Guideline Development Group for the Identification, Diagnosis & Treatment of Tobacco Addiction

Assessment of Criteria for the Drafting of Recommendations as per GradePro

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QUESTION: ***What interventions should be offered by healthcare professionals to people using health services, to identify people who smoke and help them stop?***	
POPULATION:	*General adult population (aged 18+ years)* • Pregnant women (not limited to those aged 18+ years) ○ *from the first antenatal care contact to the postpartum period (3 months)*
INTERVENTION:	*Identifying smokers in routine clinical care and offering them support to quit smoking*
COMPARISON:	*Current services/No service*
MAIN OUTCOMES:	• *Long-term smoking cessation (≥ 6 months)* • Smoking cessation during and after pregnancy; maternal and fetal outcomes where available
SETTING:	*Primary care settings, Secondary care settings, Community care settings and mental health services*
PERSPECTIVE:	*Health Sector* ☐ *Population* ☑ *Individual* ☐ A population perspective has been adopted. However, this CJF incorporates evidence from a HIQA HTA which adopted a quasi-societal perspective in its cost-effectiveness analysis and as such, costs including out-of-pocket costs falling to the individual are considered. Furthermore, through the public and patient representatives involved in the considered judgement process, acceptability and feasibility of the interventions from the individual perspective have been considered.
BACKGROUND:	***Smoking in Ireland:*** The most recent Healthy Ireland Survey (2018) reports that 20% of people aged 15 years and older describe themselves as current smokers; this compares to a smoking prevalence of 29% in 2007 *(SLAN 2007)*. In terms of numbers, there are approximately 770,000 adults who smoke in Ireland in 2018. Current government policy *Tobacco Free Ireland* sets a target that less than 5% of the population will be current smokers by 2025. This target requires a significant reduction in the current smoking prevalence rate that will not be achievable through preventing smoking initiation alone; it will require increasing the incidence of quit attempts across the population of current smokers and increasing the odds of success. ***Smoking in Pregnancy:*** Approximately 10% of pregnant women in Ireland report that they continue to smoke at the time of their first antenatal visit in 2015; this compares to 14% in 2011 (*Reynolds et al, 2017*). Fewer women are now smoking in pregnancy compared to previously; The *Growing-up in Ireland* surveys reported smoking in pregnancy prevalence rates of 18% in 1997/1998 and 28%

in 2007/2008. A profile/characteristics of those who smoke in pregnancy is that they are usually younger, have had a previous baby, unemployed, display/history of depressive symptoms, and participate in some/multiple other risky behaviours.

Tobacco Free Ireland recognises the consequences of smoking in pregnancy, and smoking cessation among pregnant women is prioritised in the *HSE Tobacco Free Ireland Programme Plan 2018-2021*.

Quitting Behaviours:
Successive surveys inform us that most smokers want to quit smoking; almost 60% of current smokers in 2018 have a positive intention to quit, and 40% of current smokers have made at least one quit attempt in the last 12 months. However, just 9% of those who smoked in the past 12 months, have successfully quit; almost half of them did so through willpower alone, and use of evidence-based smoking cessation supports is poor. The majority of those who attempted to quit their smoking did so due to concerns about their health (65%), however, just 40% of smokers reported having discussed quitting with their General practitioner, and less than one-third of smokers had discussed quitting with other health professionals. *(Healthy Ireland Survey 2018)*

Both internationally, and locally, research suggests that that if a woman who smokes is going to quit smoking during pregnancy, she will often have quit before she is in contact with the health services. (*McArdle et al, 2018, Fitzpatrick et al, 2016*) However, as many as 40% of smokers in pregnancy may not report their smoking behaviour when questioned by healthcare professionals (*Reynolds, 2017*). Another challenge is that many of those who quit smoking in pregnancy, relapse within the first few months following birth (*Jones et al, 2016*)

Background to this Guideline:
A proposal for a national clinical guideline for the identification and treatment of smokers was submitted to the National Clinical Effectiveness Committee (NCEC), Department of Health, in July 2017 by the HSE Tobacco Free Ireland Programme. This submission was assessed according to the NCEC Preliminary Prioritisation Process for National Clinical Guidelines (2015) and in September 2017, this guideline was prioritised by NCEC and was listed on the NCEC schedule of guidelines.

