those who are more likely to quit (for example lighter smokers) may be more likely to make an unassisted quit attempt. Neither does the analysis attempt to model the effect of net migration to or from Ireland, due to the uncertainty that exists in relation to the expected age/sex profile and smoking status of Irish immigrants and emigrants over the coming decades. Since this is not included in the model, national smoking prevalence rates are estimated using population projections from the CSO that do not include net migration, as including net migration in the denominator would tend to underestimate smoking prevalence in future years when net inward migration is anticipated.<sup>(102)</sup>

The annual number of people who are smoking at 18 years was estimated using CSO projections on the number of people that will reach this age each year of the simulated time period, combined with 2015 Healthy Ireland data on the proportion of people already smoking at this age, assuming that the decreasing trend observed in the prevalence of smoking among 18 year olds between 2002 and 2015 from HSE Smoking Prevalence tracker data is maintained (annual percent change [APC] -2.1%, 95% confidence interval -4% to -0.2%).<sup>(61, 102, 805)</sup>

The annual number of people taking up smoking for the first time when aged over 18 years was estimated using 2010 US data on the age at which people first started **smoking. These data were taken from the US Surgeon General's report on** tobacco use among young adults (Figure 6.13).<sup>(806)</sup>

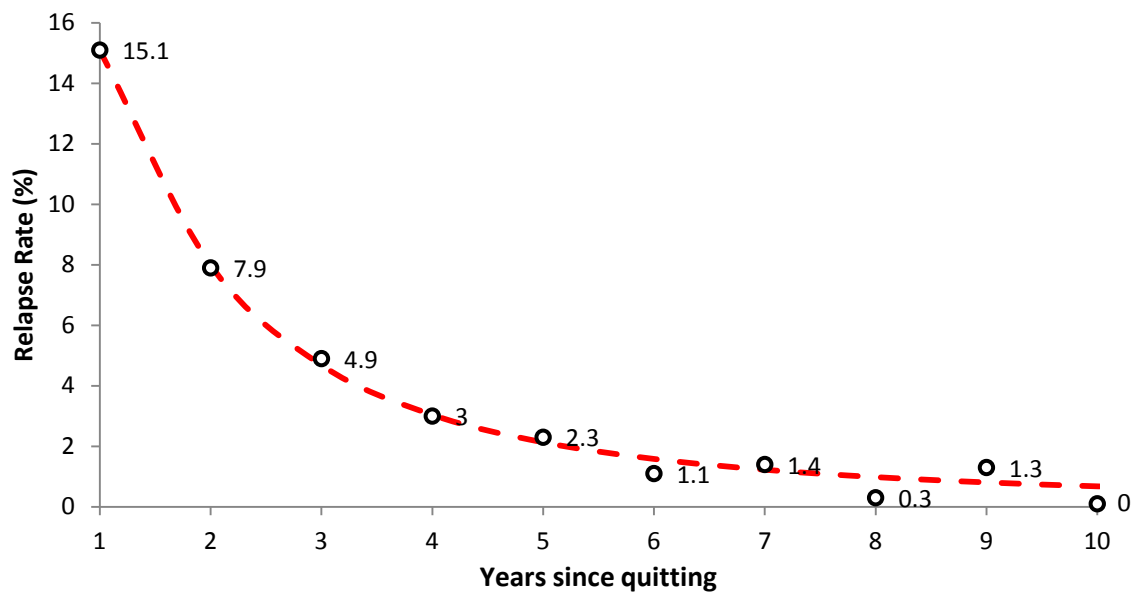
**Figure 6.13 Estimated percentage of people starting smoking by age when first tried a cigarette (US data)**



These data were applied to the population of Irish non-smokers over 18 years to estimate the total number of Irish people over 18 years who will begin smoking for the first time each year between 2016 and 2036. Again, it is assumed that the rates of first time uptake over the age of 18 years will decrease at the same rate as that for 18 year olds (APC -2.1%).

The final source of new entrants to the smoking population each year in the model is those who were former smokers at the outset, but relapse in subsequent years. To calculate this, relapse rates for people who have successfully quit smoking were estimated from the available literature. A meta-analysis of 10 studies reporting outcomes among smokers who had achieved 12-month abstinence reported an average relapse rate of 10% in the first year after quitting.<sup>(807)</sup> A separate longitudinal observational study that looked at relapse rates in 483 men who had successfully achieved continuous abstinence for two years reported annual relapse rates of between 2% and 4% between years two and six, with annual relapse rates of less than 1% for those who had remained abstinent for 10 years or more.<sup>(808)</sup> In the model, the relapse rate each year for those having achieving 12-month abstinence was based on a UK study on relapse rates from the British household panel survey published in 2010, which reported longitudinal data on the same population over 10 years.<sup>(809)</sup> The relapse curve obtained from this data is shown in Figure 6.14. Uncertainty about the rate of relapse was incorporated by varying the relapse rate by  $\pm 20\%$ .

**Figure 6.14 Annual smoking relapse rate by year since quitting**



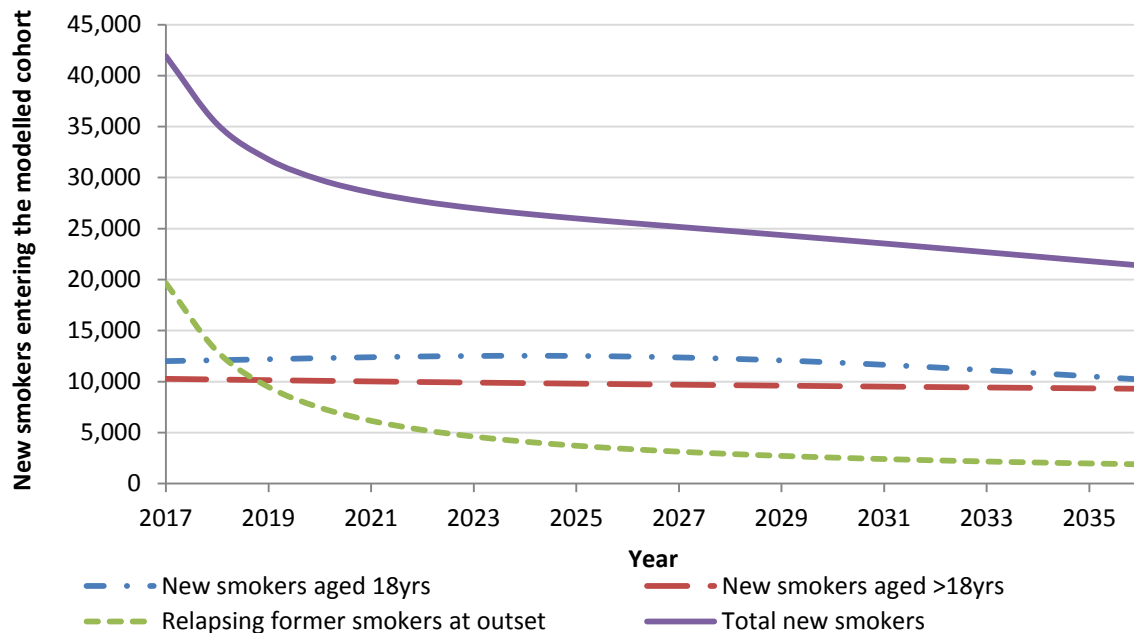
At the outset of the model, the population of former smokers includes all those who quit prior to 2016, some of whom may have quit recently and others who may have quit many years ago. This analysis assumes that former smokers are distributed uniformly over time since quitting, so the relapse rate for the group of former smokers at the outset of the model is the average relapse rate over a time horizon of 20 years. In the first year of the model this is applied to the total population of former smokers in Ireland, which was estimated using data from the Healthy Ireland survey.<sup>(61)</sup> In the second cycle of the model (2017), the remaining population of former smokers from which new entrants to the model can emerge have all quit for at least two years, since anyone who was a smoker and quit in 2016 is accounted for in the former smokers state within the model (see Figure 6.3 Markov model).

Similarly in cycle three (2018) new relapsers entering the model for the first time will be drawn from a population of former smokers who have quit for at least three years, and so on. This means that the relapse rate for those who were former smokers at the start of the simulation will decrease over time, to reflect the increase in the average duration of abstinence within this group, as will the population of former smokers to which this relapse rate is applied. Relapse rates in those who quit after 2016 are accounted for by the transition probability between the former smoker and smoker states in the model. This is calculated using the same relapse curve and is adjusted for the fact that in year two all people in the former smokers state have quit for one year (so the relapse rate is highest).

As the model progresses, the former smokers state includes a mix of people who have quit in all of the prior years since the start of the model (so the average relapse rate decreases over the 20-year time horizon).

The three sources of new smokers are combined to estimate the total number of new smokers entering the population each year over the 20-year time horizon (Figure 6.15).

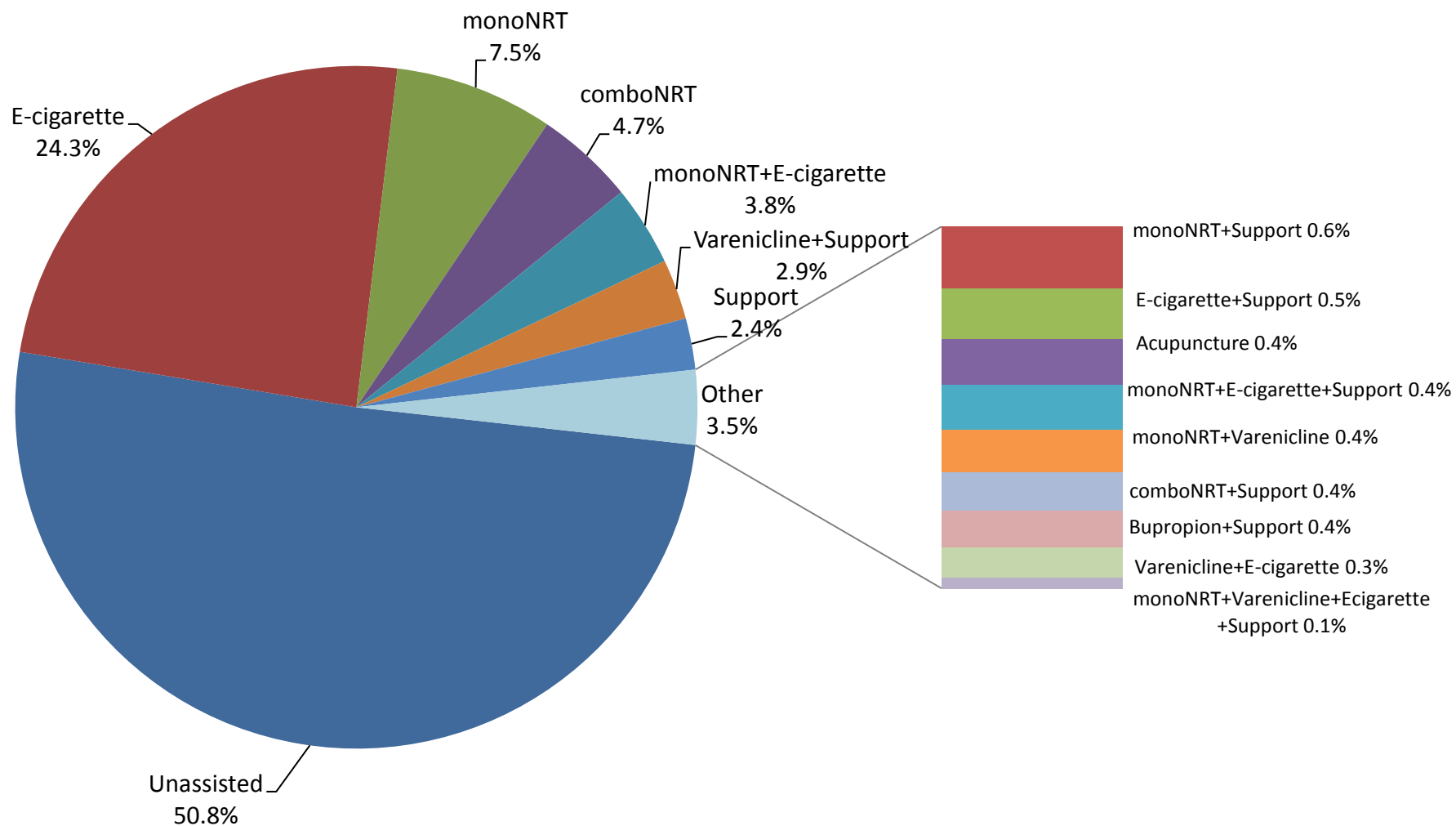
**Figure 6.15 New smokers entering the model over the 20-year time horizon**



The proportion of smokers using each type of intervention in their attempt to quit at present in Ireland was estimated using data from the Healthy Ireland survey 2015.<sup>(61)</sup> The survey included a list of pharmacological smoking cessation interventions (including e-cigarettes, NRT, varenicline or bupropion) and HSE QUIT service supports (Quit.ie, QUITline, Facebook) as well as a question about whether the person received any other form of behavioural support. Smokers who attempted to quit were asked to indicate all of the interventions they used in their effort to quit. This allows for the proportion of people who used different combinations of interventions to be estimated.

The survey did not distinguish between single NRT and combination NRT use, so the split between these two interventions was estimated based on UK data indicating that the ratio of single NRT to combination NRT use is 8:5.<sup>(810)</sup> The survey also grouped varenicline and bupropion together, so the relative use of these two interventions was estimated using Irish data from the Primary Care Reimbursement Service (PCRS) which showed a ratio of 1:8 bupropion to varenicline prescriptions.<sup>(811)</sup> Current practice in regard to the use of different smoking cessation interventions in Ireland is shown in Figure 6.16. International data indicate that, on average, smokers attempting to quit make two attempts per year.<sup>(127)</sup> This was incorporated into the analysis comparing the current standard of care to alternatives, to avoid underestimating the costs associated with failed quit attempts.

**Figure 6.16 Current standard of care for smoking cessation quit attempts in Ireland 2015 (Healthy Ireland data, excluding Refused/Don't Know respondents)**



The relative effect estimates for each of the smoking cessation interventions included in the analysis, and the baseline absolute quit rate associated with unassisted quitting were reported in the clinical effectiveness chapter (Chapter 4). These are summarised in Table 6.3.

**Table 6.3 Summary of effectiveness estimates used in the economic model**

Parameter	Effect size	95% Confidence Interval
Absolute quit rate for unassisted quitting		
Control arms with 12-month follow up (primary estimate)	7.8%	[6.5 to 9.5]
<i>Average over all control arms</i>	<i>8.6%</i>	<i>[7.6 to 9.8]</i>
<i>12-month follow up (continuous abstinence)</i>	<i>5.1%</i>	<i>[3.9 to 6.6]</i>
<i>Range of unassisted quit rates used in univariate sensitivity analysis</i>	<i>Lower bound: 3.9%</i> <i>Upper bound: 9.8%</i>	
Nicotine replacement therapy (NRT)	RR 1.68	[1.58 to 1.78]
Bupropion	RR 1.70	[1.53 to 1.87]
NRT + bupropion	RR 2.02	[1.70 to 2.40]
Electronic cigarette	RR 2.14	[1.26 to 3.35]
Cytisine	RR 2.20	[1.68 to 2.83]
Combination NRT	RR 2.22	[1.91 to 2.55]
Varenicline	RR 2.57	[2.32 to 2.85]
Varenicline + bupropion	RR 3.20	[2.05 to 4.60]
NRT + varenicline	RR 3.54	[2.57 to 4.61]
Individual counselling*	RR 1.39	[1.10 to 1.76]
Intensive advice*	RR 1.35	[1.16 to 1.58]
Telephone support*	RR 1.34	[1.19 to 1.51]
Group behavioural therapy*	RR 1.85	[1.53 to 2.23]
Behavioural support as an adjunct to pharmacotherapy	RR 1.18	[1.09 to 1.28]

\* Relative effect versus active control in the form of brief advice or written materials.



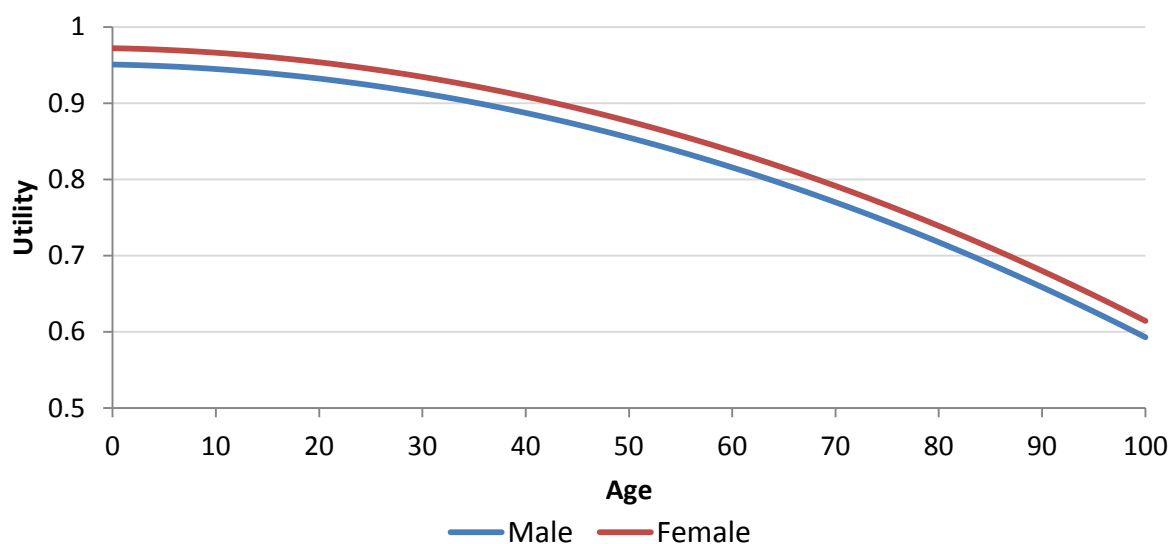
As outlined in this section, it is necessary to estimate the number of quit attempts made annually by the average smoker who is attempting to quit, for the analysis comparing the current standard of care to alternative mixes of therapies, in order to avoid underestimating the resource use associated with multiple failed quit attempts. An estimated average of two quit attempts per year for the half (50%) of smokers attempting to quit in any given year was used, based on a 2012 paper reporting data from the US, Canada, Australia and the UK.<sup>(127)</sup>

### 6.2.8 Utility parameter estimates

For the analysis comparing quality-adjusted life year (QALY) outcomes for each comparator, it is necessary to estimate both the baseline quality of life of the population of smokers and former smokers who do not have a smoking-related illness, as well as the utility weights associated with having a diagnosis of either lung cancer, stroke, IHD or COPD.

In the absence of validated Irish data, baseline quality of life by age and gender for those with no current morbidity was taken from UK estimates for a general population based on data from the Health Survey for England (Figure 6.17).<sup>(812)</sup>

**Figure 6.17 Baseline utility for a general population with no current smoking-related morbidity, by age and gender**



No intrinsic utility loss associated with smoking was incorporated in the analysis, so all of the differences in utility between comparators come from differences in the mortality rate and disease prevalence rates in each comparator arm, as determined by the number of current and former smokers in each arm.

In the absence of Irish data, estimates of the average utility weight associated with lung cancer, stroke, IHD and COPD were taken from the literature. Estimates for lung cancer, IHD and COPD were taken from a 2014 HTA carried out by the National Institute of Health Research in the UK, and the utility weight associated with stroke was taken from a 2015 HIQA HTA.<sup>(768, 813)</sup> These are shown in Table 6.4, along with the individual studies from which they originated. There is a high degree of uncertainty surrounding these estimates due to limitations in the available data and the inherent difficulties in estimating an average utility weight for diseases that can differ considerably in terms of severity. In this analysis, each utility parameter was defined as distributions that were randomly sampled over the course of 10,000 replications.

**Table 6.4 Utility estimates for disease states included in the analysis**

Health state	Utility weight	(95% Confidence interval)	Source
Lung Cancer	0.50	(0.21 to 0.95)	Trippoli 2001 <sup>(814)</sup>
Stroke	0.57	(0.46 to 0.68)	Sorensen 2011 <sup>(815)</sup> , Tengs 2003 <sup>(816)</sup>
COPD	0.63	(0.15 to 0.85)	Spencer 2005 <sup>(817)</sup>
IHD	0.63	(0.41 to 0.82)	Hay 2005 <sup>(818)</sup>

QALY outcomes for the population of smokers and former smokers in each comparator were calculated using a multiplicative approach. For example, the QALY score for males aged 50-54 years with COPD was obtained by multiplying the baseline utility for that age by the utility weight for COPD. The difference in QALYs between the smoker and former smoker populations was then calculated using data on the differing prevalence of each of the four diseases within these two cohorts, taking account of the age/gender structure. Multi-morbidity was not included in the model, so the full utility loss associated with the number of cases of each disease was calculated separately and summed for the overall population.

### 6.2.9 Cost parameter estimates

As outlined in the methods section, a limited societal perspective was adopted that included all of the cost of smoking cessation regardless of on whom they fall, as well as the direct costs of treatment for smoking-related illness. The cost of cigarettes for those continuing to smoke was not included in the primary analysis.

The costs per course of treatment for each of the pharmacological interventions was calculated using the approach outlined in the National Centre for Pharmacoeconomics (NCPE) guidelines for estimating drug costs.<sup>(819)</sup> Costs for people who continue to use products beyond the stated period were not included. Ingredient costs for licensed medicines were obtained from the Primary Care

Reimbursement Service.<sup>(811)</sup> The costs of e-cigarettes were obtained from the literature.<sup>(820)</sup>

Based on data from the Primary Care Reimbursement Service on the proportion of people who complete a full course of treatment in Ireland (assuming a minimum prescription of one month duration), an attrition rate of 40% was applied to all interventions to account for those who relapse in the early stages of their quit attempt and so do not incur the full costs of a complete course of treatment.<sup>(811)</sup> The cost of behavioural support interventions supplied through the HSE QUIT services was calculated based on the staff time required per quit attempt for the standard treatment programme provided by the HSE, and the costs of providing the telephone, text and online support services that forms part of this service. Uptake and adherence rates for the behavioural support services for the last three years was obtained from the HSE, showing the proportions of people who received each contact over the course of the standard treatment programme, which was taken into account when estimating the average cost of supporting a quit attempt using a behavioural intervention.<sup>(821, 822)</sup>

While some smoking cessation interventions are available for general sale or are licensed for over-the counter use, current practice in Ireland is that they must be **prescribed in order to be reimbursed through the HSE's Primary Care Reimbursement Service (PCRS)**. For those with a Medical Card, up to three months supply of medication may be prescribed at a time (and dispensed in monthly aliquots). The exception to this is NRT, which is the subject of additional prescribing controls. The quantity that can be prescribed and dispensed on the initial prescription is limited to two weeks supply (to order to evaluate the success of the individual therapy). Subsequent prescriptions must be prescribed on a single (as opposed to a triplicate) GMS form.

When calculating the average cost of a smoking cessation attempt using varenicline and bupropion, the cost of one GP consultation was included. The average cost of a quit attempt using NRT was calculated assuming that all those with a medical card would require two GP visits, based on PCRS data that the mean duration of NRT use is 51 days (see section 3.4.4). The method used to calculate the average cost of a GP visit for public and private patients is described in detail in Appendix 12.

Table 6.5 shows the cost of each type of smoking cessation intervention.

**Table 6.5 Costs of smoking cessation interventions**

Name	Course of treatment	Additional costs associated with treatment	Total average cost per quit attempt*
Varenicline	2mg/day for 12 weeks (1 weeks titration of 0.5mg once daily days 1-3, and 0.5mg twice daily days 4-7)	GP visit	€180.18
Bupropion	300mg/day for 12 weeks (150mg/day for first six days)	GP visit	€146.28
E-cigarettes	12 week supply (e-cigarette + 3.55ml liquid per day)	Replacement atomiser in months 2 and 3	€93.80
Single NRT	12-week course of NRT, calculated as the weighted average cost using PCRS data on the usage of each type of NRT product	Two GP visits for those with Medical Card	€139.34
Combination NRT	12-week course of NRT patch and gum	Two GP visits for those with Medical Card	€197.15
Varenicline and NRT	2mg/day for 12 weeks and 12-week course of NRT patch	GP visit+an additional GP visit for medical card holders for repeat NRT prescription	€292.28
Bupropion and NRT	300mg/day bupropion for 12 weeks and 12-week course of NRT	GP visit+an additional GP visit for medical card holders for repeat NRT prescription	€266.47
Varenicline and Bupropion	2mg varenicline and 300mg bupropion per day for 12 weeks	GP visit	€281.49
Behavioural support	Cost of HSE Standard Treatment Programme consisting of four contacts over the first month and follow-up contact at three months and 12 months, plus the average cost per contact of the QUIT multimedia support service.	None	€46.37**

\* Factoring in adherence rates derived from PCRS data, as well as dispensing and prescription fees and wholesalers rebate, where applicable, per NCPE guidelines<sup>(811, 819)</sup>, costs were varied  $\pm 20\%$  to capture uncertainty \*\*Cost of staff time limited to direct patient contact time only

The cost of providing behavioural support through the HSE QUIT service was estimated based on the staff cost of the time spent directly communicating with a person attempting to quit. This was calculated using data supplied by the HSE on staff grades, average time spent in each session, attrition rate between first contact and 12-month follow up, and the average cost per person of providing telephone and web-based services in 2015 and 2016. Staff costs were calculated per the national HTA guidelines, which included adjustment for PRSI, pension and overhead costs.<sup>(823, 824)</sup> As the costs included in the model only relate to the direct contact time with smokers making a quit attempt, they do not reflect the full costs of providing this service.

The average cost of treating a patient with each of the four smoking-related illnesses included in the analysis was calculated using Irish data on the total annual spending divided by the total number of people with a diagnosis of each disease.

The total direct costs to the HSE of inpatient and day case treatment of lung cancer, COPD, IHD and stroke were estimated from the Hospital Inpatient Enquiry database (HIPE) for 2015, which are based on 2014 prices.<sup>(825)</sup> Total secondary care costs in each disease area, and cost per patient based on prevalence rates described previously, are shown in Table 6.6.

**Table 6.6 Cost per prevalent case of inpatient and daycase treatment**

Disease (ICD Code)	Total cases (2015)* (n)	Total inpatient costs (€)	Total daycase costs (€)	Cost per prevalent case (€) [95%CI]
Lung Cancer (C34)	4,666	21,950,535	1,879,454	5,107 [3,915 to 6,499]
COPD (J41-J44)	73,901	63,756,866	375,081	868 [664 to 1,097]
Stroke (I60-I69)	88,790	79,415,753	74,941	895 [690 to 1,142]
CHD (I20-I25)	209,361	90,444,399	6,592,530	463 [352 to 588]

\* Total cases of each disease were calculated by applying the prevalence rates for each to the 2015 Irish population

Table 6.6 represents the average costs for all people with each of the relevant diagnoses, including those associated with low resource use due to having less severe disease, or having a prior history of a particular disease that is being appropriately managed, as well as those at the opposite end of the spectrum, who have more severe or acute disease.

As well as the costs of secondary care, patients with smoking-related illness also incur significant primary care costs associated with ongoing management of chronic

illness, including medication costs. However, Irish data on the overall annual costs of treatment in primary care in each disease area are not routinely reported in a manner equivalent to that of secondary care by the HIPE database.

In the absence of these data, it was necessary to rely on the currently available published literature and make simplifying assumptions. Annual primary care and medication costs for IHD and stroke were obtained from a report on European Cardiovascular Disease Statistics 2012, published by the European Society of Cardiology.<sup>(826)</sup> The annual cost of treating COPD was estimated using 2014 PCRS data on the total costs of adrenergics and other drugs for obstructive airway diseases.<sup>(827)</sup> As it is not possible to distinguish between different patient groups in the PCRS data, this medication cost includes the cost of providing these medicines for people with other respiratory diseases, such as asthma, but does not include the costs of GP consultations for the average person with a diagnosis of COPD. Neither does it include the costs of home oxygen therapy, which in 2006 was estimated to **have cost the HSE approximately €4m.**<sup>(828)</sup>

In the absence of reliable Irish data on the average cost of primary care for lung cancer patients, only primary care costs for oral chemotherapy agents (afatinib, crizotinib, erlotinib, and gefitinib) that are funded by the PCRS via the High Tech Drugs Scheme were included.<sup>(829)</sup> While it is assumed that the majority of cancer treatment and follow up is provided in secondary care (inpatient or daycase), there are other costs associated with palliative care, primary care support services, and so on that are not included in the model. The costs included in the model are therefore likely to be an underestimate of the full cost of care.

Total primary care costs in each disease area, and cost per patient based on prevalence rates, are shown in Table 6.7.

**Table 6.7 Cost per prevalent case of primary care treatment**

Disease (ICD Code)	Total Cases*	Primary Care Costs (€)	Cost per prevalent case (€)[95% CI]
IHD (I20-I25)	209,216	56,657,000	271 [207 to 342]
Stroke (I60-I69)	88,729	20,262,000	228 [174 to 288]
COPD (J41-J44)	73,657	48,760,000	662 [504 to 831]
Lung Cancer (C34)	4,666	2,590,000	555 [423 to 698]

\* Total cases were calculated for the same year for which the costs were reported; 2009 for Stroke and IHD, 2014 for COPD and 2015 for lung cancer

Given the lack of reliable Irish data with which to estimate these costs, they were varied  $\pm 20\%$  in the model, as recommended in Irish guidelines<sup>(823)</sup> to capture the uncertainty associated with them.

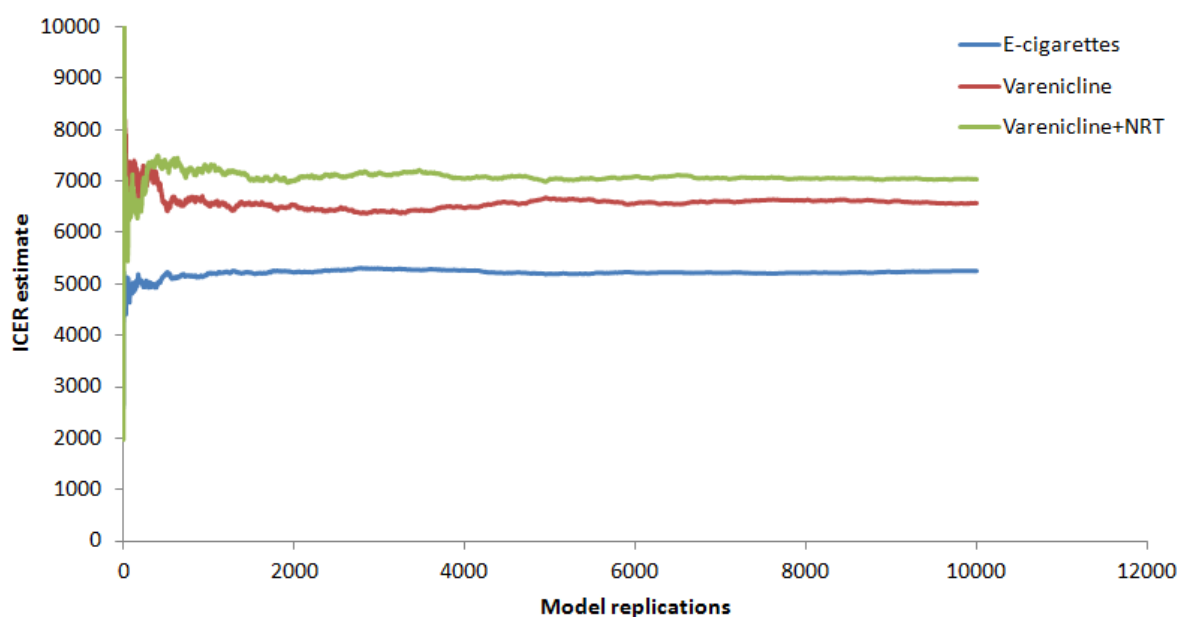
## 6.3 Cost effectiveness analysis results

Monte Carlo simulation was performed over the course of 10,000 replications to derive estimates of the costs and consequences of each comparator in the economic model. Two types of cost-effectiveness analysis were carried out. In the first, all interventions were individually compared with each other to rank each type of intervention on its own. In this analysis it was assumed that all smokers made a single quit attempt every year, all with the aid of a given intervention. In the second analysis, the cost-effectiveness of the current mix of cessation interventions in Ireland was compared with alternative treatment mixes, based on international data on achievable uptake rates for each intervention. Both of these analyses were carried out for the numbers of people quitting (quit outcomes) and quality-adjusted life years (QALY outcomes). All analysis was carried out using TreeAge Pro 2016.<sup>(830)</sup>

### 6.3.1 Cost-effectiveness analysis comparing individual interventions

To estimate the cost-effectiveness of individual interventions compared with each other, 10,000 replications of the model were performed, with parameters sampled from their range of plausible values in each replication. Figure 6.18 shows that stable ICER estimates were achieved after about 4,000 replications. This indicates that 10,000 replications were sufficient to obtain stable results from the probabilistic analysis.

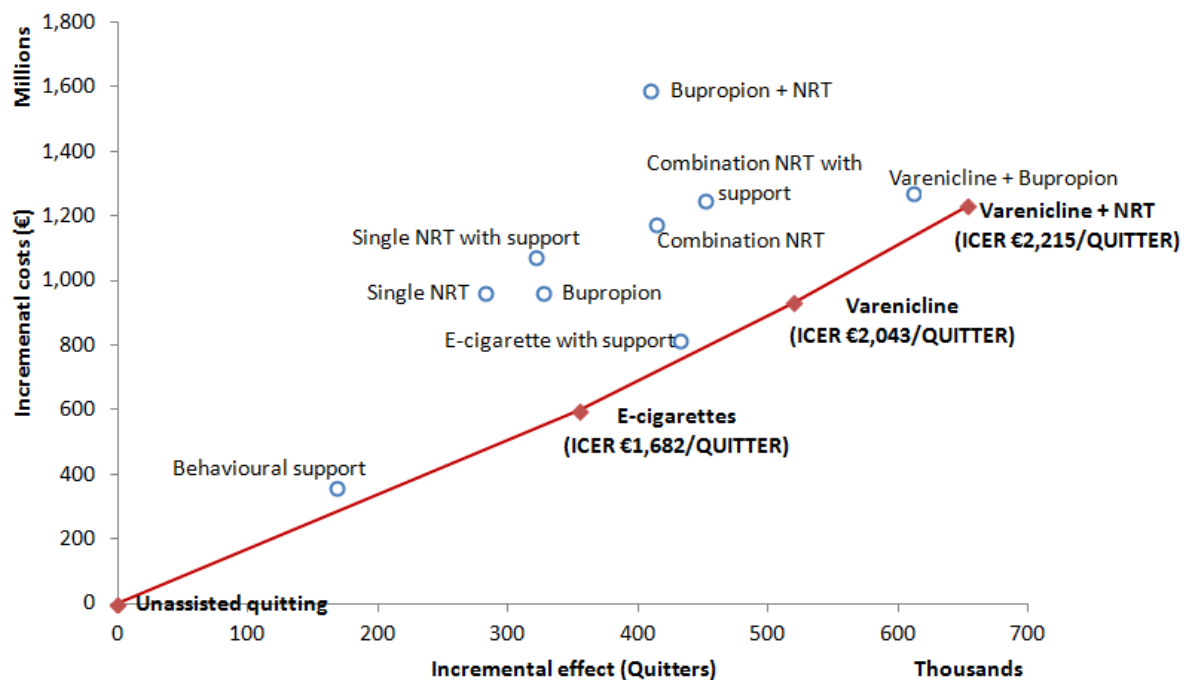
**Figure 6.18 Convergence of ICER estimates for the comparison of individual interventions (QALY outcomes)**



### Quitting outcomes

The outcome in this analysis is the number of people making a successful quit attempt (greater than six-months abstinence), and the costs are limited to the cost of providing these interventions. The cost-effectiveness plane for quit outcomes for the total Irish population of smokers over a 20-year time horizon is shown in Figure 6.19. Table 6.8 shows the incremental costs and benefits of all non-dominated strategies. This shows that the most cost-effective option is e-cigarettes, which is **associated with an average cost of €1,682** for each additional successful quitter, with the next most cost-effective choice being **varenicline (€2,043 per additional quitter** compared with e-cigarettes) followed by a combination of varenicline and NRT, **which is associated with an incremental cost per additional quitter of €2,215** compared with varenicline monotherapy.

**Figure 6.19 Cost-effectiveness plane for comparison of single smoking cessation interventions on quitting outcomes**



**Table 6.8 Incremental costs and benefits of non-dominated strategies for the comparison of individual smoking cessation interventions on quitting outcomes**

Strategy	Cost (€ million)	Incremental cost (€ million)	Effect (Quitters)	Incremental effect (Quitters)	ICER (€/Quitter)
Unaided	0	-	670,838	-	-
E-cigarettes	597.5	597.5	1,026,042	355,204	1,682
Varenicline	933.2	335.7	1,190,324	164,282	2,043
Varenicline and NRT	1230.3	297.1	1,324,461	134,137	2,215

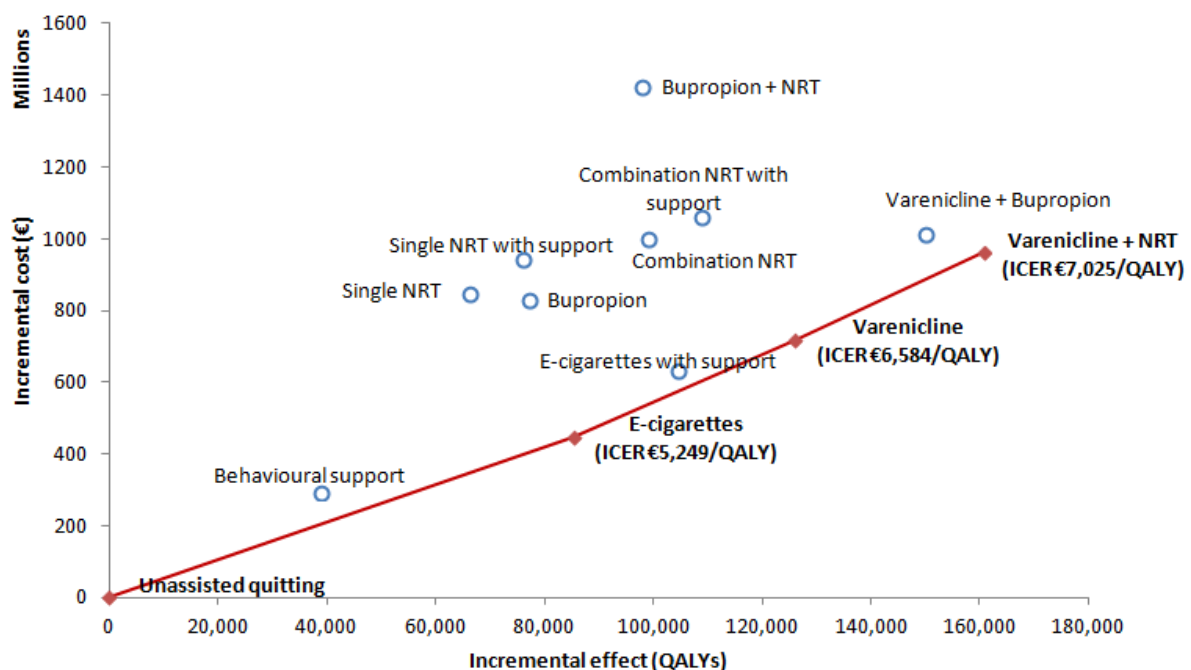


When interpreting these results it is important to note that they reflect the costs and number of expected quitters if all smokers were to make one quit attempt per year, all using a given intervention. Smokers who relapse in following years may quit again, so it is possible that they may be counted as having made a successful quit attempt multiple times. While the assumption that every single smoker will make a quit attempt, and uptake rates of each interventions will be 100% within each comparator are clearly not realistic, they are necessary in order to compare the cost-effectiveness of each intervention with each of the other interventions. In addition, while quit outcomes are helpful in determining the optimal treatment strategy within the field of smoking cessation, they do not provide a basis for comparing the cost-effectiveness of smoking cessation interventions with other clinical areas that may be funded from the same budget. To do this, one needs to examine outcomes that are common across all disease areas, such as the quality-adjusted life year (QALY). These are reported in the following section.

### *QALY outcomes*

QALY outcomes are based on the differences in average life expectancy among current and former smokers, combined with the difference in quality of life among former and current smokers due to differences in the risk of developing a smoking-related illness. The cost-effectiveness plane for QALY outcomes in Figure 6.20 and Table 6.9 shows the incremental costs, effects, and ICERs for each non-dominated strategy compared with the next best option.

**Figure 6.20 Cost-effectiveness plane for the comparison of single smoking cessation interventions on QALY outcomes**

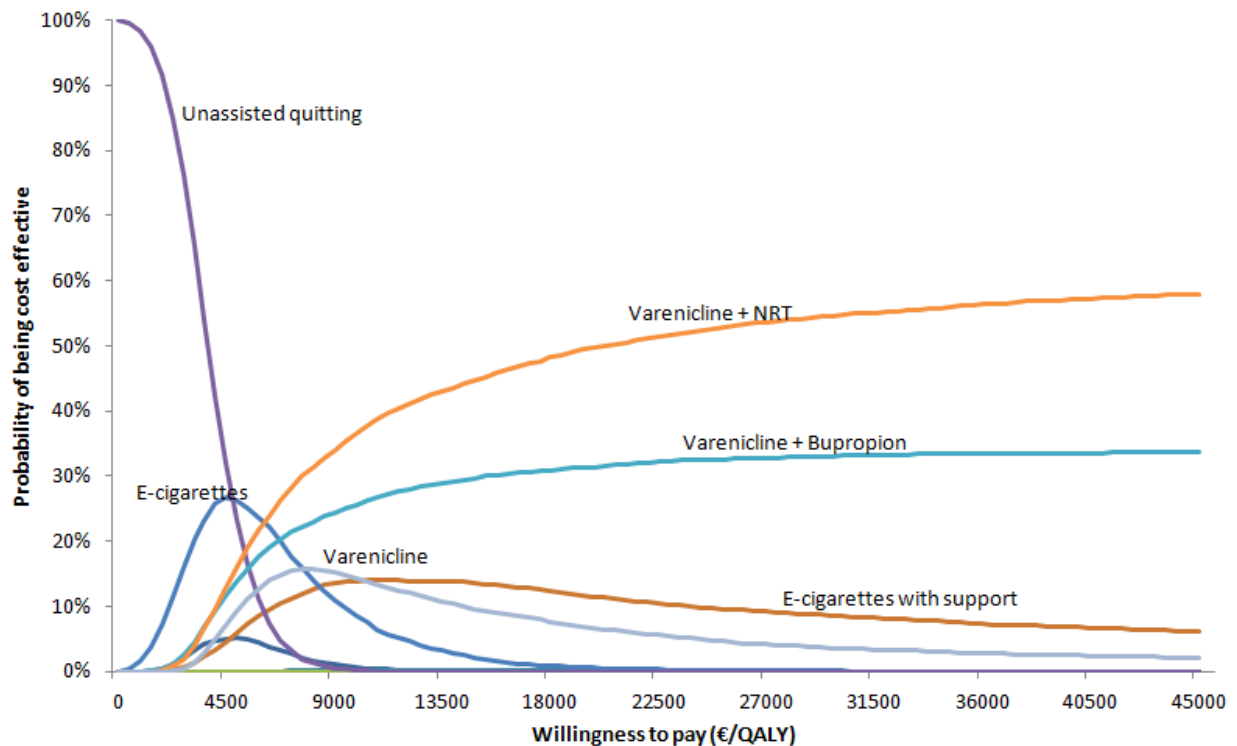


**Table 6.9 Incremental costs and benefits of non-dominated strategies for the comparison of individual smoking cessation interventions on QALY outcomes**

Strategy	Cost (€ million)	Incremental cost (€ million)	Effect (QALY)	Incremental effect (QALY)	ICER (€/QALY)
Unaided	1,727	-	11,245,423	-	-
E-cigarettes	2,174	448	11,330,680	85,257	5,249
Varenicline	2,443	269	11,371,531	40,851	6,584
Varenicline and NRT	2,686	243	11,406,139	34,608	7,025

These results show that, as per the quitting outcomes, e-cigarettes are the most cost-effective strategy compared with doing nothing, with an incremental cost of **€5,249** per additional QALY gained. Varenicline monotherapy is the next most **cost-effective treatment, with an ICER of €6,584/QALY compared with e-cigarettes**. Combination treatment using varenicline and NRT is the most cost-effective option compared with e-cigarettes, being more effective and more costly, with a slightly **higher ICER (€7,025/QALY)**. The cost-effectiveness acceptability curve (CEAC, Figure 6.21) shows that at willingness-to-pay thresholds in excess of **about €7,000/QALY**, the optimal strategy is combination varenicline and NRT. To put this in context, the willingness-to-pay threshold routinely used in Ireland to decide if pharmaceutical interventions are **cost-effective is €45,000/QALY**.<sup>(831)</sup> These results are consistent with those of previous cost-effectiveness studies, which found that smoking cessation interventions tend to be highly cost-effective (see section 6.1).

**Figure 6.21 Cost-effectiveness acceptability curve (CEAC) for comparison of individual smoking cessation interventions on QALY outcomes**

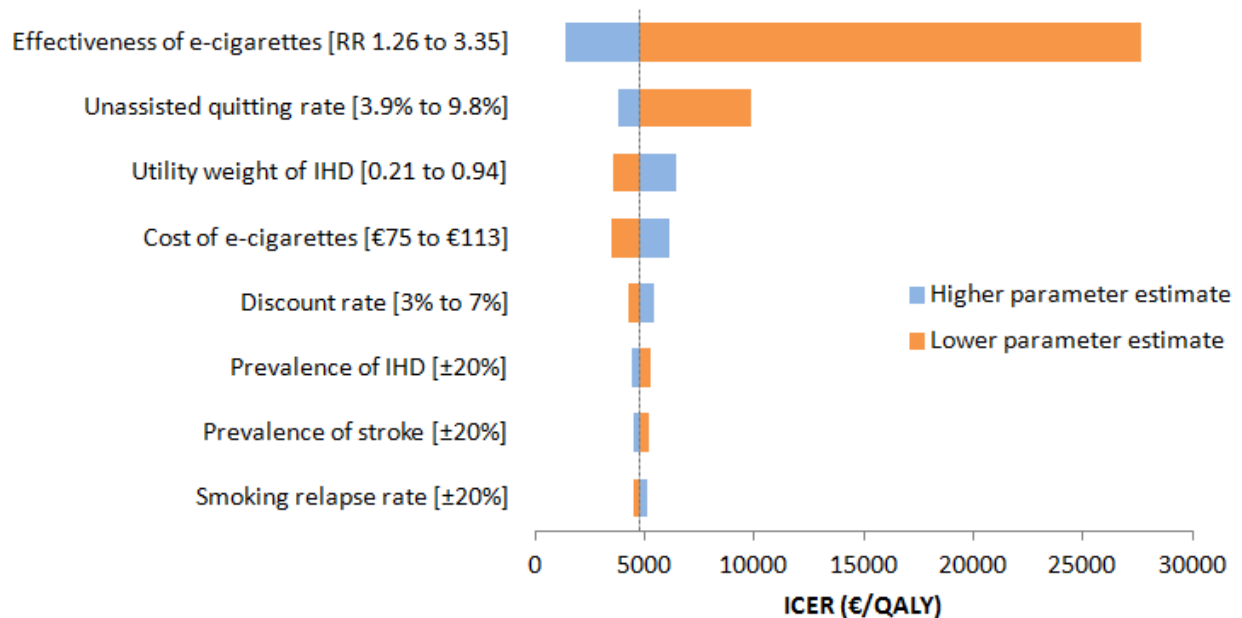


Univariate deterministic sensitivity analysis was carried out to identify how sensitive these results are to changes in the input parameters. In this type of analysis the model is run with each of the input parameters held at their upper and lower bound, while all the other parameters were assigned their mean value, to ascertain what effect it has on the ICER for a given comparison. Tornado plots for all interventions on the cost-effectiveness frontier (e-cigarettes versus unassisted quitting, varenicline versus e-cigarettes and varenicline and NRT versus varenicline) are shown in Figures 6.22, 6.23 and 6.24, respectively. These show that the results are most sensitive to the relative effectiveness results for each of these interventions, with the wide bounds around the effectiveness of e-cigarettes in particular indicating that the cost-effectiveness results may change considerably when new evidence about the effectiveness of this intervention becomes available. It also shows that the results are relatively insensitive to changes in the prevalence of smoking-related diseases and utility weight estimates.

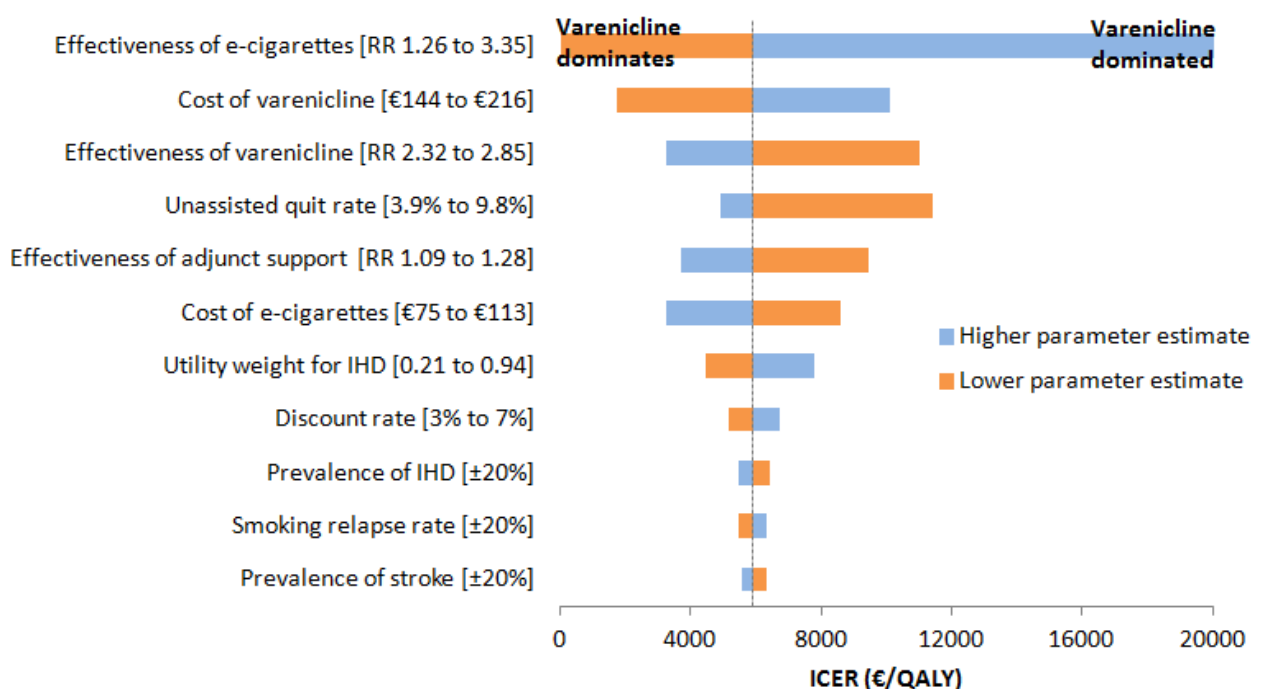
Based on these findings, the effect of changes in the estimated relative effectiveness of e-cigarettes on the overall cost-effectiveness of individual therapies was examined in a separate sensitivity analysis. This shows that e-cigarettes are dominated (less effective and more costly than alternatives) at the lower bound of effectiveness (RR 1.26) and are the only interventions that would be considered cost-effective at its

upper bound (RR 3.35, at which point the ICER for the next intervention on the frontier [varenicline and NRT] is €98,510/QALY, see Figure 6.25).