The guideline development plan was to adapt International guidelines and to contextualise them to the Irish healthcare system, drawing on the HIQA Health Technology Assessment of smoking cessation interventions as an additional source of evidence. The search for relevant smoking cessation guidelines was conducted using a systematic search strategy of scientific databases (including guideline websites; PubMed; and Google ®) from January 2006 to June 2017. The quality of the CPGs was independently assessed by at least two assessors using the Appraisal of Guidelines for Research & Evaluation II (AGREE II) instrument, and specific recommendations in guidelines were evaluated. Domain scores were considered of sufficient quality when ≥ 60%. The HIQA HTA was also quality appraised.

	Ten guidelines were retrieved; three were deemed of very poor quality across all domains and removed. In addition, two guidelines scored poorly on the 'rigour of development' domain and were removed. A currency/permissions survey highlighted intellectual property rights with another guideline. The current evidence base included in the development of this guideline includes: • Ministry of Health. 2014. *The New Zealand Guidelines for Helping People to Stop Smoking*. Wellington: Ministry of Health • US Preventative Services Task Force. *Tobacco Smoking Cessation in Adults, Including pregnant women: behavioural & pharmacotherapy interventions*. 2015. • *CAN-ADAPTT Smoking Cessation Clinical Practice Guideline (General & Pregnant Women)*. 2012. • HIQA. *Health Technology Assessment for Smoking Cessation Services in Ireland*. 2017 • WHO. *Recommendations for the prevention & management of tobacco use and second-hand smoke exposure in pregnancy. 2013.* • Martin G, Quintyne KI. A review of the evidence to inform the implementation of carbon monoxide testing during pregnancy. Smoking Cessation Guideline Group. 2019. • And finally, a report on evidence scoping to assure currency of National Stop Smoking Guideline recommendations by the guideline development groups' Evidence Team (Dr Paul Kavanagh, Ms Aishling Sheridan and Dr Keith Ian Quintyne). This guideline group will use the GRADE Evidence-to-Decision Framework as per GradePRO to move from evidence to recommendations as detailed in this document.
CONFLICT OF INTERESTS:	Conflict of interest statements were submitted by members of the Guideline Development Group. The Chair reviewed all conflict of interest statements. No interests stated were deemed to be conflicts in relation to the recommendations of this guideline.

ASSESSMENT

1.	**Problem** Is the problem a priority? *(The more serious or urgent a problem is, the more likely it is that an option that addresses the problem will be a priority)*		
	JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

	○ No
	○ Probably no
	○ Probably yes
	● Yes
	○ Varies
	○ Don't know
		• Tobacco use is the leading cause of preventable death in Ireland; one-in-five deaths (5,900) in Ireland in 2016 were attributable to smoking or exposure to second-hand smoke. *(SOTC 2018)*
		• In addition, 55,000 hospital admissions per year are as a result of smoking and exposure to second-hand-smoke; these are potentially preventable. *(SOTC 2018)*
		• The total annual cost to the health service is estimated to be over €460 million and the total cost of lost productivity is over €1 billion. *(ICF International, 2016)*
		• In 2018,
		  ○ 20% of Irish adults are current smokers.
		  ○ Six-in-ten smokers have a positive intention to quit smoking, but just one-in-ten successfully quit.
		  ○ Almost half (42%) of those who successfully quit smoking in the last 12 months did so through willpower alone and 41% used e-cigarettes. *(HI Survey 2018)*
		Smoking in Pregnancy:
		• Maternal smoking is one of the most important preventable factors associated with adverse pregnancy outcome. (*European Perinatal Report, 2018)*
		• Approximately 10% of pregnant women in Ireland smoke during pregnancy (2015); this is slightly higher than European average. (*Reynolds et al, 2017*)
		• Smoking among pregnant women has declined in high-income countries, but it nonetheless continues to account for a substantial
			• Current government policy, ***Tobacco Free Ireland*** has set a target for Ireland to be tobacco-free (prevalence of smoking <5%) by 2025. *(DoH)*
			  ○ One of the recommendations within the TFI policy is to "*Develop comprehensive national smoking cessation guidelines. These to include the minimum level of service provision that each service provider needs to have in place.*"
			  ○ Tobacco Free Ireland recognises the consequences of smoking in pregnancy, and smoking cessation among pregnant women is prioritised in the HSE Tobacco Free Ireland Programme Plan 2018-2021.
			• The ***National Maternity Strategy 2016-2026 - Creating a Better Future Together*** recognises pregnancy as a unique opportunity to focus on health & wellbeing and maternity services can offer the appropriate information and supports to enable women make behaviour changes including smoking cessation.
			• ***First Five – A Whole-of-Government Strategy for Babies, Young Children & their Families 2019-2028*** supports positive health behaviours, starting from the pre-conception period.