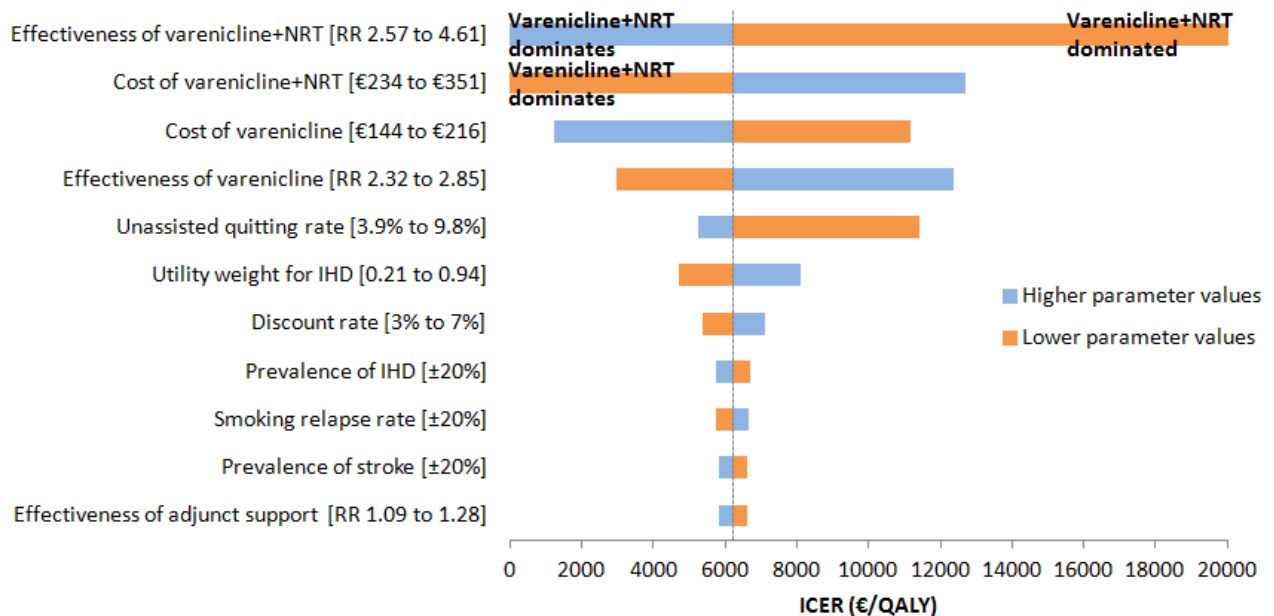
**Figure 6.22 Univariate sensitivity analysis for the comparison of e-cigarettes with unassisted quitting**



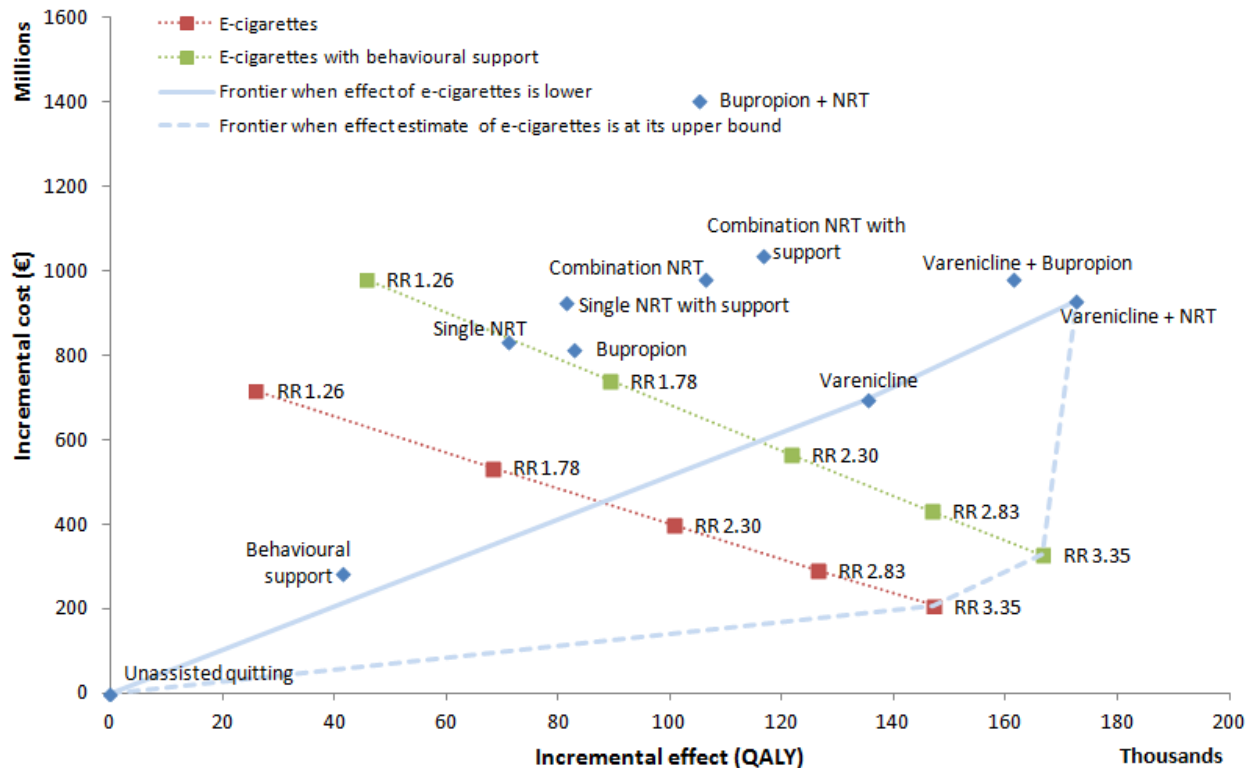
**Figure 6.23 Univariate sensitivity analysis for the comparison of varenicline with e-cigarettes**



**Figure 6.24 Univariate sensitivity analysis for the comparison of varenicline plus NRT with varenicline**



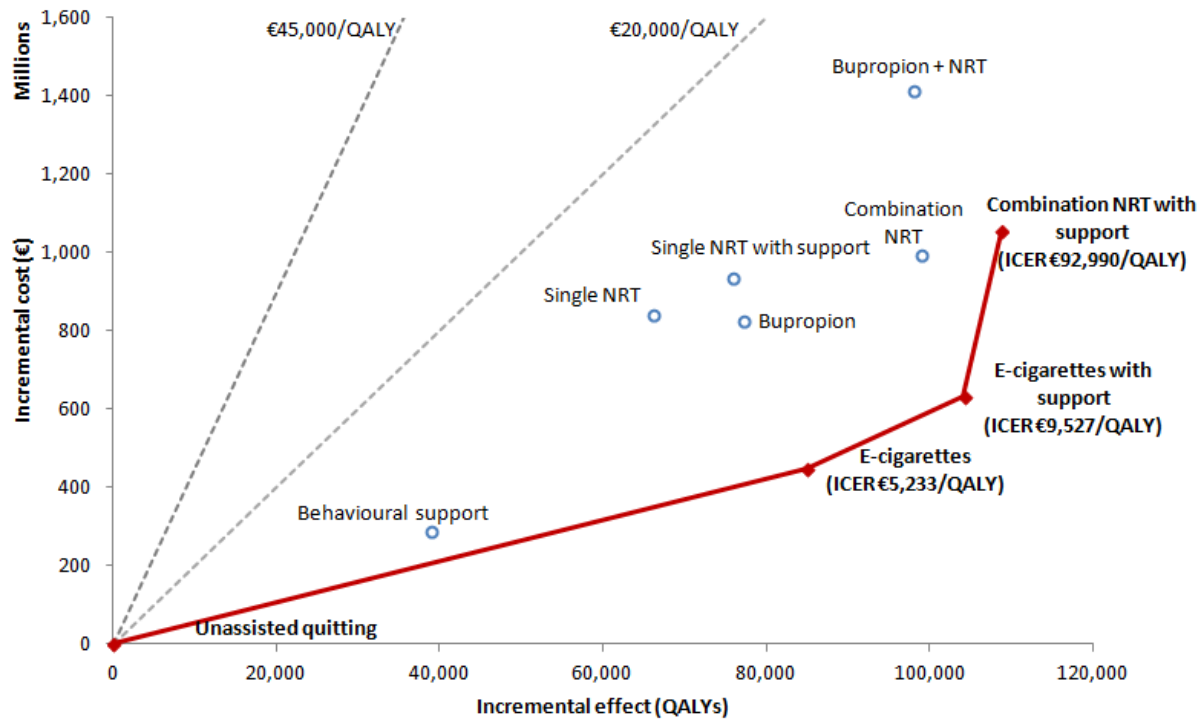
**Figure 6.25 Sensitivity analysis of varying the effect of e-cigarettes (RR 2.14, 95%CI 1.26 to 3.35) on the cost-effectiveness of individual interventions**



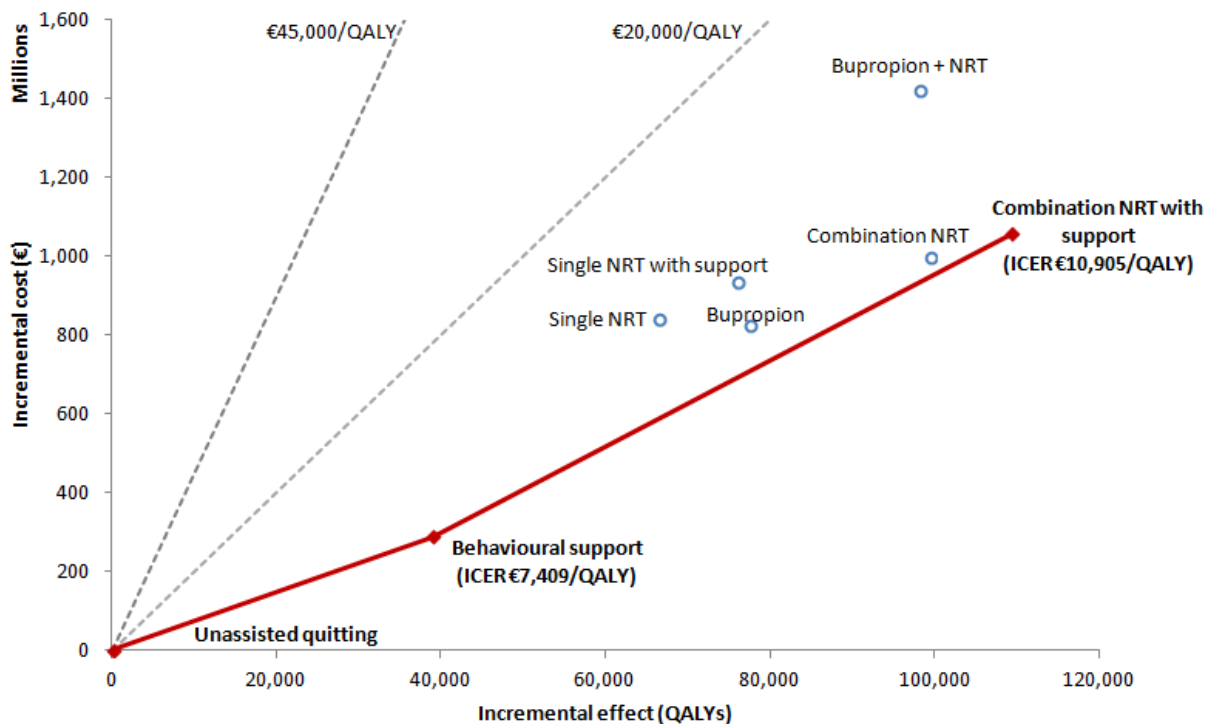
Given the low uptake rates of varenicline that have been observed in Ireland and internationally, a scenario analysis was carried out to examine the impact of removing this as an option in the analysis, both when e-cigarettes are included and

when they are excluded. This analysis is designed to look at the cost-effectiveness of the available interventions for the cohort for whom varenicline is contraindicated, not tolerated or non-preferred. The cost-effectiveness planes for these two scenarios are shown in Figures 6.26 and 6.27.

**Figure 6.26 Cost effectiveness plane for the cohort of smokers for whom varenicline is not an option, with e-cigarettes included among the remaining options**



**Figure 6.27 Cost effectiveness plane for the cohort of smokers for whom varenicline is not an option, with e-cigarettes excluded from the remaining options**



This analysis shows that among the cohort of smokers for whom varenicline is contraindicated, not tolerated or non-preferred, combination NRT is the most effective therapy, but the additional benefit gained by using this intervention compared with e-cigarettes is obtained at a high cost (Figure 6.25). Alternatively, when e-cigarettes are excluded from the analysis (to examine a scenario where future studies fail to confirm the promising results reported to date) combination NRT is shown to be highly cost-effective among those for whom varenicline is not a viable option (Figure 6.26). This implies that were the findings of the existing trials evaluating the effectiveness of e-cigarettes to be confirmed, e-cigarettes would tend to displace combination NRT as the optimal strategy among those not willing or able to choose varenicline alone, or in combination with NRT, to help them quit.

### 6.3.2 Cost-effectiveness analysis comparing current practice with alternatives

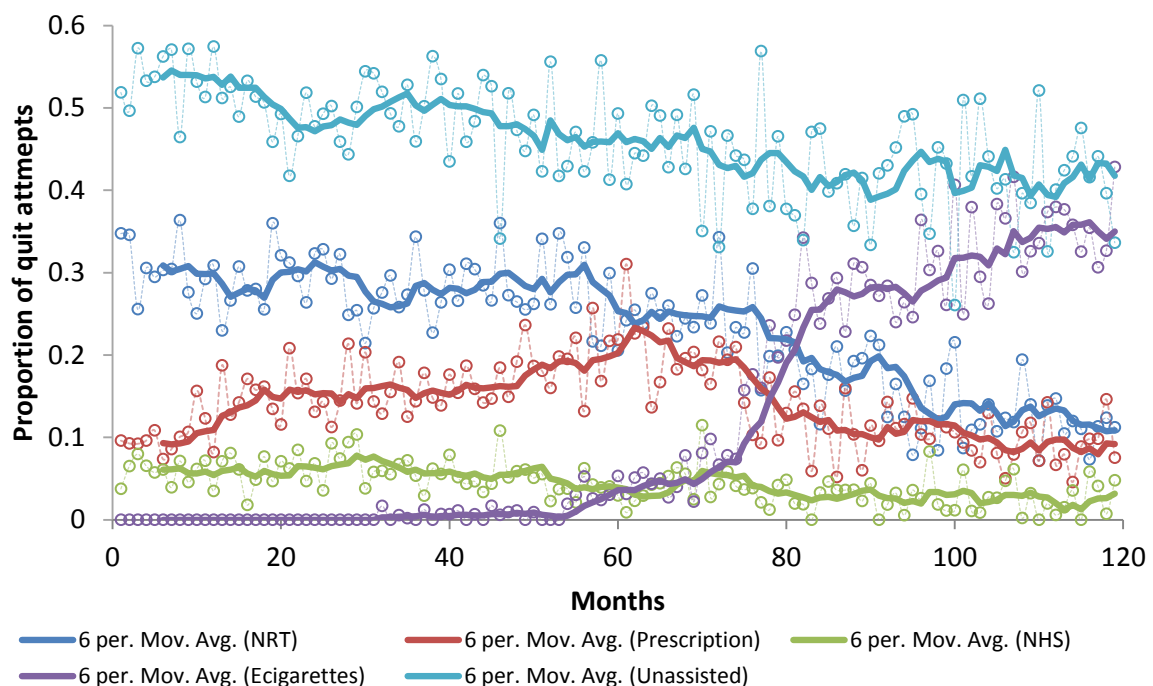
While the cost-effectiveness analysis of individual treatments allows for a comparison of how they perform in relation to each other, a more useful analysis for informing policy compares the current standard of care to plausible alternative mixes of interventions in order to identify improvements in smoking cessation services in Ireland. In this analysis the existing mix of interventions used by people making a quit attempt is compared to alternatives where more people are encouraged to choose more effective interventions. In each comparator the mix of interventions

remains constant over the 20-year time horizon. The choice of comparators is informed by data on likely changes in the uptake of various interventions over time, and peak uptake rates for individual treatments that have been observed in other countries. The purpose of this analysis is to identify improvements in the mix of interventions used in Ireland that increase overall quit rates at an acceptable cost.

### International comparisons

In England, the smoking toolkit study uses household survey data collected since 2006.<sup>(832, 833)</sup> The 2016 figures from this study indicate that during a quit attempt in the previous 12 months, 43% of smokers and ex-smokers reported using no cessation aid, 36% reported using an e-cigarette, 11% reported using over-the-counter NRT, 9% reported using a prescription medication (NRT, varenicline or bupropion), while only 3% reported using the NHS Stop Smoking Service (Figure 6.28).<sup>(834)</sup> Use of e-cigarettes as a quitting aid has increased from negligible use in 2010 to 36% in 2016, while other methods of cessation, including the use of other pharmacological interventions have declined. The authors of the Smoking Toolkit Study recently examined the association between e-cigarette use and changes in pharmacotherapy in a time series analysis.<sup>(832)</sup> They found that e-cigarette use was negatively associated with the use of prescription NRT, but had no effect on the use of over-the-counter NRT, varenicline or bupropion. They also reported that e-cigarettes had a positive association with successful quit attempts.

**Figure 6.28 Proportion of quit attempts made using smoking cessation interventions, England, Nov 2016 to Sept 2016 (6-month moving average)**





A report commissioned by the EU to establish the attitudes of Europeans towards tobacco and e-cigarettes reported on smoking cessation methods in all 28 EU countries.<sup>(835)</sup> The fieldwork for this report was carried out in the last quarter of 2014. For the UK, a higher rate of unassisted quitting (52% vs. 43%), a lower rate of e-cigarette use (19% vs. 36%) and a similar rate of smoking cessation medication use (18% vs. 20%) were reported compared with the Smoking Toolkit study.<sup>(834, 835)</sup> These differences could be due to a number of reasons, including differences in the time the study was conducted or the methods of sampling, questionnaire design or analysis. The Eurobarometer report was also conducted in 2012 and shows the change in use of cessation methods in 2014 compared with 2012. The report indicates that in the UK, smokers and ex-smokers who tried to quit in the last 12 months were less likely to have done so without assistance (decrease of 7%) and were less likely to have used a smoking cessation medication (decrease of 8%) since 2012.

The EU average shows a similar trend for both the unassisted quit rate and the use of a smoking cessation medication (a 5% and 3% drop, respectively). The UK, Ireland and Finland have the lowest unassisted quit rates (52%, 54% and 52%, respectively), with countries such as Spain and Greece having the highest unassisted quit rates (80% and 85%, respectively). This is the first Eurobarometer survey where participants were asked specifically about the use of e-cigarettes as a cessation aid. The survey shows the EU average for using e-cigarettes as a cessation aid is 10%, while the UK (19%), France (18%) and Ireland (19%) have the highest rates.<sup>(835)</sup> Overall, Ireland and the UK are very similar in terms of use of cessation aids (smoking cessation medication Ireland 17% vs. UK 18%; e-cigarettes Ireland 19% vs. UK 19%; support from health professional or use of Stop Smoking Services Ireland 6% vs. UK 7%).<sup>(835)</sup>

Sweden has the lowest prevalence of smokers in the EU28 (11%) and the highest proportion of ex-smokers (35%).<sup>(835)</sup> The Eurobarometer report indicates that in Sweden, 60% of smokers and recent ex-smokers try to quit smoking without assistance, while a high proportion use smoking cessation medications (20% compared with EU28 average of 12%). However, only 2% report using e-cigarettes and only 4% report using support from a health professional or special stop smoking service. Rutqvist reported on smoking cessation aids used by Swedish smokers in a cross-sectional survey conducted in 2009.<sup>(836)</sup> Although NRT and counselling were commonly reported as a smoking cessation aids in women in Sweden (35% nicotine gum, 22% nicotine patch and 36% counselling), snus (a type of smokeless tobacco) was the most commonly reported type of cessation aid reported by men (63% snus, 15% nicotine gum, 8% nicotine patch and 20% counselling).<sup>(836)</sup>

Data from the 2012 Eurobarometer survey were used to assess which factors determine the use of smoking cessation aids. They reported that respondents from countries with comprehensive tobacco cessation programmes who provide medication, QUITlines and other smoking cessation services free of charge are significantly more likely to use effective cessation aids.<sup>(837)</sup>

A survey conducted in Canada by the Canadian Centre for Population Health Impact reported a smoking prevalence of 14.2% in 2015.<sup>(838)</sup> Among current and former smokers who had tried to quit smoking in the past two years, 44.2% used some sort of top smoking medication (data from 2012). Of these, the nicotine transdermal patch was the most popular (26%), nicotine gum was used by 20%, and products like bupropion were reported by 19% of current and former smokers. The use of e-cigarettes as a smoking cessation aid was ascertained in an additional survey carried out by the centre in 2013, with 22.9% of current and former smokers reporting its use as a cessation aid in the previous two years.<sup>(839)</sup> Canada currently does not allow for the sale of nicotine containing e-cigarette products, and therefore more than half of those using e-cigarettes report using nicotine-free liquids.<sup>(839)</sup> In Canada the **phone number for the Smoker's Helpline was added to labels for cigarette packages** in 2012. The most recent survey, carried out in 2013, reported that 5.6% of current and former smokers who had tried to quit in the last two years had used the helpline, which was similar to estimates prior to 2012.<sup>(838)</sup>

White and colleagues utilised a national Canadian survey to examine how subsidisation policies for smoking cessation medicines in some provinces, but not others, affected medication use and quit success. They reported that a comprehensive subsidisation policy for smoking cessation medications was associated with a modest increase in NRT use and quit success, but it did not affect the use of prescription smoking cessation medications.<sup>(840)</sup>

Smoking prevalence in Australia is lower than in Ireland and the UK, but similar to Canada (14.7%).<sup>(841)</sup> A survey carried out in Australia between 2002 and 2009 shows that the use of any medication for smoking cessation (NRT, varenicline or bupropion) increased in Australia between 2002 and 2009 (32% to 52%). Use of NRT rose from 27.5% in 2002 to 39.1% in 2008, but decreased to 29.0% in 2009.<sup>(842)</sup> This coincided with the introduction of varenicline to the Australian market in 2008, and a reported increase in its use from 4.6% in 2008 to 23.9% 2009.<sup>(842)</sup> Behavioural support such as the use of a helpline, Internet or smoking cessation clinic also increased between 2002 and 2009, from 8.4% of respondents to 15% of respondents. Overall, the use of some sort of support, either pharmacotherapy and or behavioural support, increased from 37% in 2002 to 59% in 2009.<sup>(842)</sup>

More recent data from the National Drug Strategy Household Survey in 2013 suggested that the use of NRT had remained stable (31%), while the use of other

smoking cessation medications was reported as 16%. Data from this survey also indicated that 9% had contacted a helpline, 24% had asked their doctor for help, 16% reported using smoking cessation literature, 9% reported using the Internet and 13% reported using a mobile phone app. However, more than half of the **respondents reported unassisted quitting (also known as going 'cold turkey')**.<sup>(843)</sup>

The survey also asked about the dual use of e-cigarettes and tobacco smoking, and found that approximately 15% of smokers also reported using an e-cigarette in the previous 12 months.<sup>(844)</sup> A systematic review of unassisted quitting in Australia based on 19 Australian studies reported that 54% to 69% of ex-smokers quit unassisted and 41% to 58% of current smokers had attempted to quit unassisted. This indicates that unassisted quitting is the most popular method of quitting. The authors concluded that public health would benefit from a greater understanding of why so many smokers choose not to use smoking cessation aids.<sup>(134)</sup>

In the United States (US), the prevalence of smoking is similar to Canada and Australia at 15.1%.<sup>(845)</sup> **Based on the 'Healthy People 2020' report, the US aim to** reduce adult cigarette smoking to 12% prevalence by 2020.<sup>(846)</sup> The tobacco use supplement to their Current Population Survey from 2010-2011 reported that 20.1% of smokers used NRT in a quit attempt in the previous year, while 10.4% used varenicline, 3.1% used bupropion and 5.0% used e-cigarettes.<sup>(847)</sup> More recent data from a nationally representative sample of 2,028 smokers who were surveyed in 2012 and 2014 suggests a similar pattern to what has been seen in other countries, with the use of e-cigarettes for smoking cessation increasing to 24.8% and use of pharmacotherapy (NRT, varenicline and bupropion) decreasing to 17.8%.<sup>(848)</sup> Almost 10% of respondents reported using both pharmacotherapy and e-cigarettes to try and quit.<sup>(848)</sup>

Based on data from the International Tobacco Control Policy Evaluation Project (ITC -4) which included Canada, US, UK and Australia, 30% to 40% of respondents reported using more than one method of smoking cessation during the previous 12 months, suggesting multiple methods are often chosen by smokers during quit attempts.<sup>(849)</sup>

### *Summary of international data*

Overall, similar trends are seen throughout the EU and internationally. The use of e-cigarettes as a smoking cessation aid is still low in many countries, but seems to be on the increase.<sup>(832, 835, 839, 850)</sup> Of the EU28, the UK, France and Ireland have the highest proportion of smokers and recent quitters who use e-cigarettes as a smoking cessation aid.<sup>(835)</sup> The use of NRT, varenicline and bupropion seems to have peaked in some countries, with its use decreasing in recent years in the UK, Australia, US and Ireland.<sup>(833-835, 842, 847, 848)</sup> It has been suggested that the increased

use of e-cigarettes has negatively impacted on the use of prescribed NRT.<sup>(832)</sup> The unassisted quit rate is over half of all quit attempts in most countries, with the EU average for smokers and ex-smokers who tried to quit in the previous 12 months being 65%.<sup>(835)</sup> It has been suggested that more studies are necessary to discover why so many smokers choose to quit unassisted when effective cessation aids are available.<sup>(134)</sup>

### *Comparators used in the analysis of alternative standards of care*

Current preferences for smoking cessation in Ireland were obtained from the Healthy Ireland survey (see Figure 6.16). This showed that half (51%) of all quit attempts currently made are undertaken without any behavioural or pharmacological support. The single most popular smoking cessation aids are e-cigarettes, which are the only support used by approximately a quarter of people trying to quit (24%), while a further 5% use e-cigarettes in combination with some other form of therapy. The next most common cessation aid is NRT, which is used either alone or in combination in 18% of quit attempts. Prescription medication (varenicline or bupropion) is used in only about 4% of attempts.

It is of particular note that e-cigarettes have achieved such high penetration since coming to market in 2011. This mirrors the experience in the UK, where the use of e-cigarettes as a cessation aid has risen consistently over the last six years, while the use of NRT and prescription medicines has declined (Figure 6.16).<sup>(851)</sup> As of September 2016, the proportion of all UK quit attempts made with the support of e-cigarettes was approaching 40%, with no evidence that this increase is levelling off. A decreasing trend in the proportion of unassisted quit attempts was also observed in the UK data, although this had been in evidence prior to the advent of e-cigarettes. The rate of unassisted quitting has remained constant at around 41% between 2013 and 2016, despite e-cigarette use increasing substantially over this period.<sup>(851)</sup>

As discussed earlier, data on unassisted quit rates for the EU28 countries in 2014 were reported in a Eurobarometer report.<sup>(852)</sup> While there were some differences **between the 'Smoking in England' and UK data for this year (Eurobarometer reported a 52% unassisted quit rate in the UK for 2014, compared with 42% in the 'Smoking in England' dataset), the EU data show that the unassisted quitting rates in the UK and Ireland are among the lowest in the EU (52% and 54%, respectively), compared with an overall average of 65% (range 85% to 52%).** They also show that the UK and Ireland are among the most enthusiastic adopters of e-cigarettes as a smoking cessation tool, with uptake rates of 19% reported for both in 2014, while the overall average among the EU28 was 10% (range 2% to 19%).<sup>(852)</sup> This indicates that the UK data represents the lower bound for internationally observed

rates of unassisted quitting and the upper bound for the use of e-cigarettes for smoking cessation.

Given the results of the cost-effectiveness analysis of individual therapies, the potential maximum uptake of NRT in combination with varenicline in Ireland is also of interest, as this was identified as the most effective smoking cessation intervention (Chapter 4), and the most cost-effective option at conventional willingness-to-pay thresholds. Accurate estimates of current usage rates of varenicline in Ireland and the UK are difficult to ascertain as it is generally grouped with other prescription medications rather than being reported separately. However, data from the Healthy Ireland survey indicate that it is used in less than 4% of quit attempts at present.<sup>(61)</sup> International survey data on varenicline use in four countries shortly after it was first marketed show peak usage rates of 22% in the US and 15% in both Canada and Australia, but usage rates in the UK at that time were considerably lower (4%).<sup>(853)</sup> If it is assumed that any initiative by the HSE to promote the use of NRT and varenicline would have most impact among those using some form of support in their quit attempt from HSE QUIT services or their GP, with far less influence among those choosing NRT or e-cigarettes without any contact with health professional (<10%), then the upper limit for the use of combination NRT and varenicline would be 8% to 12%.

Based on these data, the alternative standards of care in Ireland that were compared to current practice in the cost-effectiveness analysis are shown in Table 6.10.