		proportion of fetal and infant morbidity and mortality. (*European Perinatal Report, 2018)* • Smoking during pregnancy is still a prevalent behaviour in many countries, with high rate in Ireland compared to many countries internationally. (*European Perinatal Report, 2018*)	• In addition, tobacco use is recognised as a **global problem**: WHO report on the global tobacco epidemic, 2017: monitoring tobacco use and prevention policies; Executive Summary. Geneva: World Health Organization; 2017. Licence: CC BY-NC-SA 3.0 IGO. • **European Perinatal Report 2015 –** core indicators of the health and care of pregnant women and babies in Europe in 2015. Many countries, including Ireland, could not provide national data on maternal smoking during pregnancy. • In September 2017, this guideline was **prioritised by NCEC** and was listed on the NCEC schedule of guidelines. (prioritisation submission & response available on request) • ***A national audit of smoking cessation services in Irish maternity units*** reported major gaps, weaknesses and variation in the provision of smoking cessation support across maternity units in Ireland. (*Reynolds et al, 2017*). • In addition, there are many gaps regarding resources on the ground, especially regarding Smoking Cessation Midwives.

2.	**Desirable Effects** How substantial are the desirable anticipated effects? *(How large are the desirable effects of the intervention taking into account the importance of the outcomes (how much they are valued), and the size of the effect (the likelihood of experiencing a benefit or how much of an improvement individuals would be likely to experience?)*		
	JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
	○ Trivial ○ Small ○ Moderate ● Large ○ Varies ○ Don't know	• Smoking causes death and disability on a large scale and it is well documented that cigarette smoking has been causally linked to diseases of nearly every organ of the body, to diminish health status and to fetal harm. *(US Department of Health & Human Services, A Report of the Surgeon General, 2014).* The burden of hospitalisation and death attributable to smoking that could be avoided through elimination of this risk factor has been quantified in Ireland: 55,000 hospitalisations and 5,900 deaths *(SOTC 2018).* • Stopping smoking results in immediate health benefits, and stopping smoking before age 40 years avoids more than 90% of the excess mortality caused by continuing smoking, while stopping before 30 years avoids more than 97% of the excess mortality. (*Pirie et al, Lancet, 2013 & Jha et al, N Engl J Med, 2013*) • Mental health and quality of life benefits are also associated with smoking cessation compared to continuing smoking. *(Taylor et al, BMJ 2014)* • Intervention from health professionals has been shown repeatedly, in randomised controlled trials, to increase the percentage of smokers who stop and remain abstinent for 6 months or more (*West et al, 2000*). • Behavioural interventions and pharmacological interventions, in combination, or alone are effective in assisting those who want to quit smoking: ○ Group behaviour therapy is the most effective behavioural intervention, almost twice as effective as an active control (defined as brief advice or written materials). ○ 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. *(HIQA HTA)* • In its HTA, HIQA have demonstrated that maximising the use of Varenicline and Varenicline in combination with NRT in Ireland would increase the number of successful quitters by 77% and 97% respectively (*(HIQA HTA 2018)*. **Benefits of Smoking Cessation pre-pregnancy or in Pregnancy:** • Maternal smoking is one of the most important preventable factors associated with adverse pregnancy outcome. • Maternal smoking can lead to poor pregnancy outcomes including ectopic pregnancy, miscarriage and stillbirth. • Maternal smoking during pregnancy impairs normal fetal growth and development and is associated with low birth weight, fetal growth restriction, stillbirth, preterm birth, and some congenital anomalies. • The effects of maternal smoking on outcomes are not limited only to the perinatal period; increasing evidence suggests it also has lifelong consequences for the child, with elevated risks of childhood obesity, neuro-behavioural and cognitive deficits, and impaired lung function, including wheezing and asthma. (*European Perinatal Report, 2015*) • Smoking cessation in the first half of pregnancy is optimal to improve outcomes, and quitting prior to conception when more treatment options are available and therapy is more likely to succeed is the ideal. • Mothers' intention to quit smoking usually reduces as the pregnancy progresses; however, smoking cessation at any stage during pregnancy has benefits and is associated with better outcomes. (*Cooper et al, 2017*) **Breath Carbon Monoxide Testing to Identify Smoking in Pregnancy:** • Studies have shown that by using BCO testing during antenatal care, combined with 'opt-out' referral to smoking cessation services, attendance to support services increased by two-fold and the probability of quitting by delivery increased by nearly two-fold.	