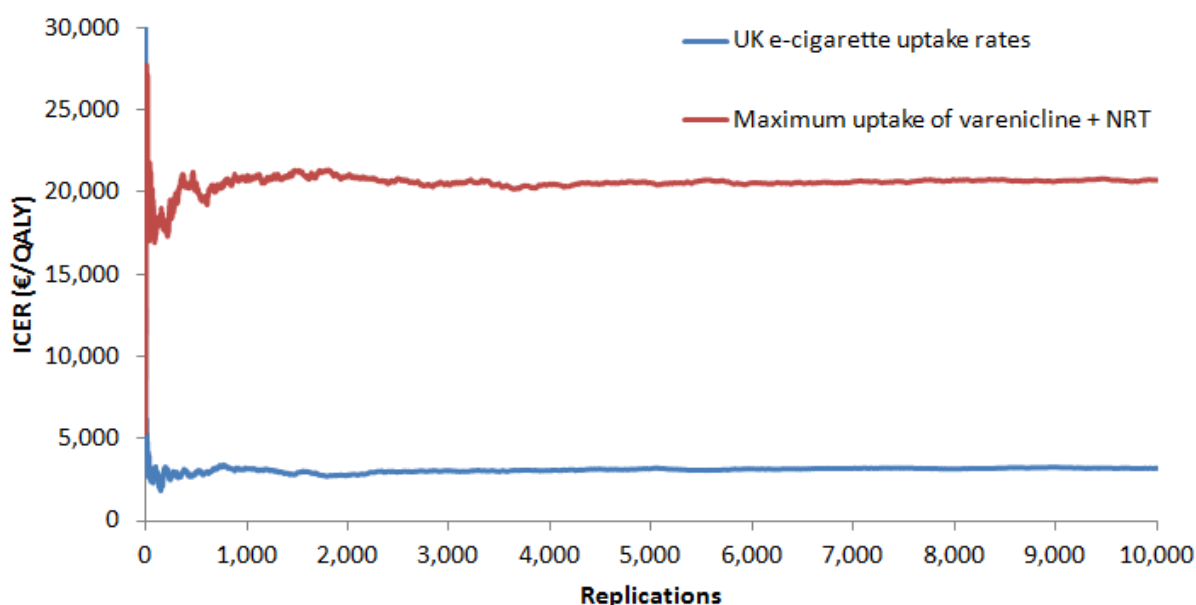
**Table 6.10 Comparators used in the analysis of the cost-effectiveness of alternatives to current practice for smoking cessation**

	Current practice in Ireland (95%CI)	Current uptake rates in England (95%CI)	Varenicline and NRT used in all receiving support (95%CI)	Varenicline and NRT used in all receiving support and 10% not receiving support (95%CI)
Unassisted quitting	51.1% (41.3 to 60.9)	40.0% (30.7 to 49.7)	51.1% (41.4 to 60.9)	51.1% (43.5 to 63.1)
E-cigarettes	26.3% (18.2 to 35.1)	45.0% (35.1 to 54.5)	26.3% (18.2 to 35.5)	23.7% (16.0 to 32.7)
Single NRT	9.5% (3.8 to 15.2)	5.9% (2.2 to 11)	9.5% (4.6 to 15.9)	8.6% (4.0 to 14.7)
Combination NRT	4.7% (4.7 to 15.9)	2.9% (0.6 to 6.9)	4.7% (1.5 to 9.7)	4.2% (1.2 to 8.9)
Varenicline	2.9% (1.5 to 9.5)	1.8% (0.2 to 5.4)	0.0% (0 to 0)	0.0% (0 to 0)
Behavioural Support	2.4% (0.6 to 6.8)	2.4% (0.4 to 6.1)	0.0% (0 to 0)	0.0% (0 to 0)
Single NRT with support	0.8% (0.4 to 6.2)	0.5% (0 to 2.5)	0.0% (0 to 0)	0.0% (0 to 0)
E-cigarette with support	0.7% (0 to 3.1)	0.4% (0 to 2.3)	0.0% (0 to 0)	0.0% (0 to 0)
NRT and Varenicline	0.8% (0 to 3.2)	0.5% (0 to 2.5)	8.4% (3.8 to 14.4)	12.5% (7.2 to 20.3)
Combination NRT with support	0.4% (0 to 2.3)	0.2% (0 to 1.6)	0.0% (0 to 0)	0.0% (0 to 0)
Bupropion	0.4% (0 to 2.2)	0.2% (0 to 1.7)	0.0% (0 to 0)	0.0% (0 to 0)

### *Model convergence*

To estimate the cost-effectiveness of alternative mixes of interventions, 10,000 replications of the model were performed, with parameters sampled from their range of plausible values in each replication. Figure 6.29 shows that stable ICER estimates were achieved after about 4,000 replications. This indicates that 10,000 replications were sufficient to obtain stable results from the probabilistic analysis.

**Figure 6.29 Convergence of ICER estimates for the comparison of individual interventions (QALY outcomes)**



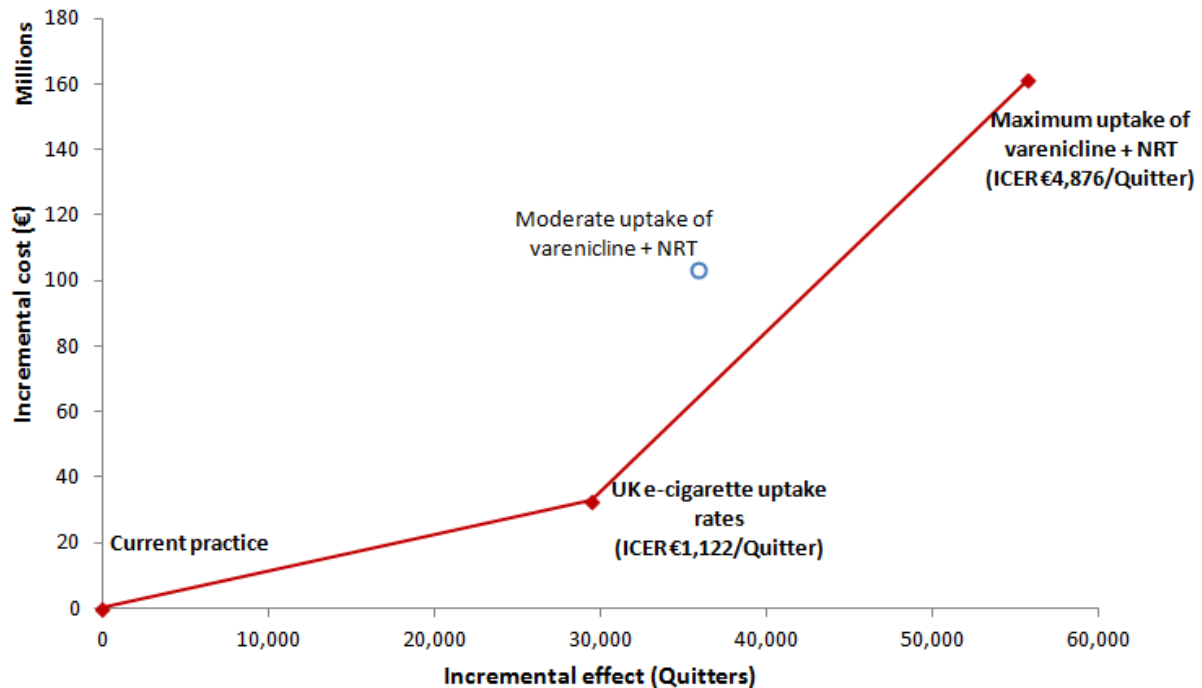
### Quitting outcomes

The incremental costs and effects over a 20-year time horizon of changes to the existing standard of care are shown in Table 6.11 and Figure 6.30. These show that an increased number of successful quitters would be expected if uptake rates of smoking cessation therapies matched those of England, which are characterised by higher uptake rates of e-cigarettes and a lower proportion of unassisted quit attempts. Outcomes would be improved still further if the uptake rate of combination varenicline and NRT was increased, even if the proportion of people opting not to use any form of support did not change.

**Table 6.11 Incremental costs and benefits of non-dominated strategies for comparison of current standard of care to alternative mixes of interventions (quitting outcomes)**

Strategy	Cost (€ million)	Incremental Cost (€ million)	Effect (Quitters)	Incremental Effect (Quitters)	ICER €/Quitter
Ireland current practice	608.85	0	570,683	0	-
Intervention mix in England	641.85	33.00	600,091	29,408	1,122
Maximum use of varenicline + NRT	770.15	128.29	626,402	26,311	4,876

**Figure 6.30 Cost-effectiveness plane for comparison of current standard of care to alternative mixes of interventions (quitting outcomes)**



#### *QALY outcomes*

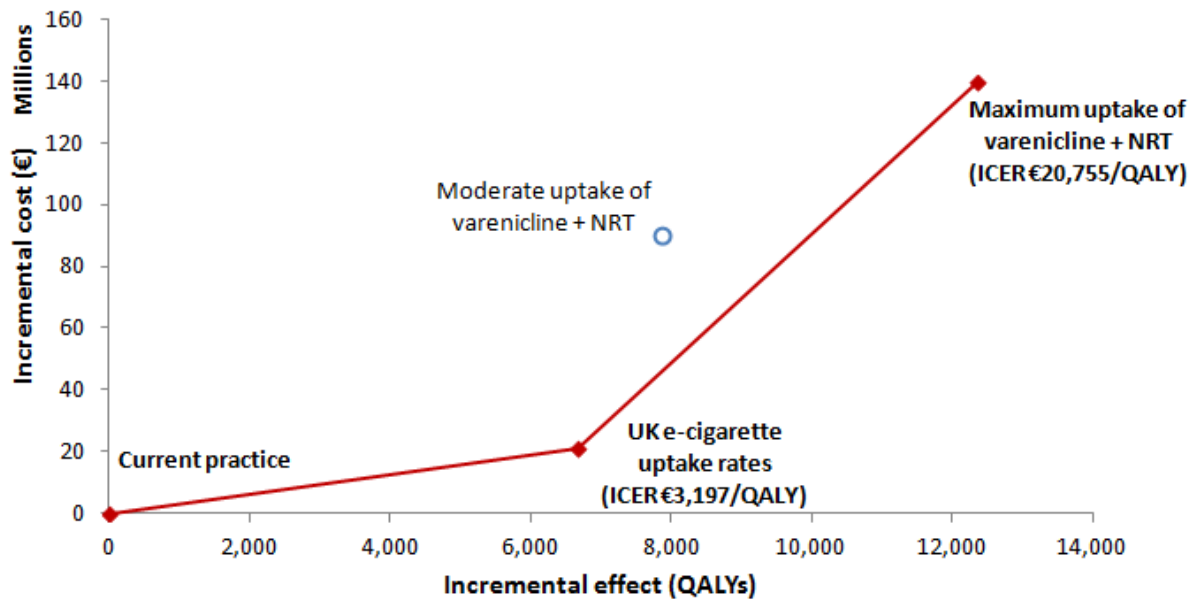
The impact of changes to the existing standard of care on QALY outcomes are shown in Table 6.12 and Figure 6.31. Again, these show that if uptake rates of smoking cessation interventions in Ireland were to follow those currently observed in England, or if the use of varenicline in combination with NRT were to increase, increases in both utility outcomes and costs could be achieved. The cost per additional QALY generated (ICER) for each of these alternatives is relatively low, so both would be considered highly cost-effective using conventional willingness-to-pay thresholds in Ireland.

**Table 6.12 Incremental costs and benefits of non-dominated strategies for comparison of current standard of care to alternative mixes of interventions (QALY outcomes)**

Strategy	Cost (€ million)	Incremental Cost (€ million)	Effect (QALY)	Incremental Effect (QALY)	ICER €/QALY
Ireland current practice	2,372.26	0	11,225,349	0	-
Intervention mix in England	2,393.55	21.29	11,232,008	6,658	3,197
Maximum use of varenicline + NRT	2,511.67	118.12	11,237,699	5,691	20,755

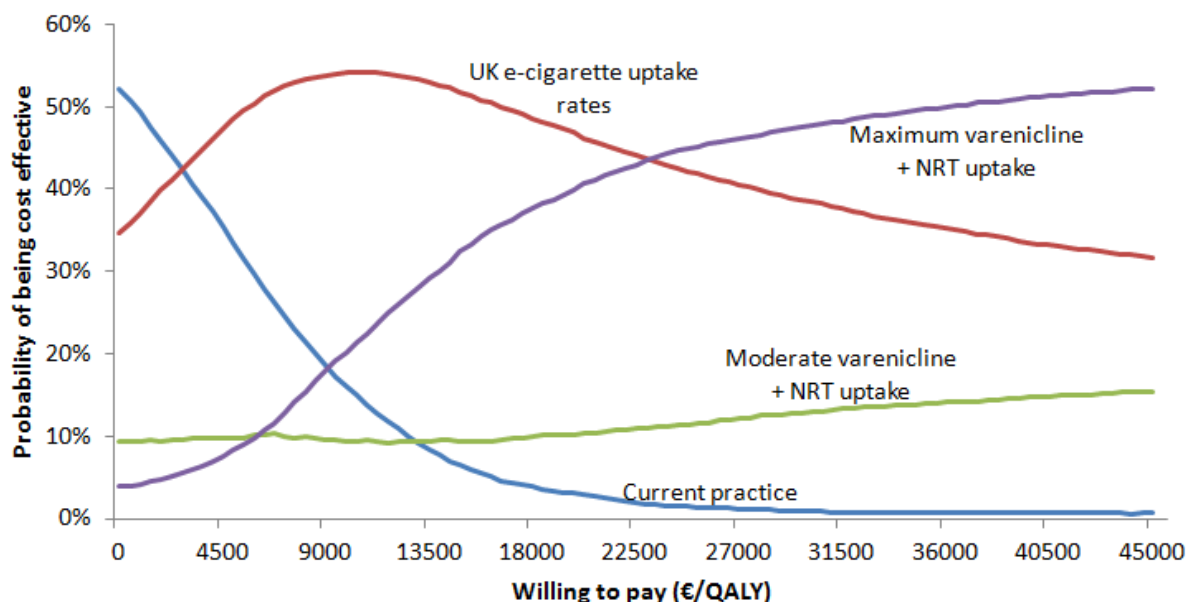


**Figure 6.31 Cost-effectiveness plane for comparison of current standard of care to alternatives (QALY outcomes)**



The relatively high degree of uncertainty around these ICER estimates is shown in a cost effectiveness acceptability curve (CEAC) in Figure 6.32.

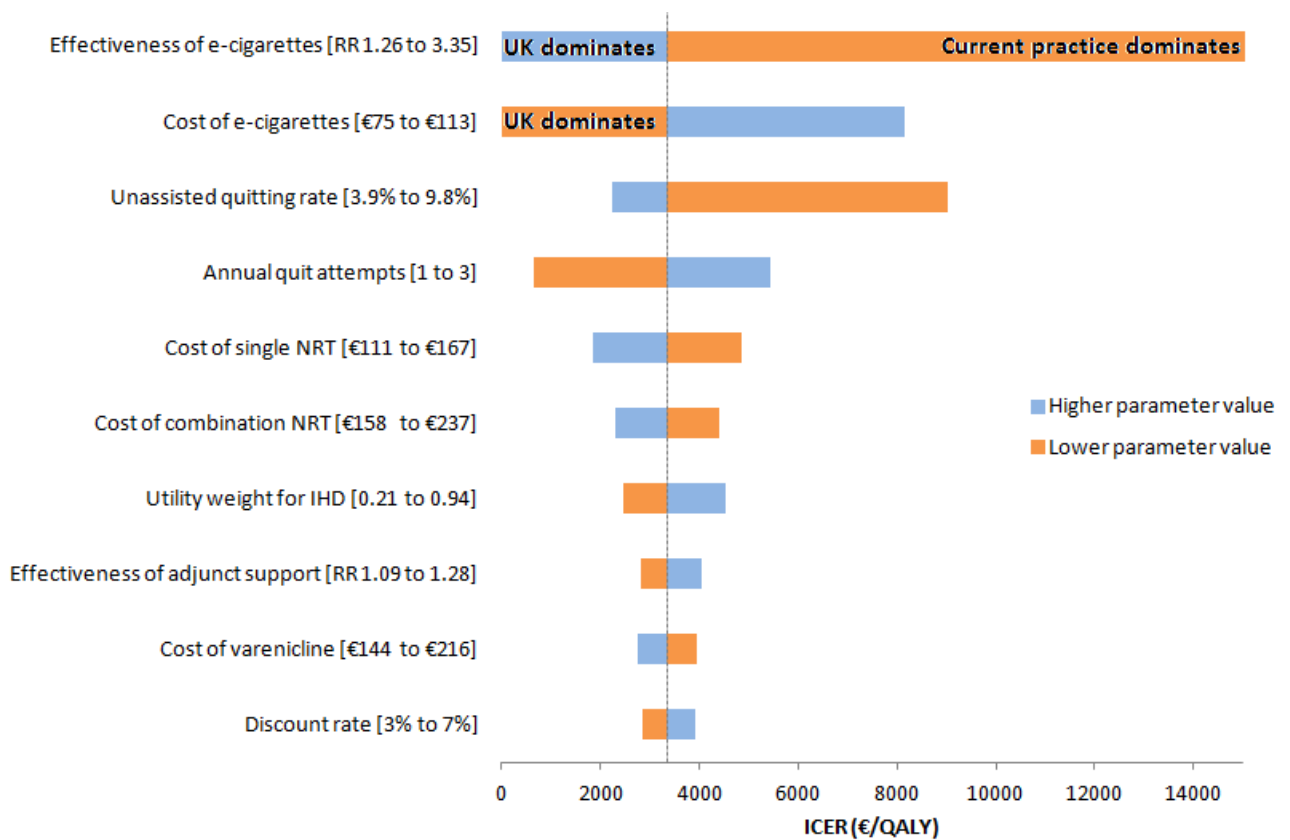
**Figure 6.32 Cost-effectiveness acceptability curve for comparison of existing standard of care to alternative mixes of interventions (QALY outcomes)**



Univariate sensitivity analysis of the comparison between the mix of interventions currently in use in Ireland, and one where e-cigarette use reaches levels currently observed in England, shows that uncertainty around the clinical effectiveness of e-cigarettes is a key driver. If the relative effect of e-cigarettes on quitting outcomes is

at its lower bound, then the current standard of care in Ireland dominates, but is dominated at its upper bound (Figure 6.33). For the results comparing the current standard of care in Ireland with a scenario characterised by maximum uptake of varenicline in combination with NRT, the effectiveness of the combination therapy is again the most influential parameter: the ICER for a comparator in which use of combination varenicline and NRT is maximised remains below conventional willingness-to-pay thresholds when the effectiveness estimate is held at its lower bound (Figure 6.34).

**Figure 6.33 Univariate sensitivity analysis for the comparison of the current standard of care to uptake rates of smoking cessation interventions in England (QALY outcomes)**



**Figure 6.34 Univariate sensitivity analysis for the comparison of the current standard of care to increased use of varenicline and NRT (varenicline and NRT used in all receiving support and 10% not receiving support, QALY outcomes)**



## 6.4 Budget impact analysis

A budget impact analysis (BIA) was carried out to estimate the total additional expenditure associated with changes to the mix of interventions used for smoking cessation in Ireland over the next five years. This analysis only includes direct costs of smoking cessation interventions for those with a Medical Card, for whom the provision of varenicline, bupropion and NRT is funded by the public health service, taking account of the fact that some people may not complete a full course of treatment. A scenario analysis estimates the total cost associated with a decision to fund a 12-week course of e-cigarettes in the same way. Costs used in the BIA include value-added tax (VAT) at 23%, where applicable.<sup>(854)</sup> The primary analysis assumes that 100% of smokers with a Medical Card who are attempting to quit using NRT will visit a GP in order to obtain a prescription, so that they can obtain a **month's supply for a prescription fee of €2.50. Unlike varenicline and bupropion,** there are restrictions as to how NRT can be prescribed and dispensed on the General Medical Scheme (GMS). The initial quantity of NRT prescribed for a patient is limited to a two-week supply in order to evaluate the effectiveness of the therapy, with further supplies dispensed in monthly aliquots.<sup>(855)</sup> The cost of a GP consultation is not included in the budget impact analysis as GPs are paid for GMS consultations through a capitation fee. Hence an increase in GMS GP consultations that is not associated with fee per item care will not result in an increased budget impact for the HSE. Neither does it include costs associated with any prospective increase in the provision of face to face behavioural interventions, due to uncertainty about the scale of any such increase, if any, that would be required as part of an overall strategy to increase smoking quit attempt rates, improve uptake of the most effective smoking cessation interventions and prevent relapse. However, displaced GP care is considered in terms of the number of additional consultations for different mixes of interventions. The additional demand that changes to the uptake of smoking cessation interventions may place on GP or nurse prescriber services is covered in Chapter 7.

Also, unlike varenicline and bupropion, NRT is freely available over-the-counter in any retail outlet, so it is unlikely that all Medical Card holders wishing to use NRT in their quit attempt will choose to obtain it through the GMS and instead pay for it out of pocket. Comparing the most recent data on the total cost of NRT medication funded through the PCRS with the full cost of NRT use among smokers with a Medical Card per Healthy Ireland survey data on usage rates, it would appear that approximately two thirds of the cost of NRT use is paid for through the GMS.<sup>(61, 829)</sup>

Table 6.13 compares the expected budget impact in year one of the analysis with the actual expenditure reported by 2015 PCRS report.<sup>(829)</sup> The budget impact analysis does not include the costs of smoking cessation interventions funded

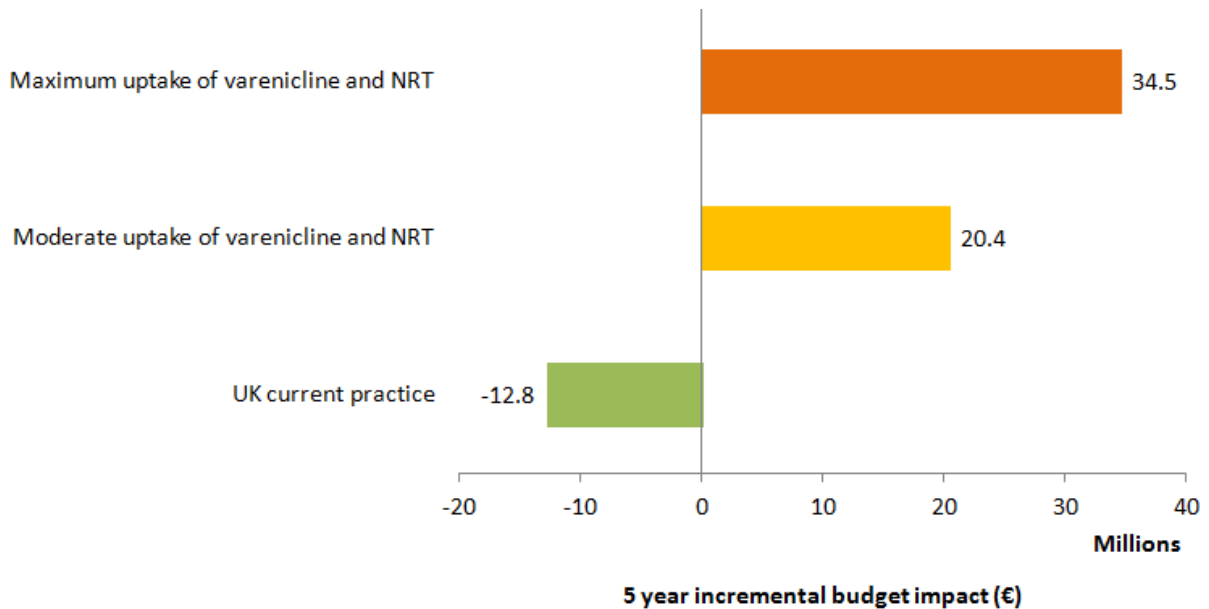
through the Drugs Payment Scheme (DPS).<sup>(856)</sup> Under the DPS scheme, the total monthly combined cost to an individual or family for approved prescribed drugs is **capped at €144 each month. While none of the smoking cessation interventions** exceed this monthly cap, it is likely that the addition of these medications will raise some **smokers' monthly expenditure above €144, which will then** impose additional costs on the health service. This does not apply in the case of NRT, as it is not covered under the DPS scheme.<sup>(855)</sup> Accurate estimates of the likely increase in DPS payments as a result of changes to routine practice for smoking cessation are difficult to predict, as they require knowledge of all other prescription medications being paid for by smokers without a Medical Card. Total DPS expenditure on varenicline (ingredient cost, excluding patient co-payments) **has declined from €1.77 million in 2009 to less than €270,000 in 2015.**

**Table 6.13 Comparison of modelled and actual total GMS expenditure on smoking cessation therapies in 2015**

Treatment	Modelled expenditure based on 2015 data (€)	Actual expenditure in 2015 (€)	% Difference (absolute difference as a percentage of actual expenditure in 2015)
Varenicline	1,843,833	1,783,575	3.4%
Bupropion	147,812	160,000	7.6%
NRT with 65% GMS reimbursement	5,141,612	4,951,645	3.8%

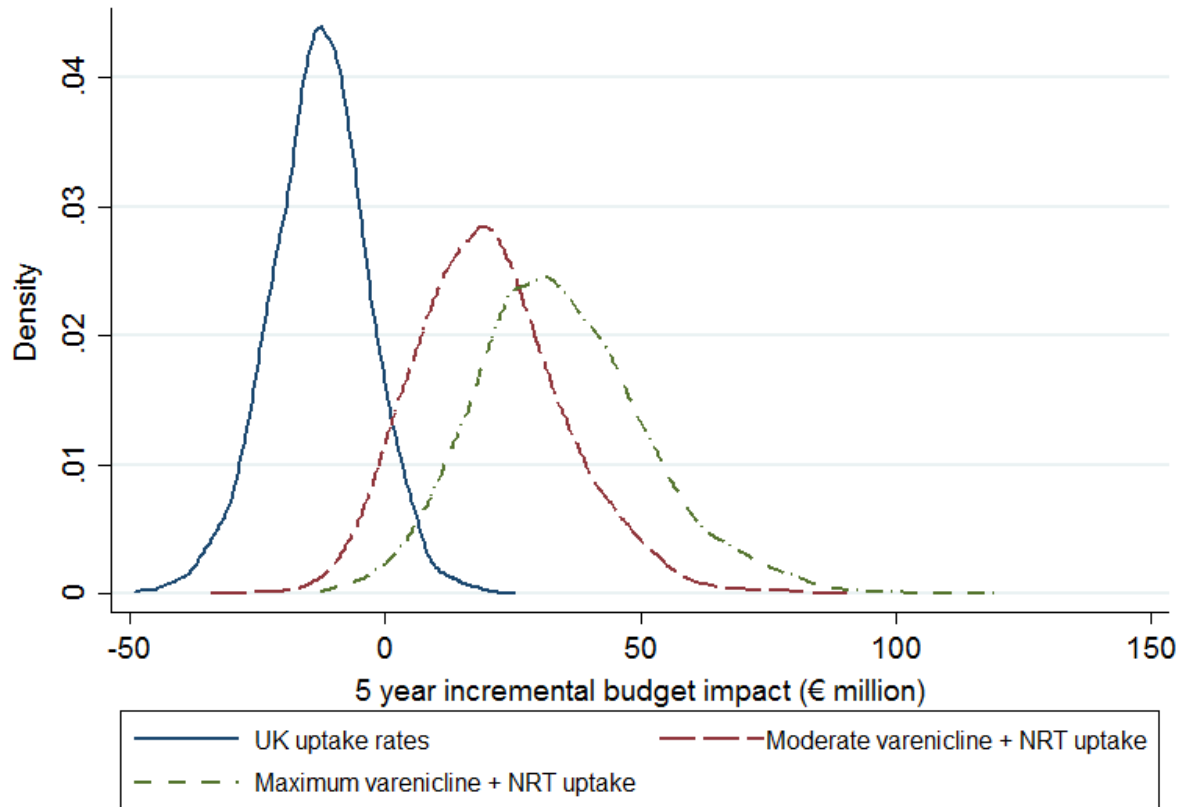
The anticipated differences in total expenditure on each of the smoking cessation therapies currently funded through the GMS was calculated for each alternative standard of care assessed in the economic evaluation. This took account of the relative reduction in the number of smokers (and therefore quit attempts) within populations in which a more effective mix of interventions is used. Figure 6.35 shows the five-year incremental budget impact for each of the alternative standards of care included in the economic analysis.

**Figure 6.35 Five-year incremental budget impact associated with the provision of GMS-funded pharmacological smoking cessation therapies in each of the modelled comparators, compared with current practice in Ireland**



The figures presented in Figure 6.35 are point estimates. To show the level of variability associated with each comparator, kernel density plots for the incremental costs for each are provided in Figure 6.36.

**Figure 6.36 Variability in the five-year incremental budget impact associated with the provision of GMS-funded pharmacological smoking cessation therapies in each of the modelled comparators, compared with current practice in Ireland**

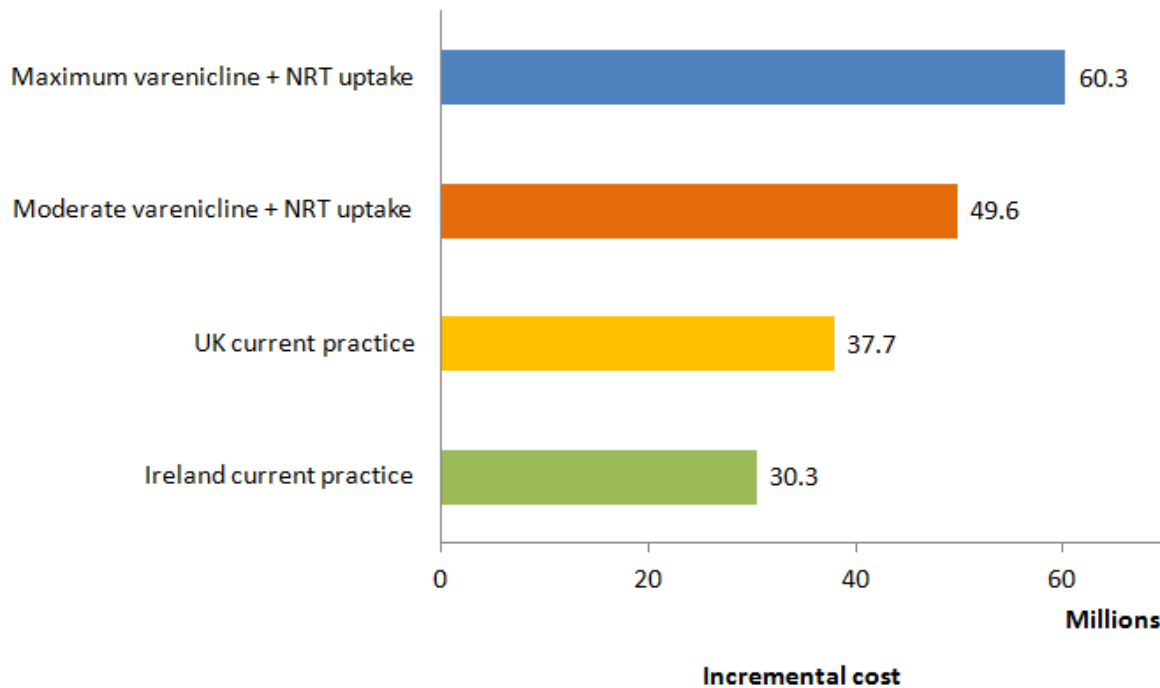


The results show that if the use of combination varenicline and NRT treatment is maximised (to 13%), it would increase the total annual cost of funding pharmacological smoking cessation interventions in Ireland **by approximately €7 million**. A more moderate increase in the use of this treatment option (to 8%) would **be associated with an incremental cost of €4 million per annum**. For both of these options, the incremental costs would decline over time as the increased effectiveness will be reflected in a lower smoking prevalence. If the relatively high uptake rates for e-cigarette observed in England were to be replicated in Ireland, without this treatment being funded through the public health system, there would be an annual decrease in expenditure on smoking **cessation interventions of around €2.6million**. The organisational implications of prospective changes in the uptake of different smoking cessation interventions, including their effect on the demand for GP or nurse prescriber consultations, is examined in section 7.2.1.2.

Alternatively, if e-cigarettes were funded in the same way as NRT, resulting in an equivalent percentage of the total cost of e-cigarette use (as a short-term aid to quitting) falling on the public health service, this would be associated with an

increase in the total cost of funding smoking cessation interventions of about €6 million per annum (Figure 6.37). If e-cigarette use rose to levels currently observed in England (45% of all those attempting to quit), the additional cost over the next five years would be in the region of €7.5 million per annum over the next five years.

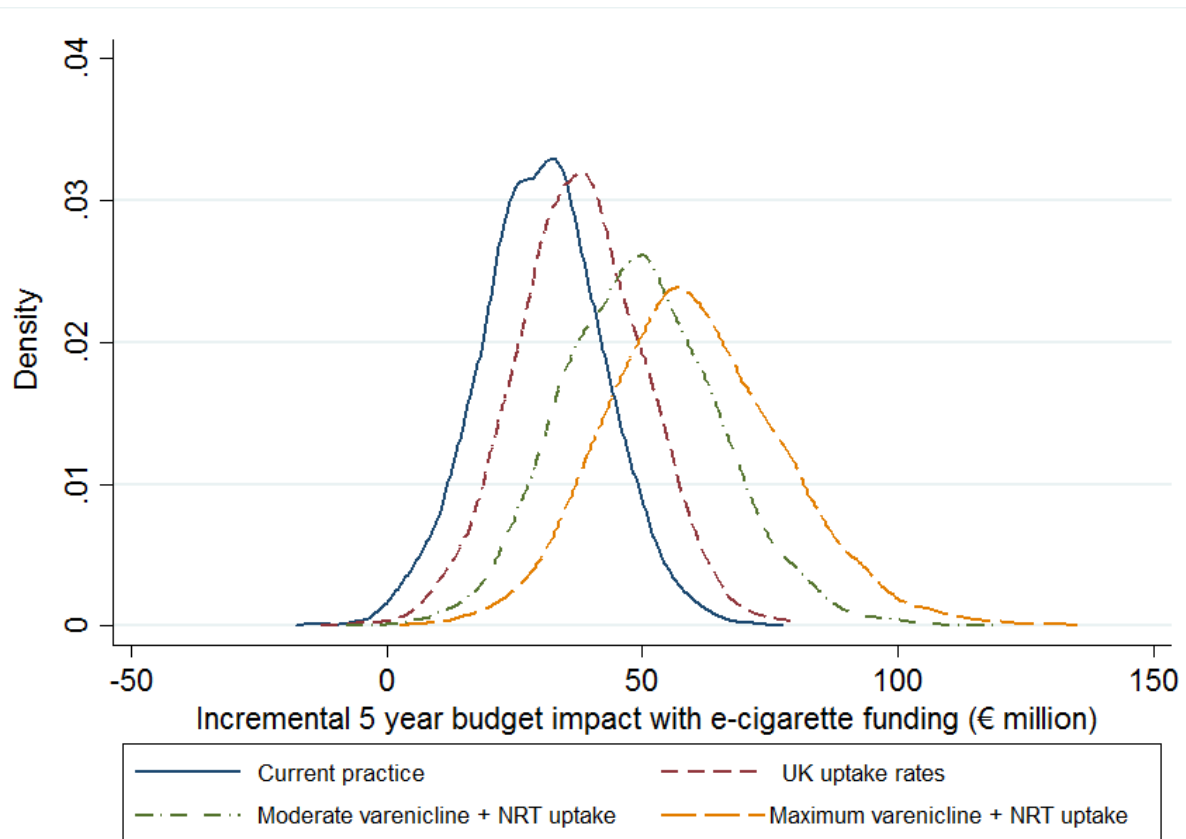
**Figure 6.37 Total five-year incremental budget impact of each comparator with reimbursement of e-cigarettes (compared to current practice with no e-cigarette reimbursement)**



The figures presented in Figure 6.37 are point estimates. To show the level of variability associated with each comparator, kernel density plots for the incremental costs for each are provided in Figure 6.38.



**Figure 6.38 Variability in the five-year incremental budget impact associated with the provision of GMS-funded smoking cessation therapies in each of the modelled comparators, compared with current practice in Ireland**



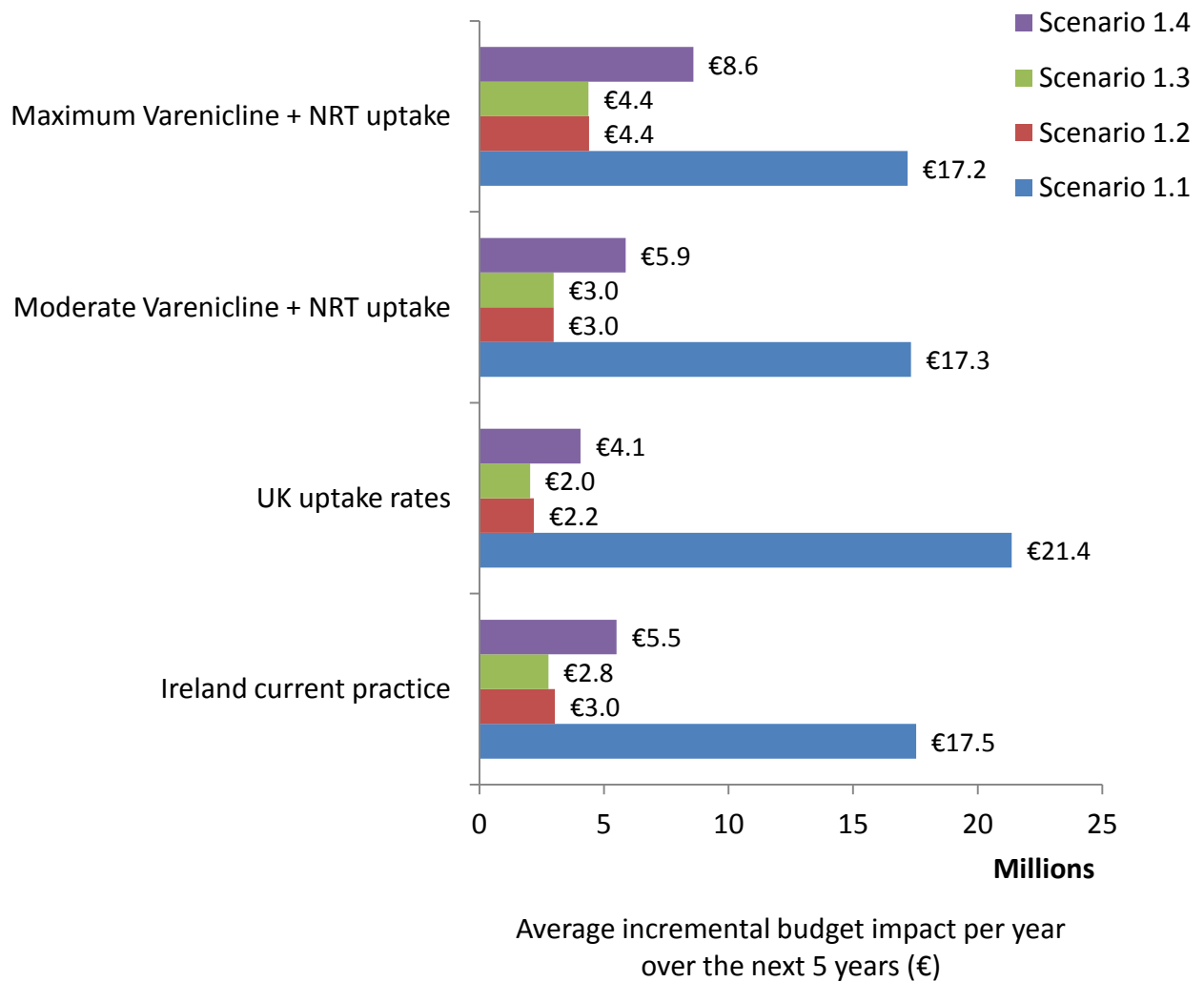
Following discussions with members of the Expert Advisory Group, a number of additional budget impact scenario analyses were identified as beneficial for policy-makers considering the different options in regard to changing the current mix of smoking cessation interventions used in Ireland. These included a scenario in which the HSE would fund two GP visits for smokers who were not eligible for free GP care, and funding being provided for non-medical card holders using varenicline, or varenicline in combination with NRT, to help them quit. These are presented below, using a number of different assumptions regarding coverage.

Scenario 1: 100% uptake of two HSE-funded GP visits (@€50 per visit) among:

- 1.1 all quitters without a medical card or GP visit card
- 1.2 all quitters without a medical card or GP visit card making a supported quit attempt with any intervention
- 1.3 all quitters without a medical card or GP visit card making a supported quit attempt with any intervention except e-cigarettes
- 1.4 the proportion of people making a supported quit attempt using any intervention except e-cigarettes doubles, and there is 100% uptake

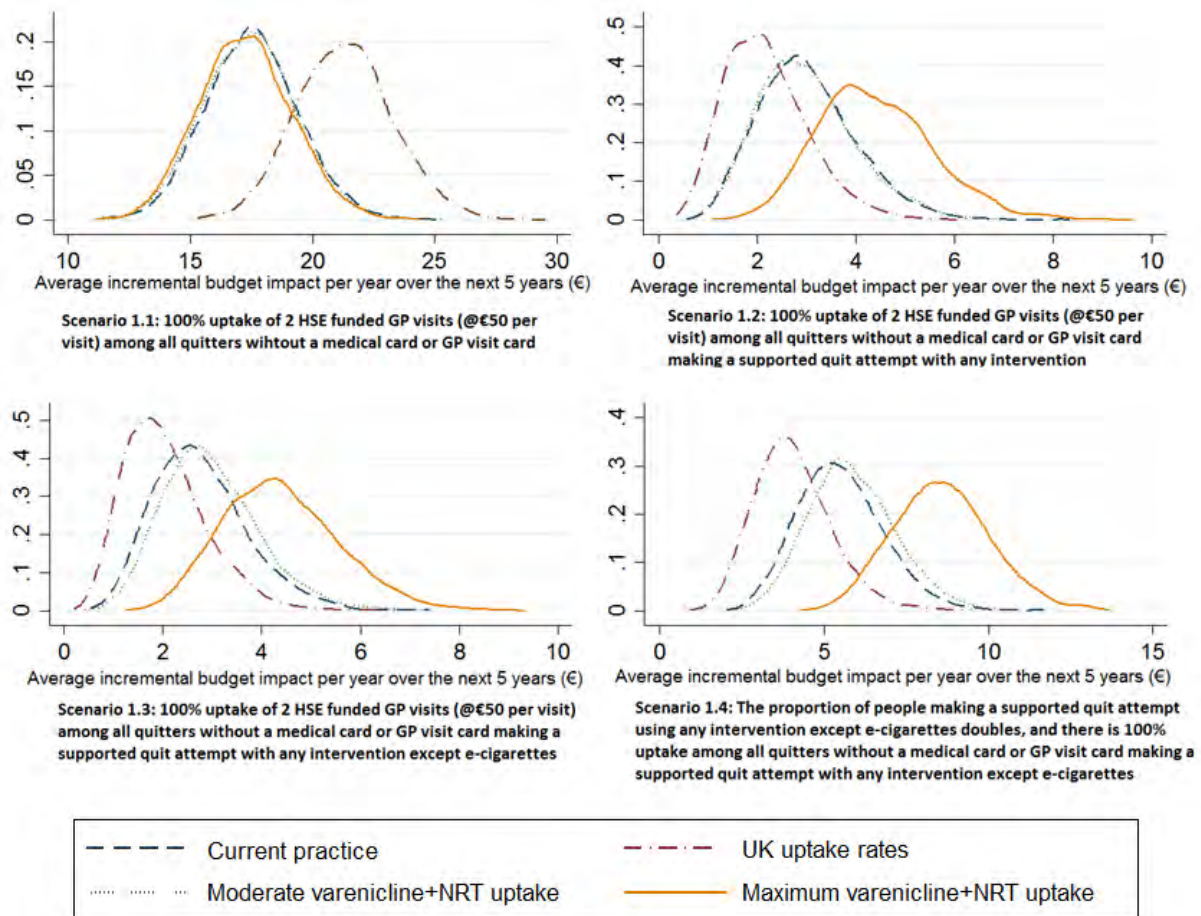
among all quitters without a medical card or GP visit card making a supported quit attempt with any intervention except e-cigarettes.

**Figure 6.39 Average annual incremental budget impact over five years for each comparator for each of the scenarios involving two HSE funded GP visits for those not eligible for free GP care (see numbered list above)**



The figures presented in Figure 6.39 are point estimates. To show the level of variability associated with each comparator, kernel density plots for the incremental costs for scenarios 1.1 to 1.4 are provided in Figure 6.40.

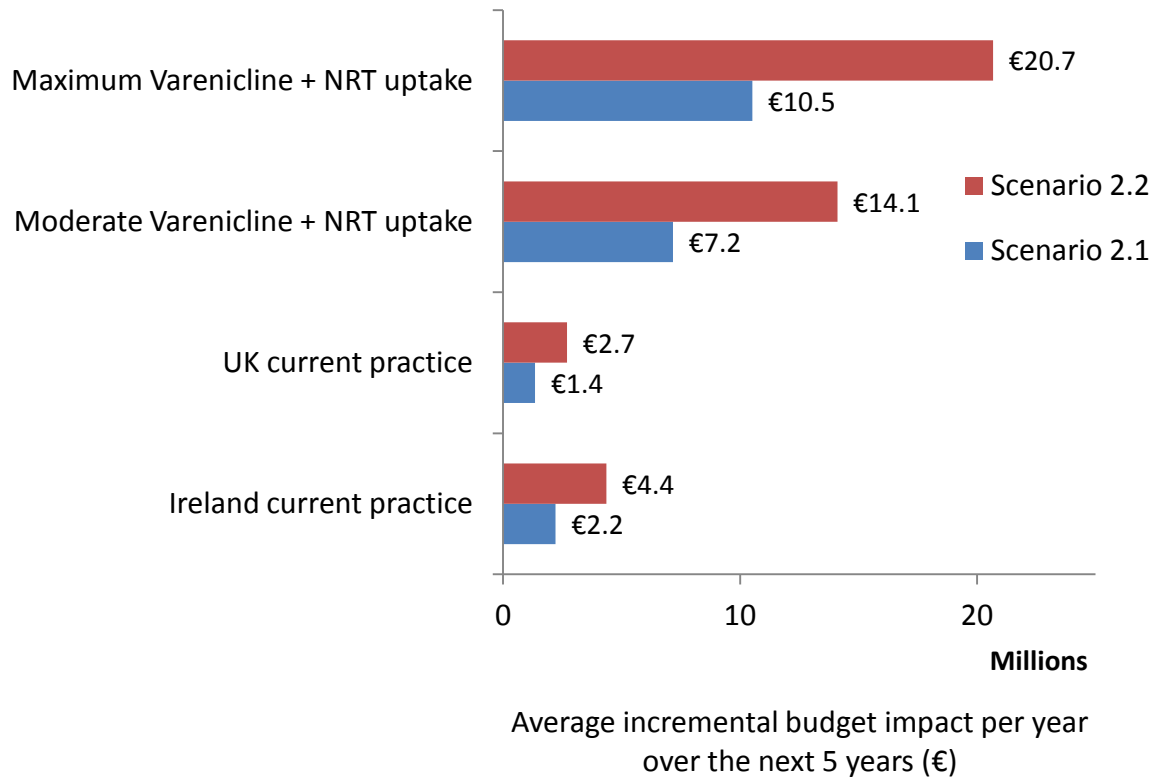
**Figure 6.40 Variability in the average annual incremental budget impact over 5 years for each of the scenarios involving two HSE funded GP visits for those not eligible for free GP care**



Scenario 2: Comparison of the additional costs of the HSE fully funding varenicline, and varenicline in combination with NRT for:

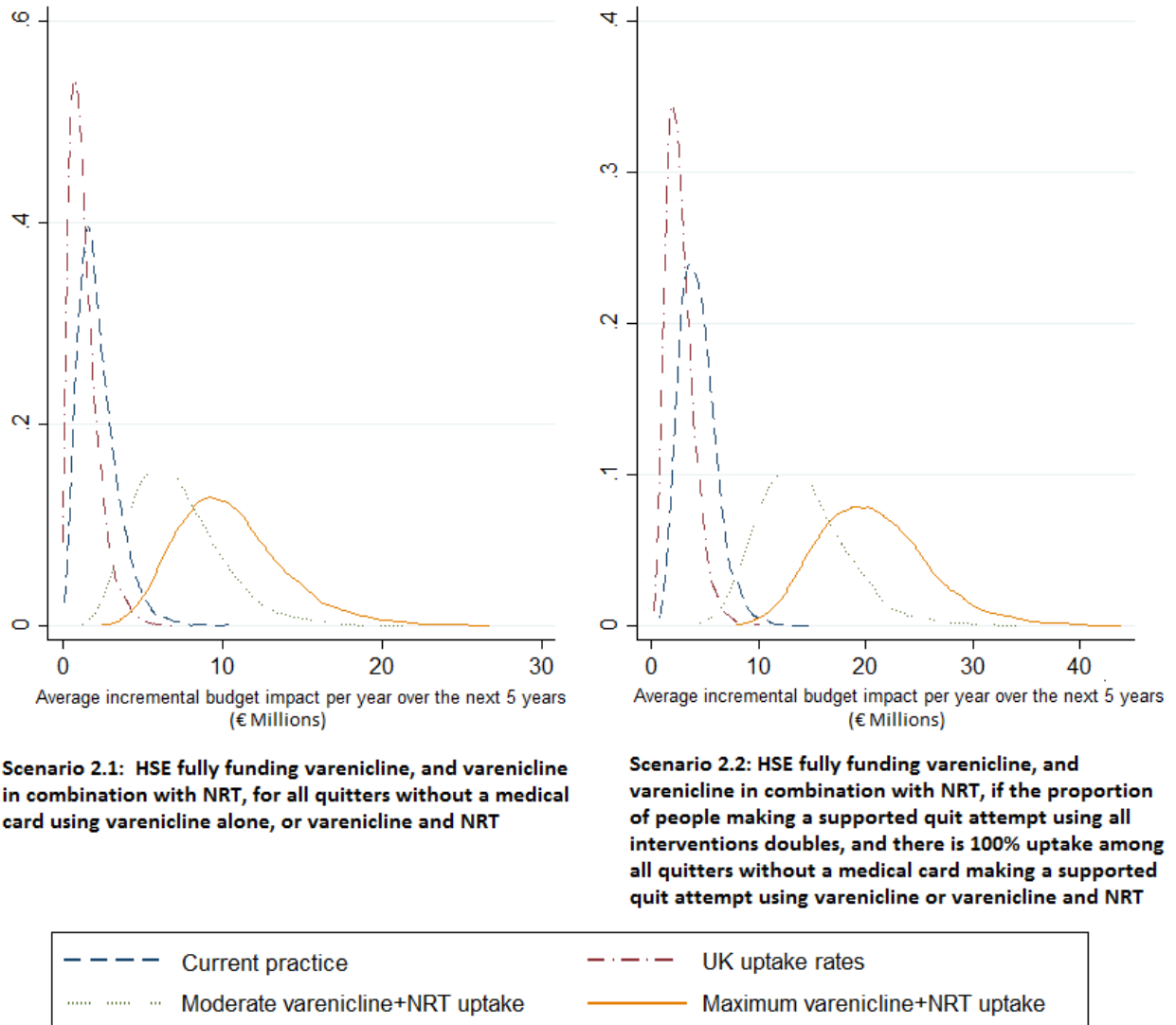
- 2.1 all quitters without a medical card using varenicline alone, or varenicline and NRT
- 2.2 the proportion of people making a supported quit attempt using all interventions doubles, and there is 100% uptake among all quitters without a medical card making a supported quit attempt using varenicline or varenicline and NRT.

**Figure 6.41 Average annual incremental budget impact over five years for each comparator for each of the scenarios involving HSE funding for varenicline and varenicline in combination with NRT for those without a medical card (see numbered list above)**



The figures presented in Figure 6.41 are point estimates. To show the level of variability associated with each comparator, kernel density plots for the incremental costs for scenarios 2.1 to 2.2 are provided in Figure 6.42.

**Figure 6.42 Variability in the average annual incremental budget impact over five years for each of the scenarios involving HSE funding for varenicline and varenicline in combination with NRT for those without a medical card**



## 6.5 Discussion

Based on the results of the cost-effectiveness analysis, all smoking cessation interventions evaluated in the economic model are cost-effective compared with unassisted quitting. E-cigarettes are the single most cost-effective option, but this result is extremely sensitive to changes to the clinical effectiveness and cost estimates used. Both of these parameters are associated with a high degree of uncertainty due to the relatively low number of available RCTs, and variability in the costs of e-cigarette products, which may change over time as a result of technical innovation, or increased regulation or taxation. The most cost-effective strategy at willingness-to-pay thresholds routinely used in Ireland is combination varenicline and NRT treatment, which is associated with a cost per additional quality-adjusted life year (QALY) **gained of €7,025** compared to the next best option (varenicline monotherapy).

Knowing the relative cost-effectiveness of individual smoking cessation therapies is only beneficial insofar as it informs efforts to change the current mix of interventions in order to maximise the uptake of those that represent the best value for money. To examine this, an analysis of prospective changes to the current standard of care in Ireland was carried out, using international data to estimate plausible maximum uptake rates of the most cost-effective treatments. The results of this analysis found that at conventional willingness-to-pay thresholds in Ireland, the optimal strategy is to maximise the use of the most effective treatment (combination varenicline and **NRT, ICER €20,755/QALY**). If the use of e-cigarettes increased to the levels currently reported in England, an increase in the average number of successful quit attempts would also be expected compared to current practice, at a lower cost per **QALY gained (ICER €3,197/QALY)**.