		• Smoking cessation interventions reduced low birth weight and pre-term birth and there was a 53.9 gramme increase in mean birthweight. *(Lit review by G Martin & KI Quintyne)*	

3.	**Undesirable Effects** How substantial are the undesirable anticipated effects? *(How large are the undesirable effects of the intervention taking into account the importance of the outcomes (how much they are valued), and the size of the effect (the likelihood of experiencing a benefit or how much of an improvement individuals would be likely to experience?)*		
	JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
	○ Large ○ Moderate ○ Small ● Trivial ○ Varies ○ Don't know	• No substantive adverse effects were identified following review of the efficacy literature associated with behavioural interventions. *(HIQA HTA 2018)* • Pharmacological interventions for smoking cessation are generally safe and well-tolerated in this population. In the absence of contraindications, these agents are undoubtedly safer than the continuation of smoking. *(HIQA HTA 2018)* **Smoking cessation in Pregnancy:** • There is some evidence of beneficial effect for NRT as an aid to smoking cessation; however, there is reluctance by many health professionals to prescribe due to safety concerns. *(HIQA HTA)*	• HIQA - Section 5 details an overview of the current evidence in relation to the safety of pharmacological smoking cessation interventions and e-cigarettes. • All pharmacological interventions referenced in guidelines and available in Ireland are licensed and regulated through Healthcare Products Regulatory Authority (HPRA) • Neither bupropion nor varenicline is licensed for use during pregnancy in Ireland • How will MECC sit with smokers? Marie O'Brien will feedback to the group with a study on acceptability re intervention in January 2019. ○ Initial findings on the acceptability of MECC among patients and clients is that MECC is well accepted by clients and patients, and there is an expectation that they will be asked about their lifestyle & behaviour change e.g. smoking cessation. • Debunking the Myths – Some health care professionals have concerns about damaging client relationships as a result of discussing/identifying smoking in pregnancy and smoking cessation. (*Naughton et al, 2018*)

			• Prior to implementation of BCOT in the UK, healthcare staff expressed concerns that BCO testing would unjustly accuse women who do not smoke of doing so, and that this would affect their relationship with the women. *(Lit review by G Martin & KI Quintyne)* • Given the findings regarding effectiveness, and the resultant recommendations, the undesirable effects of e-cigarettes are not considered since they are not a recommended intervention. 4% of people report currently using e-cigarettes; 9% of current smokers and 10% of ex smokers; 17% of those who have tried to quit smoking in the past year, and 30% of those who have successfully quit smoking, are current users of e-cigarettes (*Healthy Ireland Survey 2018*). Recently, studies on the toxicological profile and short-term safety profile of e-cigarettes have emerged (PHE, National Academies). HIQA found that the 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. In addition, HIQA has identified that 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. *(HIQA HTA 2018)*

4.	**Certainty of evidence** What is the overall certainty of the evidence of effects? *(How good an indication does the research provide of the likely effects across all the critical outcomes i.e. the likelihood that the effects will be different enough from what the research found that it might affect a decision about the intervention?*		
	JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
	○ Very low ○ Low ○ Moderate ● High ○ No included studies	• **Ask and document every person's smoking status, and advise people who smoke to stop** (HIGH – NZ, Canada and USA; HIQA, standard of care) • **Offering behaviour support:** ○ **Brief Intervention** (HIGH – NZ, Canada and USA; HIQA, standard of care / Intensive Advice RR 1.19 (95% CI 1.05 - 1.35; PI 0.84 – 1.67); ○ **Individual or Group Counselling** (4 or more, HIGH – NZ, Canada and USA (USA has specification); HIQA Individual Counselling RR 1.48 (95% CI 1.17 - 1.85; 95% PI 1.11 – 1.96) and Group behaviour Therapy RR 1.80 (95% CI 1.36 - 2.40; 95% PI 0.66 – 4.92); ○ **Phone** (HIGH – NZ, CANADA and USA; HIQA RR 1.34 (95% CI 1.19 - 1.51;95% PI 0.70 - 2.47); ○ **Text** (NZ – Moderate – conflicting); ○ **Internet-based:** (NZ – insufficient evidence; HIQA RR 1.43 (95% CI 1.02, 2.0; 95%PI 0.45, 4.51) "HIQA: The direct evidence suggests a somewhat consistent picture whereby 'do nothing' is less effective than control or active intervention. Intensive advice, telephone support, Internet-based, individual counselling and group behaviour are superior to control	This is supported by Making Every Contact Count Policy, HSE Relapse prevention is a common question which arises for healthcare professionals. The guidelines already provide some good practice points. There is now systematic review and meta-analysis evidence by Cochrane to develop these points further (see Evidence Review, December 2020). It could be added to good practice points and the appropriate section of the document could discuss the evidence. Chapter 4 HIQA report presents evidence of effectiveness of various interventions using direct and indirect approaches. As per Section 16.6.2 of the Cochrane Handbook of Systematic reviews of Intervention, this guideline has focussed on direct