There are a number of items to be considered when interpreting these results. The analysis only included four smoking-related illnesses (stroke, IHD, COPD, and lung cancer). Given the multitude of other diseases that are linked with smoking, the utility gain from smoking cessation used in the model is likely to be an underestimate. The inclusion of other smoking-related illnesses would tend to make cessation treatments even more cost-effective. Similarly, this analysis does not include the full costs of treatment for each of the four diseases due to a lack of available data. The inclusion of additional costs would again tend to make cessation interventions more cost-effective.

The utility estimates used in the model are based on differences in disease prevalence among current and former smokers. These are applied at a population level to estimate the change in the absolute number of cases in each comparator, **rather than modelling a smoker's risk of developing these diseases based on** smoking history, age, time since quitting, and other important factors that contribute

**to an individual's risk profile. While this would reflect a truer picture of the** consequences of smoking cessation, insufficient data are available to carry out this sort of detailed analysis with a reasonable degree of validity.

The analysis also does not take account of multi-morbidity; for example, the costs and utility loss associated with a current or former smoker who has both COPD and ischaemic heart disease is calculated as the full cost and full utility loss associated with both diseases. While this approximation is adequate for the purposes of comparing across comparators in which the same assumption applies, the actual costs and utility loss from having multiple concurrent diseases is unlikely to be additive. Finally, unlike some previous analyses, there is no disutility associated with smoking for those without a smoking-related illness. Inclusion of any such disutility would again tend to result in lower ICER estimates; making smoking cessation interventions more cost-effective.

The clinical effectiveness estimates for each of the individual therapies are based on a network meta-analysis of the available evidence, as outlined in Chapter 4. These are applied to the absolute quit rate for unassisted quitting to provide an estimate of the absolute quit rates for each intervention. The unassisted quit rate is therefore of key importance in the analysis. The central estimate was taken from a pooled analysis of quit rates in the control arms of studies with no or minimal intervention that reported 12-month follow up. Different quit rates are obtained when pooling data from all control arms, or when limiting to studies reporting continuous abstinence (see Table 6.3). To ensure that the data used were consistent with the relative effect size estimates for each of the interventions, the central estimate was used, with the extreme upper and lower bounds observed across all three estimates of the quit rate in the control arms used to capture the uncertainty associated with this parameter.

An additional difficulty in modelling the unassisted quit rate derives from the possibility that unassisted quit rates in a real life setting may be higher than those observed in clinical trials, due to self-selection. This would occur if smokers that are more likely to successfully quit, perhaps as a result of being less addicted, more motivated, and so on, are more likely to try unassisted quitting. Of note is a recent observational study of quit rates in the US, which found that in the majority of states (84%) unassisted quit rates were higher than assisted quit rates.<sup>(857)</sup> If a proportion of those who choose unassisted quitting do not stand to gain as much from switching to a pharmacological intervention as the model assumes, then any scenario that models a significant reduction in unassisted quit rates is of questionable validity. However, this analysis minimises this risk by ensuring that all comparators involving a reduction in unassisted quit rates are based on observed data in other countries, thus ensuring that quitting preferences are not set at

unrealistic levels, as long as the reference population can be considered comparable to Ireland.

This HTA aims to inform policy objectives in regard to the uptake rate of different therapies. However, the degree to which HSE smoking cessation services can influence overall population uptake rates is difficult to judge, particularly in light of the major changes in the uptake rate of e-cigarettes in the absence of any desire to promote their use by smoking cessation practitioners. As this analysis is based on 2015 data, there is also the possibility that other shifts in the use of particular interventions may occur in the coming years that would diminish the relevance of the results.

Of particular importance will be the results of ongoing studies on the effectiveness of e-cigarettes as a cessation intervention. These are likely to change the current estimates for this parameter and may significantly affect the results of this HTA. These issues will need to be considered by decision-makers when interpreting these results and how they can be used to inform prospective policy initiatives. However, the overall results of the analysis show that in the context of the wider health service, smoking cessation interventions are highly cost-effective, and that any attempt to increase the use of effective smoking cessation strategies among smokers wishing to quit is likely to represent good value for money.

The results of the budget impact analysis on the likely changes in expenditure on smoking cessation therapies show that efforts to maximise the use of the most effective treatment (combination varenicline and NRT) would be associated with **increased costs of up to €7 million per year**. However, this would correspond with an increase in the uptake rate of varenicline from 3.7% to 12.5%, and whether such a substantial increase can be brought about in practice is questionable. If the use of e-cigarettes in Ireland rose to levels currently observed in England (with corresponding decreases in the use of alternative smoking cessation interventions) then the cost of funding smoking cessation interventions would be expected to decrease by about **€2.6 million annually, as a result of shifting the costs back onto the individual**.

Alternatively, if e-cigarettes were funded in the same way as NRT, where about 65% of the estimated total use among Medical Card holders is reimbursed by the state, the costs of the provision of smoking cessation interventions through the **General Medical Scheme would increase by €6 million annually at current** use rates, and by **approximately €7.5 million** at use rates equivalent to those reported in the latest English data.



## 6.6 Key Points

- No previous cost-effectiveness analyses comparing alternative mixes of smoking cessation interventions with an existing standard of care were identified in a systematic review of the literature.
- A number of published studies have evaluated the cost-effectiveness of individual smoking cessation therapies compared with unassisted quitting or another intervention. The results of these studies indicate that cessation interventions tend to be highly cost-effective, with varenicline generally emerging as the most cost-effective alternative. However, none of these studies included newer treatment options such as e-cigarettes, or combination therapy with varenicline and either NRT or bupropion.
- A cost-effectiveness analysis comparing individual therapies in an Irish setting found that all would be considered cost-effective compared with unassisted quitting, with e-cigarettes and varenicline, either alone or in combination with NRT, being the most cost-effective strategies when individual therapies are compared with each other.
- The results for e-cigarettes are extremely sensitive to changes in the estimated cost and effects of this intervention. This is of particular significance given the high degree of uncertainty that exists in relation to both of these parameters in the model. Further research is very likely to have an important impact on the results of the cost-effectiveness of this intervention.
- A comparison of alternatives to the current standard of care in Ireland was carried out, using international data as an indicator of plausible changes in the use of the most cost-effective cessation interventions. This included a scenario where combination varenicline and NRT use was maximised, as well as a scenario where e-cigarette uptake reached levels recently reported in England.
- This analysis found that maximising the uptake of combined varenicline and NRT therapy **is the optimal strategy (ICER €20,755/QALY)**, but it is unclear to what extent policy initiatives can influence overall smoking cessation preferences, particularly in light of the high degree of penetration e-cigarettes have achieved in the absence of any explicit endorsement by quit services in Ireland.
- Based on the limited available evidence, continuing increases in the uptake of e-cigarettes are likely to improve the cost-effectiveness of the overall mix of cessation interventions in Ireland, by increasing the average number of successful quit attempts at an acceptable cost (ICER €3,197/QALY at uptake rates of 45% currently reported in England).
- Increasing the smoking cessation budget to promote the use of varenicline-based regimens, and combination NRT therapy for those for whom varenicline is not suitable, would be a cost-effective use of resources.
- A budget impact analysis on the incremental cost associated with changes to the existing standard of care found that maximising the use of

combination varenicline and NRT would be associated with an average **increase of approximately €7 million** in the annual cost of providing pharmacological smoking cessation interventions in Ireland.

- A scenario analysis in which uptake rates of e-cigarettes are comparable to England (while still not being reimbursed through the General Medical Scheme) found that this would result in a decrease in expenditure on **smoking cessation interventions of approximately €2.6 million per annum**. Alternatively, if e-cigarettes were to be funded to the same extent as NRT, the **additional cost to the health service would be approximately €6 million per annum at current usage rates, or €7.5 million** if this rose to usage rates currently reported in England.

## 7 Wider implications

This chapter summarises the potential issues that might arise from implementing any changes to the mix of smoking cessation interventions provided in Ireland as a result of the clinical effectiveness, safety, cost-effectiveness and budget impact evidence in this HTA. These issues are grouped into two sections:

- Section 7.1 describes the ethical, societal and legal considerations
- Section 7.2 describes the organisational issues (the current configuration of services and potential issues for the implementation of services) for each of the three populations; unselected adults in a community setting, the maternity and mental health subgroups.

### 7.1 Ethical, societal and legal considerations

#### 7.1.1 Introduction

This section discusses the relevant ethical, societal and legal considerations arising within the broader public health context, as well as in relation to some of the specific interventions detailed in this report.

#### 7.1.2 Ethical principles

Public health is concerned with promoting and protecting the health of the population. Collective interventions undertaken for the benefit of population health often involve or require government action, such as promoting a healthy diet to combat rising obesity levels or sun protection campaigns to inform citizens of skin cancer risks and so on. Collective action to promote and protect population health also occurs at the global level, such as the activities of the World Health Organization.

Broadly speaking, ethics is the science or study of the morality of human acts through the medium of natural reason.<sup>(858)</sup> Medical ethics applies general ethical principles to solve the moral problems of the medical profession. It involves analysing the concepts, assumptions, beliefs, attitudes, emotions, reasons and arguments underlying medico-moral decisions.<sup>(859)</sup> Public health ethics primarily deals with the moral foundations and justifications for public health, the various ethical challenges raised by limited resources for promoting health, and the real or perceived tensions between collective benefits and individual liberty.<sup>(860)</sup>

Many different approaches to medical ethics may be adopted. The most common **approach used in practice is known as 'principlism'**, which has been adopted by many professional bodies and associations as a framework for ethical guidance. Principlism, also known as the Four Principles approach, focuses on respect for

autonomy, beneficence, non-maleficence, and justice.<sup>(861)</sup> However, some philosophers argue that the principles of dignity, precaution, and solidarity reflect the European ethos better than the liberal concepts of autonomy, harm, and justice. They argue that these principles elevate prudence over hedonism, communality over individualism, and moral sense over pragmatism.<sup>(862)</sup>

The following sections look at what these different principles mean and how they might apply in the context of smoking cessation interventions.

#### 7.1.2.1 Respect for autonomy

The word autonomy means self-rule, or **making one's own deliberate decisions**. Respect for autonomy is of vital significance in the medical context. Patients must be consulted with and informed about their healthcare and the choices available. Doctors are required to obtain informed consent from patients before any treatment or intervention is carried out (except in cases of incapacity or medical emergency). This requires careful disclosure to patients of the risks and benefits of particular interventions or actions. Respecting autonomy also requires maintaining patient confidentiality, practising appropriate behaviour and using good.

##### *Application to smoking cessation interventions:*

Existing tobacco controls encourage prevention and smoking cessation, while also respecting adult autonomy and protecting others from the associated harms and costs. Autonomy in decision-making is the norm, despite evidence of nicotine dependence. Warning labels inform consumers, smoking laws protect third parties from passive smoking, taxes internalise the social costs of smoking, and age limits and marketing restrictions exist to protect minors.<sup>(863)</sup>

Smoking cessation intervention could take the form of either a harm-reduction strategy or a more absolutist approach. A harm-reduction strategy aims to eliminate the damaging effects of a particular behaviour, without eliminating the behaviour itself. A more absolutist approach would seek to eliminate the behaviour entirely. For example, illicit drug addiction and prostitution are perceived to be inherently wrong, and in many countries are criminally prosecuted. However, alternative harm-reduction strategies also exist such as the provision of needle exchanges and safe injection kits to injection drug users, and the use of methadone to treat opiate addiction.<sup>(864)</sup>

Although smoking is harmful to the smoker and to third parties who inhale tobacco smoke, it is not generally considered to be morally wrong and is therefore a matter of individual choice. However, the individual choice to smoke may be considered to be morally wrong where others, particularly children or young people, are exposed to the risk of harm. Public health initiatives in recent years have attempted to ensure

that individual choice is more informed by advertising campaigns and plain packaging regulations.

As such, any smoking cessation intervention must be made available in a way that continues to promote the autonomy of the individual. This can be done by providing information concerning the risks and benefits associated with the particular intervention. This may be challenging in the case of some interventions, such as e-cigarettes, as comprehensive safety evaluations cannot be made in the face of incomplete evidence, meaning the public cannot be given full information on which to base their decisions. In general, the provision of inaccurate information on comparative risk is fundamentally unethical as it fails to allow consumers to make informed choices.<sup>(864)</sup> In circumstances where the long-term health risks of an intervention, such as e-cigarettes, are not possible to quantify precisely, medical professionals should explain the known risks and benefits to patients, including a statement of uncertainty about unknown risks where relevant.

#### 7.1.2.2 Beneficence and non-maleficence

The ultimate aim in healthcare is to produce net benefit over harm, while recognising that it is inevitable for some risk of harm to exist when medical intervention takes place. Beneficence is the traditional Hippocratic duty to prioritise **the patient's** best interests, while non-maleficence is the duty not to cause harm or risk of harm to patients. These duties mean that those who treat patients must be appropriately qualified, so as not to put patients at undue risk. Healthcare professions undertake to provide appropriate training and education to prospective and current practitioners to ensure patients are adequately protected.

#### *Application to smoking cessation interventions*

The benefit of smoking cessation interventions is that they increase the chances of long-term quitting in those who are motivated to stop smoking. In turn, this lowers the risk of developing lung cancer, heart disease and respiratory problems. The harms associated with the interventions are largely associated with pharmacological interventions and e-cigarettes.

#### *E-cigarettes*

While Public Health England reports that e-cigarettes are thought to be 95% less harmful than tobacco cigarettes, it is still unknown whether they will ultimately reduce harm.<sup>(26)</sup> For example, reducing the number of lives lost, reducing numbers of new smokers, increasing numbers of those who successfully stop smoking and so on. The international public health community is currently divided about whether to endorse a device whose safety and efficacy for smoking cessation is unclear. While

e-cigarettes are safer compared with tobacco smoke, there is insufficient evidence thus far to state that they do not cause any harm.

There are concerns that if e-cigarette use becomes socially normalised, large numbers of people who have never smoked might take up smoking e-cigarettes, thus exposing themselves to health and financial risks that would otherwise be avoided. There is international evidence that people who have never smoked, particularly teenagers,<sup>(865, 866)</sup> are taking up e-cigarettes. It is also possible that e-cigarettes will have a **'gateway effect'** for non-smokers who take up e-cigarettes, and they may later migrate to tobacco cigarettes or marijuana. Smokers who use e-cigarettes as a smoking cessation aid may in effect be swapping tobacco for another dependency, leading to long-term e-cigarette use and continued nicotine dependency. If those people used a different cessation aid such as NRT, they may be more likely to become nicotine free.

The tobacco control community are wary of accepting harm reducing products, such as e-cigarettes. Increased initiation and decreased quitting arising from public misperceptions of the products could have a negative population-wide health impact.<sup>(867)</sup> If e-cigarettes make smoking socially acceptable, this could be seen as a retrograde step after decades of anti-smoking efforts. However, from the perspective of harm reduction, it is unlikely that the population level harms resulting from e-cigarette uptake among non-smokers would overshadow the public health gains obtained from tobacco harm reduction among current smokers.

#### 7.1.2.3 Justice

Justice generally means fairness, and may be described as the moral obligation to act on the basis of fair adjudication between competing claims. This can be subdivided into three categories of obligations:

1. distributive justice which involves the fair distribution of resources;
2. rights-**based justice which involves respect for people's rights**;
3. legal justice which involves respect for morally acceptable laws.

Many moral conflicts can arise in this context, for example, how to decide between equally deserving patients when providing a scarce resource. There are also issues in regard to the wider use of resources, conscious that payment must be made for those resources either by the patient, an insurer or the state. A public health programme must consider equity of access and the rationale or justification for selecting particular population groups.

### *Application to smoking cessation interventions*

The harms that result from tobacco use are not experienced equally by all segments of the population. Health disparities exist in tobacco as in other health-related fields.<sup>(867)</sup> A harm-reducing strategy may fail if net harm is reduced, but in a way that is socially unjust; for example, some socially or economically vulnerable group becomes more at risk of harm or less able to benefit from the harm reduction strategies. Smoking rates are higher among people with a mental illness and those in lower socio-economic groups. These people are over represented in the population targeted by cessation interventions. If the HSE were to favour one or more smoking cessation intervention over others, the autonomy of the individual might be impacted if they cannot choose the intervention that most suits them. Although all interventions would continue to be available for purchase, this might negatively affect those in lower socio-economic groups who cannot afford to pay for alternative interventions out of pocket.

#### **7.1.2.4 Conclusion**

Saving lives and safeguarding health is accepted as important by policy makers. However, the action to increase good health at the expense of the state has exercised many governments, activists, academics and medical practitioners alike. The legal and moral responsibility of the state to save life and prevent disease, as well as promote good health for its citizens has been the subject of longstanding debate. Health policy, such as whether to introduce a disease screening programme, or to provide a vaccine, must take account of not only applying ethical principles to individuals but also the benefit, costs and risks to the public.

It must be considered whether it is morally acceptable for the HSE or clinicians to promote a product whose long-term health effects are unknown. Cautionary policies based on the precautionary principle are significant in terms of public-health ethics. These policies state that when scientific data are contradictory or quantitatively scarce, it may be necessary to make temporary decisions that can be modified on the basis of new facts that eventually become known. A cautionary approach might be considered appropriate where there is a lack of evidence on potential long-term risks associated with some smoking cessation interventions, such as e-cigarettes. This approach must advise smokers who wish to quit of all the cessation interventions available, while providing as much information as possible in relation to safety and efficacy. Such a policy would have to be reviewed on a regular basis as new international research evidence becomes available.

#### **7.1.3 Regulation**

Ethical issues also arise in relation to the regulation of public health interventions. Measures adopted by states must try to meet the objective of improving population

health. This is possible by providing information to consumers that is as accurate as possible, in order to uphold autonomy. Broader public health interests must be protected by aiming to reduce smoking rates in the population generally and safeguarding vulnerable groups, such as young people.

Questions for consideration here include whether e-cigarettes should be regulated as strictly as tobacco cigarettes due to the unknown health effects of vapours on bystanders, particularly pregnant women. However, regulating both in the same way might give the message that they are both similar, which in turn might result in increased inter-changeability between products.

Marketing and advertising is also important in the public perception of smoking cessation interventions. The government also has an ethical duty to ensure that the media portrayal of the product is appropriately aligned with its known degree of risk. The EU Tobacco Products Directive which came into force in member states in May 2016 sets rules governing the manufacture, presentation and sale of tobacco and related products, including electronic cigarettes, which aim at harmonising the quality and safety requirements of the products for the benefit of consumers.<sup>(23)</sup> In addition, rules on packaging and labelling ensure that consumers are better informed.

#### 7.1.3.1 Potential medico-legal liability

There have been a small number of legal actions in the United States in relation to the safety of e-cigarettes that have exploded and caused injury to consumers. These actions have been taken against manufacturers and turn on product liability law, and are thus not a matter for the state or individual clinicians.

New problems could arise if future research shows that negative health effects, which are currently unknown, arise from the use of e-cigarettes. As this product is not currently licensed as a medicinal product, it does not come within the remit of the Health Products Regulatory Authority (HPRA) to assess and monitor its safety and efficacy for licensing purposes. It is important to note that there are risks and side-effects with almost all over-the-counter products that may be purchased, even pharmacological products such as aspirin or paracetamol.

Where appropriate warnings and information leaflets containing accurate information are included with the sale of any such product, it is difficult to see how a legal action might successfully be taken with the benefit of hindsight in future years. It is important that the government continues to fulfil its moral and legal duty to the public with regular reviews of international research data and updates of consumer information. This can help encourage smoking cessation through various means and provide as accurate and up-to-date information as possible to consumers.



Similar considerations apply to individual clinicians who advise their patients to use a particular smoking cessation method. Current legal principles state a clinician will not be held liable for negligence if they act in accordance with the standards of the medical profession and do what any other reasonable doctor of the same specialty would do in the circumstances. However, there is a caveat that the clinician will not escape liability if there are obvious and inherent defects in the practice.

In relation to potential liability for breach of the doctrine of informed consent, the Irish courts have taken a patient-centred approach to this issue. This means that doctors are under an obligation to inform patients of any material risk which the doctor knows or should reasonably be aware of in relation to the proposed treatment. These issues further underline the importance of accurate and up-to-date information being made available to enable patients and consumers to make an informed choice.

## **7.2 Organisational implications**

This analysis of the clinical effectiveness and cost-effectiveness of smoking cessation interventions is designed to identify potential improvements in the delivery of these services in Ireland. However, there may be significant organisational implications associated with efforts to change the mix of interventions offered to smokers, and this also needs to be considered by decision-makers. These issues range from the need for additional staff and resources to support increases in the delivery of existing interventions, to significant reorganisation of services required to deliver new interventions or existing interventions in a different way. This section discusses the potential organisational implications associated with the findings of the HTA.

### **7.2.1 Unselected adults**

As noted in Chapter 1, the primary population of interest for this review was unselected adult smokers in a community setting. This is the group broadly targeted by national quit campaigns and accounts for the majority of those using existing smoking cessation services.

#### **7.2.1.1 Current configuration of services**

The HSE provides and promotes a wide range of smoking cessation services, ranging from HSE QUIT clinics and courses, primary care supports provided by GPs, pharmacists and dentists, online and social media supports on [www.quit.ie](http://www.quit.ie) and Facebook and a QUITline telephone support service. Tobacco cessation support services work to nationally agreed standards (National Standard For Tobacco Cessation Support Programme).<sup>(50)</sup>

Current HSE policy is that every person who engages with front-line HSE staff should be asked about their smoking status and the response should be documented. Every smoker should be advised to quit and offered support; this is known as brief intervention and should be provided at every opportunity. The HSE distinguishes this support from the intensive cessation support services that are provided by trained cessation specialists working in community or hospital settings, or with the national QUITline.

Intensive cessation support is delivered by cessation specialists with dedicated time to deliver support. An intensive intervention is a consultation that lasts in excess of 10 minutes. Intensive interventions usually involve a number of structured consultations provided over a defined period of time (that is, a Cessation Support Programme).

While registered nurse prescribers may prescribe smoking cessation medications, currently there is only such prescriber in the smoking cessation services. Almost all smokers wishing to use medications for which a prescription is required must obtain a prescription from a medical doctor. For those who wish to have smoking cessation medication reimbursed through the Primary Care Reimbursement Scheme (PCRS), they must obtain a prescription from a GP holding a contract with the PCRS. This may involve an additional GP visit for patients not initiating this discussion as part of their usual care. However, while consultations in general practice may discuss **patients' lifestyle habits and their contribution to patients' health, there currently** exists no agreement for general practitioners to provide targeted smoking cessation interventions or services under the GMS contract. Increasing the number of nurse prescribers in smoking cessation services would help alleviate the need for additional GP visits for those receiving support as part of their quit attempt. In turn, this may make smoking cessation medication more accessible and increase the uptake of these types of interventions. However, interventions designed to increase uptake are not within the scope of this HTA, and a review of the available evidence for these measures would be needed before the effect of any increase in nurse prescribing on the uptake of individual interventions could be estimated.

A Cessation Support Programme is a structured programme which incorporates a **series of contacts or consultations tailored to meet the client's needs**. Clients may be referred to this service from all services within the HSE or through self-referral. This **programme involves ongoing support at intervals pre and post the client's quit date**, and for a period of one month following the quit date. The programme involves the monitoring of quit status at two further points (three months and 12 months).

Tobacco cessation services vary from region to region due to differences in the availability of dedicated resources. All regional tobacco cessation specialists have undertaken nationally recognised training. Tobacco cessation specialists may also have other roles in tobacco control such as training, research, support for smoke-free policy development and strategic planning for tobacco control.

Depending on the region, the following interventions are available:

- **Face-to-face support.** An intervention offering one-to-one support, in person, between a Tobacco Cessation Specialist and a smoker. This behavioural intervention consists of advice, discussion and exercises.
- **Telephone support.** This support may be proactive, reactive or SMS-based. Tobacco Cessation Specialists can call the client following a referral from another service (a proactive service) or the client can call the service (a reactive service).

- **Group support.** This involves support through a closed group of smokers in a structured format. Groups are facilitated by Tobacco Cessation Specialists and are held weekly (usually for six weeks).
- **Online support.** Proactive or reactive support is available online (such as, email) by a Tobacco Cessation Specialist.

Data from the **HSE's** 2015 annual report indicate that 11,949 smokers received support from a cessation counsellor that year.<sup>(868)</sup> A total of 1,279 healthcare professionals were trained through 131 training programmes, while 30 staff were trained to provide intensive tobacco cessation specialist support to smokers. An ongoing commitment to training is evident in the **HSE's 2017** service plan, with a target to train an additional 1,350 front-line staff in 2017.<sup>(869)</sup>

Between 2013 and 2015, on average, 8,513 smokers received intensive smoking cessation support from HSE smoking cessation services, with just over half (51%) entering a cessation support programme. Access to telephone support is provided through the QUITline which is available for 48 hours a week. This extends to 77 hours a week in the month of January to cope with increased demand at that time. Demand for online support is evident through traffic on [www.quit.ie](http://www.quit.ie). In September 2016, there were over 1,400 visitors to the site; 1,258 of these created a QUITplan and 530 requested a call from an advisor. Nationally, there are 39 smoking cessation practitioners providing an average of 16 hours per week (range 0 to 39) in direct cessation activity.<sup>(870)</sup>

A smoking cessation programme also provides assistance with choice of cessation medication and monitoring effective use of same. Varenicline and bupropion are prescription-only medications. While certain NRT products are now available over the counter. For reimbursement through the Primary Care Reimbursement Service (PCRS) they must first be prescribed by a practitioner registered with the PCRS. In addition to physicians, midwives and nurses may prescribe medicinal products if they are registered as Registered Nurse Prescribers with the Nursing and Midwifery Board of Ireland (NMBI).

Varenicline and bupropion, classified as drugs used in nicotine dependence, are included in the Drugs Payments Scheme (DPS) and can be reimbursed through the PCRS for Medical Card holders.

NRT is not included in the Drugs Payment Scheme (DPS). For reimbursement through the PCRS, the following criteria apply:<sup>(871)</sup>

1. The quantity to be prescribed and dispensed on the initial prescription must **be limited to a two weeks' supply in order to evaluate the success of the therapy.**

2. NRT may not be prescribed on General Medical Scheme repeat prescription forms.

More than one formulation (for example, NRT patch with NRT gum) may be prescribed. This is known as combination NRT, and patients are not limited to a maximum duration of therapy. However, while consistent with the criteria for reimbursement of any medications for Medical Card holders, some of the criteria may act as a barrier to access and discourage certain patients from availing of these interventions. If a medication is prescribed (or recommended in the case of over-the-counter NRT) **by a provider other than the patient's GP, the patient must** arrange for it to be transcribed onto a dedicated General Medical Scheme prescription to be reimbursed through the PCRS. In the case of NRT, limiting the **initial prescription to a two weeks' supply and disallowing the use of repeat** prescriptions may lead to additional GP visits and act as a barrier to access. Excluding NRT from the Drugs Payment Scheme may also act as a barrier to access for some patients.

The cost of NRT is the economic analysis reflected these additional controls on the prescribing of NRT, which necessitate an additional GP visit for the average smoker with a medical card using NRT as part of their quit attempt. The impact of these additional controls therefore tends to make NRT-based interventions less cost effective compared with other interventions.

In addition to HSE services, there are also likely to be some additional supports provided through private health insurers or occupational health schemes. However, the impact of these services on overall smoking cessation is difficult to determine due to a lack of centralised data on the quantity and type of services offered, and the number of smokers accessing them.

#### 7.2.1.2 Evidence and implications for practice

The analysis of the clinical and cost-effectiveness of smoking cessation interventions found that all interventions evaluated were cost-effective compared with unassisted quitting. Combination varenicline and nicotine replacement therapy (NRT) was found to be the optimal smoking cessation strategy when all interventions were compared with each other. The opinion of the Health Products Regulatory Authority (HPRA) was sought in an attempt to clarify whether this would constitute off-label use of these interventions, as neither explicitly recommends use of the other in the summary of product characteristics documentation. The HRP A indicated that, provided each product is used in accordance with the approved product information, prescribing two products for the same condition should not necessarily be construed as off-label use. This issue was also raised with HSE smoking cessation practitioners who reported that although the use of varenicline in combination with NRT was

considered rare, it is currently used by a proportion of Irish smokers to help them quit. This is consistent with the results of the Healthy Ireland survey.<sup>(61)</sup>

While including studies that examined the effect of this treatment is important in making sure that the HTA reflects the totality of evidence in this area, the potential implications of widespread uptake of a relatively new combination of existing interventions is something that will need to be considered as part of the development of clinical practice guidelines and national health policy. Increased use of NRT and varenicline will also have implications for licensed prescribers, due to an increase in the number of smokers requiring prescriptions. However, if smokers increasingly choose to use e-cigarettes in their quit attempt without seeking the advice of medical practitioners, demand on these services would decrease. The additional number of GP or nurse prescriber consultations associated with each of the comparators included in the HTA is shown in Table 7.1. These estimates are based on the following assumptions:

- all those with a Medical Card who use NRT will obtain a prescription,
- no GP consultation will be sought for unassisted quit attempts or those involving e-cigarettes alone,
- and, everyone taking varenicline or bupropion will require a single consultation.

**Table 7.1 Differences in the average annual number of GP or nurse prescriber consultations required for each comparator over a 5-year time horizon\***

	Current practice (Ireland)	E-cigarette uptake rates in England	Moderate Varenicline & NRT uptake	Maximum Varenicline & NRT uptake
Average annual number of prescriptions needed	87,475	54,485	114,938	139,109
% change	Reference point	-38%	31%	59%

\*Assuming current mechanisms for reimbursement of cessation aids remain unchanged and that e-cigarettes are not reimbursed by the publicly-funded healthcare system.

Table 7.1 shows that significant increases in the use of e-cigarettes as the sole quitting aid would lead to a substantial drop in the number of consultations needed annually. A 38% decrease in consultations is anticipated if e-cigarette use reaches the levels observed in England (that is an increase from 26% to 45% of annual quit attempts). Alternatively, if e-cigarette use remained stable and the use of varenicline and NRT was increased, additional demands would be placed on health services. To put these changes in context, increased uptake of e-cigarettes would be associated with approximately 12 fewer consultations per GP annually, while maximising the

uptake of varenicline and NRT would be associated with an average of 18 additional consultation per GP over the course of a year.

It is likely that the numbers of consultations required for each strategy provided in Table 7.1 overestimates the scale of the incremental activity required as many smoking cessation interventions are opportunistic, with healthcare professionals availing of opportunities to encourage cessation as part of consultations primarily directed at other areas of care. Furthermore, the projected figures do not account for reductions in the number of consultations required due to a reduction in smoking-related illnesses associated with a lower smoking prevalence for each of these comparators. Any decision to reimburse e-cigarettes through the Primary Care Reimbursement Scheme (PCRS) in a similar way to NRT would place additional demands on prescribing services. However, unlike NRT, no e-cigarette is currently licensed as a medicinal product in Ireland, so it is unclear exactly how any such a funding scheme would operate.

As discussed in Chapter 4, the evidence is unable to differentiate between the effectiveness of different types of behavioural support when provided in addition to pharmacotherapy. While the optimal type of behavioural support to provide is unclear, the addition of any type of behavioural support to a pharmacological intervention increases the chances of successful quitting. The limited evidence is especially problematic given the significant amount of time and resources needed to train health professionals in the delivery of behavioural support interventions, and the fact that changing the type of support provided (for example, from brief advice to individual counselling or group behaviour therapy) may be logistically more challenging than substituting one pharmacotherapy intervention for another.

It is also worth noting that the reported cessation outcomes associated with behavioural interventions do not capture the full benefit of these services, which are also designed to raise awareness of the harms of smoking in order to discourage people from starting and to motivate more smokers to make a quit attempt. As described in section 3.4.4, a wide range of smoking cessation supports is currently available through health services in Ireland. This includes brief interventions, pharmacological therapies, counselling, online and social media supports, QUITline telephone support, courses, and specialist quit clinics. Additional staff training may also be required to ensure all staff engaged in smoking cessation are aware of the most up-to-date evidence on the potential benefits and harms of different smoking cessation interventions, particularly e-cigarettes, if these are to be included among the treatments options discussed with smokers.

As well as having implications for providing smoking cessation interventions, changes in current practice may also affect resource use in the services that provide care for smoking-related diseases, such as lung cancer and ischaemic heart disease.

A number of simplifying assumptions were made in the model to estimate cost-effectiveness in order to estimate the long-term changes in disease prevalence as a result of lower smoking prevalence. It was assumed that prevalence rates of smoking-related illness in former smokers would apply to the population of former smokers in the model each year. In the time horizon for the budget impact (five years), all of these former smokers have quit for between one and five years, whereas disease prevalence rates applied to this group are drawn from cross-sectional studies that included smokers who had given up decades previously, as well as those who had only managed to quit recently. While the comparison of different strategies in this assumption is still valid, it likely overestimates the reduction in smoking-related disease prevalence in any given comparator in the short term.

However, as the time horizon is extended, the model should converge on an approximation that is more indicative of the absolute prevalence in each group. This occurs as, by year 20, the former smokers group includes people who have quit over the course of two decades, and is therefore more consistent with the population that was used to calculate the relative risk of each disease in former smokers. Reliably estimating the changes in disease prevalence in the short term would require detailed information on risk profile by year since quitting, along with information on smoking history (pack years), age at starting and age at quitting, which is not readily available. Differences in the estimated number of prevalent cases of each disease per year by the end of the 20-year time horizon (2,036) among the cohort who were smokers on or after 2016, are shown in Table 7.2.

**Table 7.2 Decrease in the annual number of deaths and prevalent cases of smoking-related illnesses in each comparator compared with routine care by 2036 in those who were smokers on or after 2016**

	Deaths averted	Lung cancer cases averted	COPD cases averted	IHD cases averted	Stroke cases averted
E-cigarette uptake rates in England	71	54	27	790	515
Moderate varenicline & NRT uptake	86	65	32	966	630
Maximum varenicline & NRT uptake	134	102	50	1,501	979

This analysis shows the uncertainty that exists in relation to e-cigarette use and the impact this will have over the coming years. The available RCT evidence on the effectiveness of e-cigarettes consists of two trials, neither of which demonstrated a



statistically significant effect on their own, but when pooled showed benefit compared with non-nicotine e-cigarette controls. While the results of ongoing studies are awaited, the potential implications of strong evidence for advocating e-cigarette use should be considered.

As shown in Table 7.2 and in the economic analysis, increased use of e-cigarettes may be associated with decreased demand on prescribing services and reductions in public spending on smoking cessation therapies under current funding arrangements, by shifting costs back onto smokers. However, these additional costs to smokers are offset by the savings they will achieve during a period of abstinence from cigarettes. As such, the absence of General Medical Scheme funding of e-cigarettes is unlikely to be a barrier to most smokers. However, if smokers increasingly choose to use e-cigarettes in their quit attempt without seeking support from healthcare professionals, it may result in an ever increasing proportion of smoking cessation activity being undertaken without the involvement of organised smoking cessation services. This could lead to the loss of beneficial effect of adjunct behavioural support, resulting in suboptimal quitting rates.

As noted in Chapter 3, there are a number of national surveys that capture data on smoking prevalence and uptake of smoking cessation interventions in Ireland. The monthly HSE Smoking Prevalence Tracker provides longitudinal data on prevalence of smoking and e-cigarette use while the Healthy Ireland survey provides useful data on prevalence and cessation attempts. Data are also available from the Slán survey, Eurobarometer surveys on tobacco use and the Health Behaviour in School-aged Children (HBSC) survey. Tobacco Free Ireland, the national tobacco control policy document published in October 2013, also recommended that a national database for the collection and collation of data from all smoking cessation services should be established.<sup>(872)</sup> This would provide useful information on how frequently cessation interventions are offered to smokers, their uptake and the outcomes achieved.

### **7.2.2 Mental health services**

In contrast to the decline in smoking prevalence in the general population, smoking among those with mental illness has changed little over the past 20 years according to international data.<sup>(498)</sup> People with mental health problems smoke significantly more and are more dependent on nicotine than the population as a whole, with levels about three times higher than those observed in the general population. Chapter 3 describes the effect of smoking on health and the prevalence of smoking and smoking cessation in mental health populations in Ireland.

As noted in Chapter 1, the mental health population in this HTA is defined by the setting and services through which care is provided for patients with mental illness (rather than defining them by their underlying illness). This definition aims to

maximise the usefulness of this analysis in informing future national guidelines and policy making. The organisational issues described in this section are specific to those accessing secondary mental health services, including patients accessing inpatient, residential and long-term care for serious mental illness in hospitals, psychiatric and specialist units and secure hospitals, and patients who are within the care of specialist community-based multidisciplinary mental health teams.

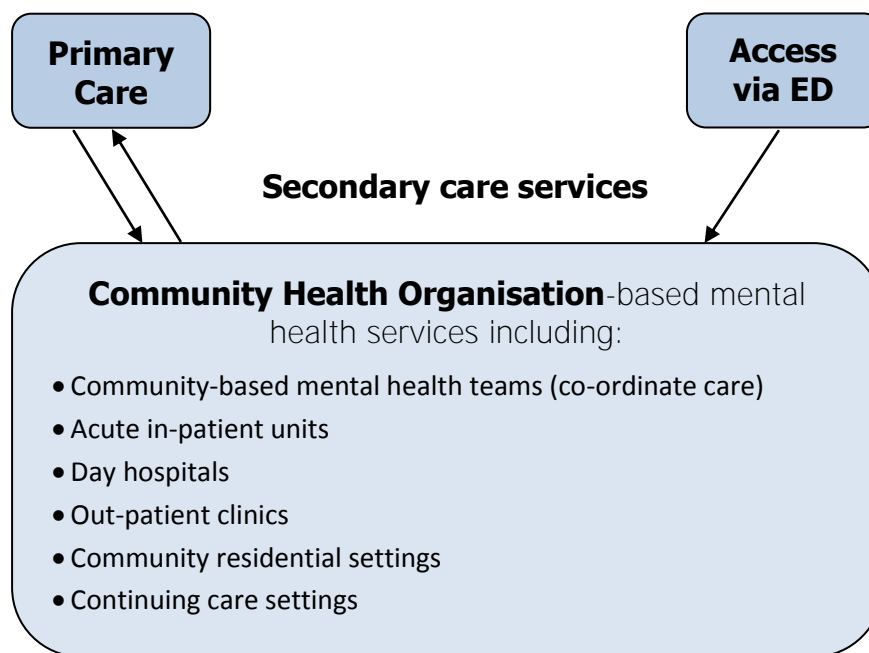
#### 7.2.2.1 Current configuration of mental health services

The Mental Health Division was established by the HSE in 2013 and is accountable for specialist secondary mental health services in Ireland.<sup>(873)</sup> An overview of the services provided is detailed in their 2016 report, *Delivering Specialist Mental Health Services 2014-2015*.<sup>(873)</sup> This highlights that primary care is typically the first point of contact for people with mental health issues, however, some attend the emergency department (ED) in an emergency situation where a psychiatric assessment is available 24/7.<sup>(873)</sup> Following assessment at primary care or ED level, the next step is to access secondary mental health services via the community health organisation as described in Figure 7.1. Community mental health teams are a key component of service delivery and are the first-line of acute secondary mental healthcare provision.<sup>(873)</sup>

The Mental Health Division reports that over 90% of mental health needs can be successfully treated within the primary care setting, with less than 10% referred to specialist community-based mental health teams for assessment or treatment.<sup>(873)</sup> Of this 10%, they report that approximately one in ten experience acute phases of their illness necessitating acute inpatient care.<sup>(873)</sup>

*A Report of the Expert Group on Mental Health Policy - A Vision for Change* (2006) noted a general perception among providers of mental healthcare that the mental health service is grossly under-resourced, both in financial terms and in the range of staffing and physical resource required to provide a quality service.<sup>(874)</sup> This report set out a plan for improving the delivery of mental health services.<sup>(874)</sup> Progress against this plan, in particular in relation to staffing, was documented in a 2016 **report** '*Delivering Specialist Mental Health Services 2014-2015*'. The 2016 report stated that in December 2015 there was a total of 1,758 staff in the General Adult Community Mental Health Service (1,548 clinical), which represents 80% of the staffing levels recommended in the Vision for Change report.<sup>(874)</sup> Mental health services also include clinician and peer-led information programmes, some of which were developed by the HSE in response to the Vision for Change Report. These include the EOLAS programme for people with a diagnosis of schizophrenia and bipolar disorder, their family members and significant others.<sup>(875)</sup> These provide education and training for participants about managing mental health, their diagnosis, medication use and behavioural interventions.

**Figure 7.1 Accessing mental health services in Ireland**



Note: ED – emergency department

#### 7.2.2.2 Mental Health population

The Healthy Ireland survey (2015) reports that probable mental health problems are indicated in 9% of the Irish population aged 15 and over.<sup>(518)</sup> Based on Central Statistic Office (CSO) population estimates for 2015, this equates to approximately 400,000 people.<sup>(876)</sup> A probable mental health problem was calculated using the MHI-5 score (Mental Health Inventory) which provides an estimate comparable to other measures of psychological distress, associated with service use and decreased level of functioning, with scores of 56 or less indicating a probable mental health problem.<sup>(877)</sup>

The mental health subgroup specifically considered in this report comprises those patients attending secondary mental health services. As noted previously, it is estimated that the majority of mental health needs can be successfully treated in primary care, with less than 10% being referred to secondary mental health services. Delivery of community mental healthcare is categorised by service type, that is child and adolescent, general mental health, and psychiatry of old age services. In 2015, a total of 37,091 new cases were offered an appointment by community general mental health teams with 9,836 new cases offered an appointment by the psychiatry of old age services.<sup>(751)</sup> A proportion of new cases seen will have previously attended the service and been discharged. Re-referral rates are 31.1% for community general mental health teams and 32.6% for psychiatry of old age services.

A report on the activities of Irish Psychiatric Units and Hospitals from the National Psychiatric In-patient Reporting System (NPIRS) provides details of national and regional admissions, discharges and deaths.<sup>(490)</sup> The report, published by the Health Research Board, details a total of 17,860 admissions to Irish psychiatric units and hospitals in 2015, a rate of 389.3 per 100,000 total population. The majority of these admissions related to depressive disorders (26.9%), schizophrenia, schizotypal and delusional disorders (19.9%), and mania (10.7%). Readmissions were common, accounting for 11,746 admissions in 2015 (rate of 256.0 per 100,000). The report also shows 17,662 discharges, with an average length of stay of 36.1 days, and 94% of all discharges occurring within three months of admission in 2015.

#### 7.2.2.3 Smoking and mental health – current legislation and guidelines

A ban on smoking in enclosed workplaces in Ireland was introduced under Section 47 of the Public Health (Tobacco) Acts 2002 and 2004 to prohibit the smoking of tobacco products in all indoor workplaces with limited exemptions. This came into effect in 2004 and under the legislation, certain premises were exempt at the time, one of those listed premises being a standalone psychiatric hospital (that is to say, not attached to an acute site). The basis for this exemption was the practical difficulties anticipated in not permitting smoking by residents. At the time, smoking was an accepted component of the culture of many mental health settings, making cessation more difficult. A recent report from the Royal College of Physicians and Royal College of Psychiatrists in the UK stated that smoke-free policies are a vital means of changing this culture.<sup>(498)</sup>

However, a secure hospital in the UK which went smoke-free was challenged in the High Court by service users who argued their human rights were breached under Article 8 of the Human Rights Act.<sup>(498)</sup> The High Court found that the service users **had no 'legal right to smoke' and noted that it had a duty to take 'all reasonable precautions' to protect staff from** second-hand smoke.<sup>(498)</sup> In addition, implementation of the legislative requirements in Ireland does not negate the duty of care that the HSE and senior management have to protect the health and safety of its staff from second-hand smoke.

The HSE Tobacco Free Campus Policy, endorsed by senior management in 2012, aims to make all of its workplaces and campuses smoke free, and is being implemented in a phased way across all HSE services.<sup>(878)</sup> The organisational policy requires all HSE sites and services whether owned leased or funded by the HSE to implement a Tobacco Free Campus Policy prohibiting smoking in all indoor areas and outdoor campus grounds, thereby providing a supportive environment for cessation. Aside from providing a supportive environment, one of the key purposes of the policy is to treat tobacco addiction as a healthcare issue. Data from the **HSE's** 2015 annual report indicate that successful implementation was achieved in 39% of

mental health units and 24% of mental health residential services.<sup>(868)</sup> This contrasts with a 99% successful implementation rate in primary care settings.

The national tobacco control policy document (Tobacco Free Ireland) makes a series of recommendations to reduce smoking prevalence in the overall population.<sup>(872)</sup> It makes reference to *Best practice guidelines for tobacco management in the mental health setting* which were introduced by the HSE and Health Promoting Hospitals Network (2008).<sup>(879)</sup> They state that smoking is treated as a care issue for all clients in mental health settings, and that smoking cessation support should be made available to staff and clients in an effort to reduce consumption. See Table 7.3.

**Table 7.3 Best practice guidelines for tobacco management in mental health (2008)**

Smoking is treated as a care issue for all clients in mental health settings	
<b>A.</b>	Establish a system to identify and record the smoking status of all clients on admission and incorporate into overall client care plans, including specific smoking cessation techniques.
<b>B.</b>	All nicotine dependant clients should have appropriate pharmacological therapies including NRT made available to them.
<b>C.</b>	All medications should be carefully monitored during the quitting process and while the client is being treated for nicotine dependence.
<b>D.</b>	Awareness raising campaigns highlighting smoking-related problems specific to clients of mental health services should be used to inform clients, staff and visitors to bring about cultural change.
Smoking cessation support should be made available to staff and clients in an effort to reduce consumption	
<b>A.</b>	All organisations / services should have a smoking cessation service or access to a smoking cessation service with a designated smoking cessation facilitator trained in mental health for the purpose of helping smokers, staff and clients to quit.
<b>B.</b>	<b>Continuously assess smoker's readiness to change and devise a comprehensive</b> smoking cessation support programme for staff and clients to include pharmacological therapies and knowledge on all researched alternative methods for smoking cessation support.
<b>C.</b>	Specific resources should be allocated for the cessation service, to ensure that systematic referral and audit systems are in place and that clients are followed up after quitting.
<b>D.</b>	Information on smoking and smoking cessation methods should be widely available to all staff, clients and the community.

Targeting smoking prevalence in the mental health population has also been a specific focus in other countries. The UK aims to reduce smoking prevalence in the

mental health population to less than 5% by 2035, and has produced several reports and guidelines for smoking cessation in mental health, which set standards and provide implementation guidelines for the delivery of smoking cessation interventions.<sup>(474, 498, 880-883)</sup>

A smoking cessation and mental health brief for front-line staff was published by the HSE in 2016 which aims to support and guide staff in their day-to-day interactions with clients and service users.<sup>(884)</sup> This was based on the 2014 National Centre for Smoking Cessation and Training briefing document in the UK. The HSE guidelines **recommend 30 seconds of brief advice incorporating an 'act' step which recommends** NRT (patch, gum/lozenge, inhaler, mouth spray), varenicline and bupropion as cessation aids. The guidelines note that NRT should be offered to all smokers to reduce nicotine withdrawal symptoms throughout the duration of an inpatient stay, even if they have no intention of quitting or show no desire to stop smoking. These recommendations are primarily based on evidence of effectiveness in the unselected adult population.

#### 7.2.2.4 Evidence and implications for practice

Treatment for smokers typically comprises pharmacological intervention with NRT, varenicline or bupropion, combined with regular behavioural support. The efficacy, safety and cost-effectiveness of these interventions in the general unselected adult population have been established in Chapters 4, 5 and 6 of this report. In the absence of evidence to the contrary, it is generally assumed that smoking cessation interventions that are effective in the general unselected adult population of smokers are likely also to be effective in those with common mental disorders. Observational and post-marketing surveillance data have shown inconsistent findings relating to neuropsychiatric adverse events for bupropion and varenicline. However, the 2016 EAGLES trial found no evidence of a significant increase in neuropsychiatric adverse events attributable to varenicline or bupropion relative to nicotine patch or placebo in patients with or without pre-existing psychiatric disorders.

Ten studies relevant to the population accessing secondary mental health services were identified in a systematic review of the literature. Nine randomised controlled trials (RCTs) related to those with schizophrenia or schizoaffective disorder, while one RCT related to those with bipolar disorder. Trials tended not to involve long follow-up periods, thus limiting the available evidence for this review. These were generally small studies and typically comprised mono- or combination pharmacotherapy (NRT including combination NRT and, or bupropion), with adjunctive individual or group behavioural programmes specifically designed for those with serious mental illness. Only one trial investigating the effect of varenicline was identified for inclusion. Evidence of a beneficial treatment was only found for bupropion when used as an adjunct to behavioural therapy and NRT in a population

with schizophrenia or schizoaffective disorder. Despite the intensity of the interventions offered, absolute quit rates in the control arms tended to be low compared to those in the general population.

A number of issues contribute to the limited availability of evidence in this population, such as:

- the common practice of excluding people with mental disorders from RCTs of drug therapy,
- the difficulty of recruiting and retaining those with serious mental illness in clinical trials, and
- the shorter duration of follow up in many of the available trials.

As noted in Chapter 5, while the EAGLES trial provided evidence of the safety and efficacy of varenicline, bupropion, and NRT in individuals with a history of psychiatric disorder, this was limited to those who were stable and treated or who had previous psychiatric conditions that were in remission. It also excluded those who were at risk of suicide or self-harm. Therefore, the findings may not be generalisable to those attending secondary care mental health services, particularly those who are untreated or symptomatically unstable.

As other systematic reviews published in this area have stated, better evidence is required to determine the optimal smoking cessation interventions in smokers with mental health issues. Researchers have speculated that harm reduction, through reducing the number of cigarettes smoked per day, may help with future cessation (see Chapter 4). Since this population are more likely to be heavy smokers, focusing on an initial reduction would reduce nicotine levels and may help with future cessation. A review of the evidence on preventing long-term relapse would also be helpful. While there has been significant growth in the use of e-cigarettes among smokers internationally, there are limited data in relation to their use in the mental health population. Further research as to their safety and efficacy, and their potential role as a cessation aid or as part of a harm reduction strategy, is needed in this cohort.

While legislation prohibiting smoking in public buildings and best practice guidelines to support service providers are in place, the extent to which smoking cessation interventions are consistently being offered to or availed of by smokers in the secondary mental health services in Ireland is unknown. The national tobacco control policy document, published in 2013, also recommended that a national database for the collection and collation of data from all smoking cessation services should be established.<sup>(872)</sup> Availability of this data would provide useful information on the type and extent of cessation interventions being offered to smokers attending secondary care mental health services, their uptake, and the outcomes achieved.



International data as well as limited national data from the 2007 Slán survey suggest that current messages are not reaching these populations, given the minimal decline in smoking prevalence. Specialist inpatient and community mental health services are particularly suited to the provision of tailored support by experienced mental health staff. However, this is likely to have resource implications both for providing interventions and ensuring that all staff have been trained in their delivery given the existing staffing constraints.

Aside from the mental health staff trained in provision of brief advice, data from the HSE's 2015 annual report indicate that of 30 staff trained to provide intensive tobacco cessation support to smokers, 14 were from mental health services.<sup>(868)</sup> Given the high admission rate and length of stay, in particular for those with schizophrenia, admission may provide an opportunity to intervene to reduce smoking. This would allow for supervision and monitoring for exacerbation of psychiatric symptoms during a cessation attempt, particularly given the requirements of smoke-free environments in this setting.

A number of issues specific to those with serious mental illness should be included as part of provider and patient education in relation to smoking cessation. It is noted that smokers with serious mental illness tend to have a heavier nicotine dependency with increased intensity in terms of the number of cigarettes smoked and the amount of nicotine extracted per cigarette. As in the unselected adult population, combination NRT (for example, use of a transdermal patch plus a faster-acting product such as a spray or gum) may be more effective than monotherapy to minimise nicotine withdrawal and enhance quit rates.

As noted in Section 3.4.2, metabolism of several psychotropic drugs and antidepressants is increased in cigarette smokers, reducing their blood level of antipsychotic drugs by as much as 50%. In the event of increased uptake of smoking cessation interventions, education is necessary to ensure that patients and providers are aware that stopping smoking could reduce the dose of antipsychotic required. As these interactions are not caused by nicotine, this is also relevant to those who use NRT or e-cigarettes in their cessation attempt.

### 7.2.3 Maternity services

#### 7.2.3.1 Current configuration of services

In 2014 a total of 66,338 women gave birth to babies weighing greater than or equal to 500g in Ireland. Almost all (99.8%) of these babies are born in the **country's 15 maternity units and four maternity hospitals. Maternity units provide** care to women and their babies in units situated in a general hospital, while maternity hospitals are stand-alone hospitals. The four stand-alone maternity hospitals in Dublin and Limerick will, in due course, re-locate to new state-of-the-art



hospitals on the campuses of adult teaching hospitals. Planned home births comprise 0.2% of births in Ireland. The HSE provides planned home birth services to families choosing this model of maternity care predominantly in association with Self Employed Community Midwives (SECMs), along with services based in two maternity units (Cork University Maternity Hospital, Waterford Regional Hospital) and one maternity hospital (the National Maternity Hospital, Dublin).

Currently, the Maternity and Infant Care Scheme provides an agreed programme of maternity care, free of charge, to all expectant mothers who are ordinarily resident in Ireland. This service is provided by a GP **of a woman's choice and a consultant** obstetrician in a maternity unit or a maternity hospital. The National Maternity Strategy encourages women to avail of this scheme and states that women should continue to have the option to receive their antenatal care as part of a shared model of care with their GP.