		and, based on limited evidence, there is no statistically significant evidence of any one offering a treatment benefit over another" • **Offering pharmacological support** ○ USPSTF Blanket Statement – GRADE HIGH "*provide U.S. Food and Drug Administration (FDA)–approved pharmacotherapy for cessation to adults who use tobacco*" ○ **NRT** (HIGH NZ; HIQA RR 1.59 (95% CI 1.50 - 1.69, PI 1.12 - 2.25)); for at least 8 weeks (HIGH NZ). ○ **Bupropion** (HIGH NZ; HIQA RR 1.65 (95% CI 1.51 – 1.79, PI (1.47-1.84)); ○ **Bupropion + NRT** (HIQA RR 1;73 (95% CI 1.39 - 2.15) ○ **Cystine** (HIQA RR 1.87 (95% CI 1.48 - 2.38)) – not licensed ○ **Combo NRT** (HIGH NZ; HIQA RR 1.71 (95% CI 1.30 - 2.25)) ○ **Varenicline** (HIGH NZ; HIQA RR 2.66 (95% CI 2.25 – 3.15; PI 1.52 - 4.66) ○ **Varenicline + NRT** (HIQA RR (vs Varenicline monotherapy, 2 studies) 1.42 (1.13 – 1.79)) ○ **E-Cigarettes:** The USPSTF concludes that the current evidence is insufficient to recommend electronic nicotine delivery systems (ENDS) for tobacco cessation in adults; HIQA RR 2.29 (95% CI 1.05 – 4.96) – "It would be appropriate to await the results of ongoing trials before deciding whether e-cigarettes should be recommended in preference to combination NRT for populations where varenicline is contraindicated, not tolerated or non-preferred." • **Offer Combined behaviour and pharmacological support**: HIGH – Canada, USA; HIQA "The effectiveness of pharmacological interventions is improved by an average of 18% by providing any type of adjunct behavioural therapy".) • **Most effective support - HIQA HTA**: ○ Varenicline was the most effective single therapy on direct analysis of evidence, with a risk ratio of 2.66. Varenicline is the most effective monotherapy, and has a small, but not statistically significant treatment benefit compared to combination NRT ○ NRT and Bupropion are similarly effective, with risk ratios close to 1.60.	<u>comparisons</u> as it's considered these take preference where available. Behavioural summary at Table 4.12: Treatment effects based on direct evidence; • Note to handling of data on effectiveness of behavioural supports by HIQA – in particular, the comparator/control (brief advice/written materials) (*See AppendixA*) Text-messaging is used by the HSE QUIT programme. Its effectiveness is supported by a systematic review and meta-analysis by Cochrane (Evidence update, December 2020). The GDG considered adding it to recommendations on behavioural support and to the appropriate section of the document. Pharmacotherapy summary at Table 4.4: Treatment effects based on direct evidence: pharmacological studies available at document end (*See AppendixB*) **Pharmacological Considerations:** • Cystine not licensed in Ireland. • Nortriptyline is now available for use in Ireland. It was omitted from the initial HIQA HTA. Its effectiveness is supported