Midwives routinely document the smoking status of women in the medical record at the first antenatal visit to a maternity unit or a maternity hospital. Of the four maternity hospitals, on-site smoking cessation services are only available in two hospitals. There are no on-site services at the National Maternity Hospital, Dublin or **the Coombe Women and Infant's University Hospital, Dublin**. These two maternity hospitals, however, have nearby community smoking cessation services available to them. Three of the 15 maternity units do not have on-site smoking cessation **services: St Luke's Hospital, Kilkenny; Mayo General Hospital and Portluncula Hospital**. There is very limited onsite service in the South Tipperary Unit. While there **are nearby community services available to St Luke's Hospital, Kilkenny, there are none available to Mayo General Hospital or Portluncula Hospital**. These units must refer patients to QUITline.<sup>(885)</sup>

Two maternity units use the carbon monoxide breath test to validate self-reported smoking status. While multiple readings may be obtained during the course of a pregnancy, repeated use of biochemical verification is not consistent. NICE guidelines recommend **that midwives assess a woman's exposure to tobacco smoke** at the booking and subsequent appointments through discussion and use of a carbon monoxide breath test.<sup>(886)</sup> The implementation of routine carbon monoxide breath testing would have resource implications for Irish maternity services.

Based on the current configuration of maternity services and the need to make every contact count, healthcare professionals in a position to provide smoking cessation interventions in pregnancy include:

- GPs,
- midwives working within maternity units, maternity hospitals and community services provided by these units or hospitals,

- self-employed community midwives
- consultant obstetricians,
- non-consultant hospital doctors (NCHDs), and
- fertility specialists.

GPs in particular have several opportunities at visits both prior to and during pregnancy to educate and support women to stop smoking. GPs are also usually the first healthcare professional that a woman encounters in pregnancy.

While the analysis of the clinical effectiveness of smoking cessation interventions in pregnancy did not include specific interventions in the postnatal period, GPs, midwives, public health nurses and paediatricians are in a position to offer ongoing support during this period, including relapse prevention and referral to services available to the general population.

### 7.2.3.2 Smoking cessation interventions in pregnancy

Chapter 4 provides a detailed discussion on the clinical effectiveness of smoking cessation interventions during pregnancy. Due to the fact that bupropion and varenicline are not indicated for use in pregnancy, NRT is the only licensed pharmacotherapy available to pregnant smokers who wish to quit, and its efficacy appears to be lower in this cohort than in non-pregnant smokers. A range of behavioural interventions in pregnancy were reviewed, and there is evidence that counselling, health education and financial incentives improve cessation rates. It is worth noting that the largest body of evidence related to counselling interventions (44 studies, with a total of 17,796 participants). The quantity of evidence was lower for the other interventions evaluated, consisting of financial incentives (three studies; n=681), health education (six studies; n=1,425), feedback (five studies; n=950), and NRT (eight studies, n=2,199).

A wide range of types and intensity of counselling interventions were evaluated, including; brief advice, telephone counselling, face-to-face counselling based on the 5A's, counselling based on cognitive behavioural therapy, counselling based on motivational interviewing and psychotherapy sessions with a mental health therapist. Some interventions were delivered as a once off, while others involved multiple interactions with the healthcare professional. It is unclear if any form of counselling was more effective than others.

Counselling interventions were provided by a range of healthcare professionals including GPs,<sup>(573)</sup> midwives,<sup>(540, 577, 887-890)</sup> smoking cessation counsellors,<sup>(891)</sup> health educators,<sup>(526, 542, 892-894)</sup> mental health therapists,<sup>(545)</sup> veteran staff members of a quitline or telephone helpline,<sup>(525)</sup> medical students,<sup>(574)</sup> general resident doctors,<sup>(547)</sup> an anaesthetist<sup>(895)</sup> and physicians.<sup>(575, 896)</sup> It is unclear if the effectiveness of

counselling varies according to the discipline of the healthcare professional, the choice of which would affect the resources necessary.

The type of health education interventions also varied and occurred in forms including; a pamphlet,<sup>(552)</sup> a booklet,<sup>(551)</sup> a self-help manual,<sup>(548, 550)</sup> automated tailored text messages<sup>(549)</sup> or a fully automated smoking cessation website which was structured, tailored and personalised. The implementation or augmentation of health education interventions may have fewer resource implications than other interventions. However, there will be a requirement for all staff interacting with pregnant women to be aware of the range of interventions available, and their potential benefits and harms, to ensure that consistent advice is provided.

Financial incentives were found to be the most effective intervention for smoking cessation in late pregnancy. This finding is based on only three studies, however; further research in this area is warranted. If financial incentives were implemented, carbon monoxide breath testing would be necessary in all maternity units and maternity hospitals so that self-reported smoking status could be validated biochemically. This would require staff training and investment in handheld carbon monoxide monitors and mouthpieces. If urinary cotinine were utilised as a marker for smoking cessation, nicotine products (NRT and e-cigarettes) would also result in a positive reading.

Similarly, feedback interventions may incur significant resource implications. Participants studied were given feedback about urinary cotinine levels<sup>(554)</sup> or information about the negative effects of smoking at the time of an 18-week ultrasound scan and an additional 32-week ultrasound scan,<sup>(556)</sup> or had an ultrasound feedback session lasting approximately 30 minutes at the time of the 18-week ultrasound scan.<sup>(555)</sup> If feedback were implemented, urinary cotinine measurement or carbon monoxide breath testing would be necessary. In the case of ultrasound feedback interventions, additional ultrasound scans would be necessary. All three interventions require higher resources in terms of time, training and finances.

The efficacy and safety of e-cigarettes in pregnancy is unknown. Currently the Royal College of Obstetricians and Gynaecologists in the UK do not recommend e-cigarettes as a cessation aide.<sup>(699)</sup> See Chapter 5. Due to the rising prevalence of e-cigarette use, it is possible that they are also being used by pregnant women to aid cessation. While this area requires further research, the potential harms and benefits of e-cigarettes should be discussed with pregnant women when providing health education or cessation interventions to ensure informed decision-making.

### 7.2.3.3 Implications for practice

Smoking during pregnancy is a significant problem in Ireland. The Growing Up in Ireland study (2007) estimates that 13% of mothers smoked during all three trimesters, and 18% smoked at least at some stage during pregnancy.<sup>(117)</sup>

Based on the evidence, pregnant women who smoke should be offered a psychosocial intervention in the first instance. Counselling is the type of psychosocial intervention with the largest body of evidence to support its effectiveness. It is unclear if any type of counselling is more effective than another and it is also unclear if the effectiveness of counselling varies according to the discipline of the healthcare professional. The most significant resource implication for the implementation of counselling is time, both in antenatal clinics and training time. Re-visiting smoking status at antenatal clinic visits at appropriate intervals will require additional clinic time. This will have implications for the organisation of antenatal clinics both in terms of the duration of an appointment and the number of appointment slots available.

NRT should only be offered to women when psychosocial interventions have been unsuccessful. Licensed prescribers must use their professional judgment when offering women a prescription for NRT, and it should only be provided following discussion about the potential risks and benefits. This advice is in keeping with that recommended in international guidelines. For example, the National Institute for Health and Care Excellence (NICE) recommends that healthcare professionals only prescribe NRT once pregnant women have stopped smoking, or have set a quit date and that only two weeks of NRT are prescribed from the day women have agreed to stop.<sup>(605)</sup> Women should only be given subsequent prescriptions once they have demonstrated at the time of re-assessment that they are still not smoking.

For reimbursement through the Primary Care Reimbursement Service (PCRS), NRT must be prescribed on a dedicated General Medical Scheme prescription by a prescriber who is registered with the PCRS. As noted in Section 8.1.1, reimbursement is limited to Medical Card holders. If providers increase prescribing NRT in hospital and community-based antenatal clinics, there would be implications for primary care providers as Medical Card holders will need to first bring their prescription to their GP for it to be transcribed onto the relevant prescription form. In addition to physicians, midwives and nurses may prescribe medicinal products if registered as Registered Nurse Prescribers (RNPs) with the Nursing and Midwifery Board of Ireland (NMBI). The total number of nurses and midwives registered as RNPs with the NMBI is 141, however only one is dedicated to smoking cessation services.<sup>(628, 753)</sup>

Tobacco Free Ireland, **Ireland's national tobacco control policy document published** in 2013, recommends providing targeted approaches for pregnant women and women in the postnatal period and training all front-line healthcare workers in smoking cessation interventions, as part of their routine work.<sup>(872)</sup> In addition, it recommends establishing a national database for the collection and collation of data from all smoking cessation services.<sup>(872)</sup> This would provide useful information on the type and extent to which cessation interventions are offered to pregnant women, their uptake, and the outcomes achieved.

Maternity services must therefore ensure that front-line healthcare professionals are trained in some form of counselling intervention. The HSE currently delivers evidence-based brief intervention in smoking cessation training courses, targeting front-line health professionals as per the HSE National Service Plan and Tobacco Control Programme Action Plan. For smoking cessation, brief interventions involve opportunistic advice, discussion, negotiation and encouragement. This typically takes between three and 10 minutes. Interventions may involve referral to a more intensive treatment. Interventions should be recorded and followed up as appropriate. Additional forms of counselling, available free of charge to all smokers, include the telephone-based counselling service QUITline and the Internet-based service [www.quit.ie](http://www.quit.ie), both funded by the HSE.

This follows the World Health Organization (WHO) recommendations, published in 2013, on the management of tobacco use and second-hand smoke exposure in pregnancy.<sup>(25)</sup> The WHO recommends that psychosocial interventions should be offered to pregnant women who are current or former tobacco users as early in pregnancy as possible. These psychosocial interventions involve behavioural support that may include one or more of the following: counselling, health education, incentives and peer or social support. No evidence of effectiveness for peer or social support was found in this evaluation. The WHO also recommends that healthcare providers should ask all pregnant women about their tobacco use (past and present) as early as possible in pregnancy and at every antenatal care visit. Pregnant women with prior history of tobacco use should be asked about their current tobacco use at every antenatal care visit because of their risk of relapse.

**Ireland's first National Maternity Strategy was published in January 2016.**<sup>(897)</sup> This acknowledges that pregnancy and birth is a time when women have a unique opportunity to focus on their health and wellbeing and that of their baby. Healthcare professionals, by providing appropriate information and supports, can make '**every contact count**' to support positive behavioural change in women, in particular around reducing lifestyle behaviours with harmful effects such as smoking. However, healthcare professionals must be mindful of the social factors that can affect a **woman's ability to make positive choices. Maternity units and maternity hospitals**

should be tobacco-free campuses and have an on-site smoking cessation service available for pregnant women.<sup>(897)</sup> The Strategy also recommends that midwives and other front-line healthcare professionals have formalised and documented training in smoking cessation.

Furthermore, the *National Standards for Safer Better Maternity Services*, launched on 21 December 2016, include a number of specific features on smoking cessation in pregnancy and the training needs and competencies of staff.

### 7.3 Key Points

- Smoking is not generally considered to be morally wrong and as such is a matter of individual choice for the consumer. Therefore, any smoking cessation intervention must be made available in a way that promotes the autonomy of the individual by providing information on the risks and benefits associated with the particular intervention.
- There are concerns about the social normalisation of some cessation aids, such as e-cigarettes, leading to new use by people who have never smoked, later migration to tobacco cigarettes, long-term nicotine dependency, and other potential as yet unknown harms.
- In relation to potential long-term risks associated with some smoking cessation interventions such as e-cigarettes, smokers who wish to quit are advised of all the cessation interventions and provided with as much information as possible in relation to safety and efficacy. Such a policy would have to be reviewed on a regular basis as new international research data becomes available.
- **Marketing and advertising contribute to the public's perception of smoking cessation interventions**, so the government has an ethical duty to ensure that the media portrayal of any cessation product is appropriately aligned with its known degree of risk. The recent EU Tobacco Products Directive addresses this by aiming to harmonise the quality and safety requirements of tobacco products and e-cigarettes for the benefit of consumers.
- Concern has been expressed about potential future legal liability if future research shows that there are (currently unknown) negative health effects arising from the use of e-cigarettes. Provided appropriate warnings and information leaflets containing accurate information are included with the sale of any such product, it is difficult to see how a legal action might successfully be taken in future years.
- From an organisational perspective, efforts to increase the use of varenicline and NRT among unselected adults will place additional demands on GP or nurse prescriber services. If use of this intervention reaches plausible maximum levels, the number of prescriptions required could increase by over 50%. Alternatively, if e-cigarette use in Ireland (26%) rose to levels currently reported in England (45%), the number of prescriptions required could fall by nearly 40%, assuming the current funding model remains unchanged.
- Increasing the smoking cessation budget to promote the use of varenicline-

based regimens, and combination NRT therapy for those for whom varenicline is not suitable, would be a cost-effective use of resources. To facilitate this, potential barriers to increased uptake of smoking cessation interventions should be examined by the HSE and the Department of Health. This should include a review of dispensing rules for NRT on the General Medical Services (GMS), current exclusion of NRT from Drugs Payment Scheme (DPS) reimbursement, as well as the very limited number of nurse prescribers within smoking cessation services in Ireland.

- In the long term, decreased smoking prevalence will result in a lower prevalence of smoking-related diseases and decreased demands on services providing treatment for these conditions. However, these changes are unlikely to become apparent for some years.
- There is limited evidence on the effectiveness of smoking cessation interventions in the mental health population because of difficulties in recruiting and conducting randomised controlled trials (RCTs) in this population. Beneficial results were found for bupropion as an adjunct to behavioural therapy and NRT in a population with schizophrenia or schizoaffective disorder. In the absence of evidence to the contrary, it is generally assumed that interventions that are effective in the general population will also be beneficial in mental health populations.
- International data suggest that smoking prevalence among the mental health population has changed little over the past 20 years. Given the high prevalence, particularly in inpatients, there may be resource implications both for providing interventions and staff training, particularly given the staffing constraints that exist in mental health settings.
- The available evidence indicates that pregnant women who smoke should be offered a psychosocial intervention in the first instance. As counselling is the type of psychosocial intervention with the largest body of evidence to support its effectiveness, maternity services should ensure that all front-line staff are trained in some form of counselling intervention. Evidence for the effectiveness of NRT for smoking cessation in pregnancy is equivocal.
- The most significant resource implication for the implementation of counselling is time, both in training time in the antenatal clinics.
- Other smoking cessation interventions that are effective in pregnancy will have varying levels of resource implications. Health education interventions may require fewer resources, while incentives and feedback interventions may require more intensive resources in terms of time, training and finances.



## **8 Summary and conclusions**

### **8.1 Summary of findings**

The purpose of this HTA is to inform policy designed to maximise the number of smokers who successfully quit, given the resources allocated for the provision of these services in Ireland. In doing so, it brings together the best available evidence on the safety, effectiveness and costs of different smoking cessation interventions, their current usage rates and plausible changes in usage based on international experience, as well as Irish data on smoking prevalence and demographic projections over the next 20 years.

More than 5,400 deaths occur each year in Ireland due to smoking. Approximately 19% of Irish people aged 15 years and over smoke daily, with a further 4% smoking occasionally. The prevalence is higher in men (24.3%) than women (21.2%), and highest in people aged 25 to 29 years (33.4%). Smoking prevalence follows a socio-economic gradient, whereby the prevalence is highest in those in the lowest socio-economic group. There is limited Irish data on the prevalence of smoking in pregnancy and in those with mental health disorders. Smoking prevalence is noted to be correlated with the severity of the mental illness, with prevalence rates of 33% to 70% reported for those with bipolar disorder and 45% to 88% for those with schizophrenia.

At any given time, the majority of smokers are thinking about quitting, and most have made multiple prior unsuccessful attempts to quit. In Ireland, half of those attempting to quit do so unaided. A further 29% of smokers trying to quit use e-cigarettes (alone or in combination with another intervention) as an aid. Approximately 16% of quit attempts are made using some form of pharmacotherapy (for example, nicotine replacement therapy [NRT]).

A review of the clinical effectiveness and safety of pharmacological and behavioural smoking cessation interventions in helping smokers achieve long-term cessation was carried out for three separate populations: unselected adults, users of secondary care mental health services and pregnant women. The mental health subgroup identified in this assessment relates to those attending secondary mental health services and therefore may be considered applicable to those with more severe and enduring mental illnesses. The Mental Health Division reports that over 90% of mental health needs can be successfully treated within the primary care setting. While the general adult population considered in this report will comprise those with mild to moderate mental health conditions, the efficacy of smoking cessation interventions for this cohort was not specifically considered in this report.



In a general population of adult smokers, all pharmacological interventions were more effective than no treatment. Varenicline was the most effective monotherapy (RR 2.57, 95% CI: 2.32 – 2.85), and varenicline with NRT was the most effective dual therapy (RR 3.54, 95% CI: 2.57 – 4.61). The analysis of the effectiveness of behavioural therapies was complicated by considerable heterogeneity in how these interventions were defined.

**All evaluated therapies were more effective than an alternative of 'do nothing'.** When compared with control, defined as brief advice or written materials, group behaviour therapy was the most effective behavioural intervention (RR 1.85, 95% CI: 1.53 – 2.23). The only statistically significant evidence of a beneficial treatment for people attending secondary care mental health services was bupropion when used as in addition to behavioural therapy and NRT in a population with schizophrenia or schizoaffective disorder (RR 3.86, 95% CI: 1.01 – 14.80). Among pregnant women there was some evidence of a beneficial effect with NRT, but this did not reach statistical significance (RR 1.41; 95% CI: 0.99 to 2.00). There was also evidence to suggest counselling, health education and financial incentives increase cessation rates in pregnant smokers.

A review of the safety profile of these interventions found that pharmacological therapies for smoking cessation are generally safe and well-tolerated in those for whom these treatments are not contraindicated. No substantive evidence of adverse events associated with behavioural interventions for smoking cessation was identified. However, there are limited options available for certain patient groups, including pregnant women and mental health populations, due to contraindications to the use of selected pharmacological interventions. The safety of e-cigarettes is an evolving area of research. While believed to be considerably safer than smoking, evidence on long-term safety has yet to be established.

A cost-effectiveness analysis comparing individual interventions in an Irish setting found that all interventions would be considered cost-effective compared with unassisted quitting, with e-cigarettes and varenicline, alone or in combination with NRT, being the most cost-effective strategies when individual therapies are compared to each other. The results for e-cigarettes are extremely sensitive to changes in the estimated cost and effects of this intervention. This is of particular significance given the high degree of uncertainty that exists in relation to both of these parameters in the model. Further research is very likely to have an important impact on the results of the cost-effectiveness of e-cigarettes.

A comparison of alternatives to the current standard of care in Ireland was carried out, using international data as an indicator of plausible changes in the usage of the most cost-effective cessation interventions. This included a scenario where use of combination varenicline and NRT was maximised, as well as a scenario where e-

cigarette uptake reached levels recently reported in England. This analysis found that maximising the uptake of varenicline and NRT is the optimal strategy, with an incremental cost-effectiveness ratio (ICER) of €20,755 per quality-adjusted life year (QALY). However, it is unclear to what extent policy initiatives can influence overall smoking cessation preferences, particularly in light of the high degree of penetration that e-cigarettes have achieved in the absence of any explicit endorsement by smoking cessation services in Ireland. Continuing increases in the uptake of e-cigarettes are likely to improve the cost-effectiveness of the overall mix of cessation interventions in Ireland, by increasing the number of successful quit attempts at an acceptable cost (ICER €3,197/QALY). Increasing the smoking cessation budget to promote the use of varenicline-based regimens, and combination NRT therapy for those for whom varenicline is not suitable, would be a cost-effective use of resources.

A budget impact analysis on the incremental cost associated with changes to the existing standard of care was carried out. This analysis found that maximising the use of varenicline and NRT would be associated with an average increase of **approximately €7 million** in the annual cost of providing pharmacological smoking cessation interventions in Ireland. A scenario analysis in which uptake rates of e-cigarettes are comparable to England (while still not being reimbursed through the Primary Care Reimbursement Service [PCRS]) found that this would result in savings **of approximately €2.6 million per annum due to a decline in the uptake of other** prescribed pharmacotherapies. Alternatively, in a hypothetical situation where e-cigarettes were funded to the same extent as NRT, the additional cost to the health **service would be approximately €6 million per annum at current usage rates, or €7.5 million per annum** if this rose to usage rates currently reported in England. However, it is unclear how any such funding programme would operate given the propensity for long-term e-cigarette use and the fact that no e-cigarette product is currently licensed as a medicinal product in Ireland.

The HTA also examined any wider implications that changes to the provision of these services may have for patients, the health service, and society in general. From an ethical perspective, smoking is not generally considered to be morally wrong and therefore is a matter of individual choice for the consumer. Any smoking cessation intervention must be made available in a way that promotes the autonomy of the individual by providing information on the risks and benefits associated with the particular intervention. In balancing ethical considerations of benefit versus harm, cessation aids have been shown to increase the chances of long-term quitting among those who are motivated to stop smoking, but there are concerns about the social normalisation of some aids, such as e-cigarettes, leading to new use by never smokers, later migration to tobacco cigarettes, long-term nicotine dependency, and other potential as yet unknown harms. In the absence of clear evidence in relation

to potential long-term risks associated with some smoking cessation interventions, such as e-cigarettes, empowering smokers to make informed decisions would involve continuing to inform them of all the cessation interventions while providing as much information as possible in relation to safety and efficacy as well as known risks and side-effects.

From an organisational perspective, efforts to increase the use of varenicline and NRT will place additional demands on GP or nurse prescriber services. If use of this intervention reaches plausible maximum levels, the number of prescriptions required could increase by over 50%. Alternatively, if e-cigarette use in Ireland (26%) rose to the levels currently reported in England (45%), the number of prescriptions required could fall by nearly 40%, assuming that smokers choose this option without seeking medical advice.

E-cigarettes are unusual insofar as they are the only intervention in this analysis that is not advocated by HSE QUIT services or funded through the public health system. If the results reported so far are confirmed in subsequent trials and e-cigarette usage continues to rise, there is a risk that an ever greater proportion of smoking cessation activity will be undertaken without any involvement of trained smoking cessation staff. This means the potential benefit of providing e-cigarettes in conjunction with behavioural support interventions may be lost. Given the growing use of e-cigarettes, it is imperative that their potential benefit and harms continue to be discussed with smokers to ensure informed decision-making in relation to their use. As new evidence emerges, there are likely to be ongoing resource implications for the health service to educate providers on this topic and to ensure that consistent advice is provided. In the long term, decreased smoking prevalence will result in a lower prevalence of smoking-related diseases and decreased demands on services providing treatment for these conditions. However, these changes are unlikely to become apparent for many years.

## **8.2 Discussion**

Quitting smoking is a complex, iterative process in which the choice of cessation intervention is only one of many factors that influence outcomes. However, there is good evidence that cessation rates can be improved if smokers choosing to make an assisted quit attempt are encouraged to use more effective interventions. A cost-effectiveness analysis of individual therapies found that while all included treatments were cost-effective compared with unassisted quitting, e-cigarettes and varenicline, alone or in combination with NRT, provide the best value for money on average. However, the pooled effect estimate for e-cigarettes is based on two trials, neither of which showed a statistically significant benefit within the trial itself. Both trials had absolute quit rates in the control and intervention arms that were low compared with

average absolute quit rates among trials of other interventions with comparable relative effect sizes.

Given the lack of available studies and the wide range of rapidly evolving products, there is a high level of uncertainty surrounding both the clinical effectiveness and costs of this intervention. Furthermore, the results of the cost-effectiveness analysis of e-cigarettes are extremely sensitive to changes in both these parameters. There is also considerable uncertainty about the long-term health effects of e-cigarette use, and concerns that their widespread promotion by health professionals could ultimately prove counterproductive by renormalising nicotine consumption or acting as a gateway to tobacco use among new generations of people who have never previously smoked. The results for varenicline and NRT in combination are also based on a pooled analysis of two studies comparing it to varenicline alone, one of which failed to show a statistically significant effect. However, there are a multitude of studies demonstrating the effectiveness of both varenicline alone and NRT alone versus placebo.

Translating the results of the cost-effectiveness analysis into meaningful improvements in smoking outcomes is impacted by the ability of the health service to influence uptake rates of interventions, particularly given the existing low uptake rates of the most effective interventions in Ireland and elsewhere. A cost-effectiveness analysis was carried out to compare the current uptake of cessation therapies among smokers trying to quit in Ireland with alternative mixes of interventions. This was also informed by international data on smoking cessation preferences. The analysis found that increasing the uptake of combination varenicline and NRT to plausible maximum levels was the optimal strategy for improving quit rates. This would also be associated with significant additional drugs costs and increases in demand for GP and nurse prescribing services.

A more likely scenario, however, is that e-cigarette use will continue to grow in popularity as an aid to smoking cessation. Increased e-cigarette use would also likely result in lower expenditure by the public health system on other prescription drugs due to a decline in their uptake, assuming the current funding model remains unchanged. Based on the limited available evidence, this would also be expected to improve quit outcomes compared with current practice, though less than that of maximising use of varenicline and NRT in combination. These results are again subject to the caveats outline above and are likely to change once further research becomes available.

For those choosing to make a quit attempt without the aid of pharmacotherapy or e-cigarettes, there is good evidence to show that behavioural support increases quit rates when compared with no support. There is insufficient evidence to reliably compare the effectiveness of different types of behavioural support in combination with pharmacotherapy, but existing studies show the addition of any type of

behavioural support is associated with a beneficial effect on quitting outcomes. This analysis focused solely on quit outcomes and as such, it does not consider other potential benefits of behavioural support and educational interventions in lowering smoking prevalence; for example, motivating more people to want to quit or decreasing the proportion of people who start smoking.

The evidence for smoking cessation treatments among specific subgroups of the population is more limited. Although there is a lack of data on the relative effectiveness of different smoking cessation interventions for people attending secondary care mental health services, high-intensity programmes combining pharmacotherapy and behavioural support have been shown to improve quit outcomes in this group. Among pregnant women, behavioural support interventions such as counselling, health education and the use of financial incentives were shown to significantly improve quit outcomes during pregnancy.

### **8.3 Conclusion**

Smoking cessation services should seek to maximise the uptake of varenicline, alone or in combination with NRT, among smokers wishing to use some type of pharmacological support in their quit attempt. While the available results for e-cigarettes are promising, given the current lack of evidence to demonstrate their effectiveness as an aid to smoking cessation, it is reasonable to await the results of ongoing trials before deciding whether to recommend e-cigarettes in preference to combination NRT for populations where varenicline is contraindicated, not tolerated or non-preferred. If additional evidence confirms the effectiveness of e-cigarettes as a smoking cessation aid, a decision to advocate their use should take into consideration any additional information on the long-term safety of e-cigarettes use, as well as any emerging data in relation to concerns about the social normalisation of e-cigarettes leading to increased uptake among people who have never smoked, or later migration to tobacco cigarettes.

Providing behavioural support, either alone or in combination with pharmacological interventions, increases the chances of long-term smoking cessation and should continue to be provided to all smokers who would like to avail of this option to help them quit.

Pregnant women who smoke should be offered a psychosocial intervention in the first instance. The psychosocial intervention with the largest body of evidence to support its effectiveness is counselling.

While the evidence for smoking cessation interventions among those attending secondary mental health services is very limited, high-intensity interventions combining pharmacotherapy and behavioural support have been shown to improve quit outcomes. However, further research on the effectiveness of smoking cessation interventions in this population is needed.

## 9 References

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## **10 Appendices**

All appendices to the report are available to download as a separate document on the HIQA website. Please see [www.hiqa.ie/healthcare/health-technology-assessment](http://www.hiqa.ie/healthcare/health-technology-assessment) for more information.

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