		○ Advise to Minister: "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. 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". **Smoking In pregnancy:** • **Identify smokers & exposure to SHS:** ○ USPSTF: "The USPSTF recommends that clinicians ask all pregnant women about tobacco use, advise them to stop using tobacco, and provide behavioral interventions for cessation to pregnant women who use tobacco." (HIGH). ○ WHO: "Health-care providers should ask all pregnant women about their tobacco use (past and present) and exposure to SHS, as early as possible in the pregnancy, and at every antenatal care visit." [LOW] • **Use of Breath Carbon Monoxide Testing to Identify Smokers:** ○ Lit Review: ▪ BCO testing during antenatal care, combined with opt-out referral to smoking cessation services, increased attendances to support services two-fold and the probability of quitting by delivery increased by nearly two-fold. [MODERATE]	by a systematic review and meta-analysis by Cochrane (See evidence update, December 2020). The GDG added to recommendations on pharmacotherapy and the appropriate sections of the guidance document were updated. **Alternative/other supports or services for smoking cessation:** Consider quelling myths re alternative/other supports or services for smoking cessation in this guideline? – these are challenges in everyday practice The GDG examined new evidence on Allen Carr along with evidence team comments (Evidence Update, December 2020) and considered if good practice points for healthcare professionals on how to respond to queries on a range of non-recommended interventions (including e-cigarettes, AC method, hypnotherapy and acupuncture) should be considered. The appropriate sections in the guideline document were updated. **Most effective supports – HIQA HTA** HIQA conclusions re ranking based on network estimates, were considered with

		▪ BCO testing compliments routine history taking by should not replace it as this may produce false negative. [LOW] ▪ A cut-off of 7ppm is likely to be optimal for identifying smoking. [LOW] • **Engage with partners and/or household contacts:** ○ Canada: "Partners, friends and family members should also be offered smoking cessation interventions. "[MODERATE] ○ WHO: ▪ Health-care providers should provide pregnant women, their partners and other household members with advice and information about the risks of SHS exposure from all forms of smoked tobacco as well as strategies to reduce SHS in the home. [LOW] ▪ Health-care providers should, wherever possible, engage directly with partners and other household members to inform them of the risks of SHS exposure to pregnant women from all forms of smoked tobacco, and to promote reduction of exposure and offer smoking cessation support. [LOW] • **Offering support:** ○ New Zealand: ▪ "All health care workers should briefly advise pregnant and breastfeeding women who smoke to stop." [HIGH] ▪ Advise on the benefits of having smoke free homes and cars. [MODERATE] ○ USPSTF: "The USPSTF recommends that clinicians ask all pregnant women about tobacco use, advise them to stop using tobacco, and provide behavioral interventions for cessation to pregnant women who use tobacco." (HIGH). ○ Canada: ▪ Smoking cessation should be encouraged for all pregnant, breastfeeding and postpartum women. [HIGH] ▪ A smoke-free home environment should be encouraged for pregnant and breastfeeding women to avoid exposure to second-hand smoke. [MODERATE] ○ WHO: Health-care providers should provide pregnant women, their partners and other household members with advice and information about the risks of SHS exposure from all forms of	reference to Cochrane Handbook. 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). 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. 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. The variation in the level of evidence used by both guidelines may be reflective of the very different healthcare models that the WHO report on. In 2017, Just 1/19 units nationally conducts BCO test in pregnancy. *(Reynolds et al, 2017)*. Anecdotal reports suggest that this number may have increased since then.

		smoked tobacco as well as strategies to reduce SHS in the home. [LOW] • **Offering behavioural support:** ○ New Zealand: ▪ Offer all pregnant and breastfeeding women who smoke multi-session, behavioural, stop-smoking interventions without delay from a dedicated stop-smoking service. [HIGH] ▪ Where women have had a smoke free pregnancy, offer them help to remain smoke free after birth.[Grade ☑] ○ USPSTF: "The USPSTF recommends that clinicians ask all pregnant women about tobacco use, advise them to stop using tobacco, and provide behavioral interventions for cessation to pregnant women who use tobacco." (HIGH). ○ Canada: "During pregnancy and breastfeeding, counselling is recommended as first line treatment for smoking cessation." [HIGH] ○ HIQA HTA: ▪ **Health education:** (RR 1.43, 95%CI: 1.07 – 1.92) ▪ **Counselling:** (RR 1.35, 95% CI: 1.17 – 1.57). ▪ **Financial incentives:** (RR 2.28, 95% CI: 1.55 – 3.34). ○ WHO: Health-care providers should routinely offer advice and psychosocial interventions for tobacco cessation to all pregnant women, who are either current tobacco users or recent tobacco quitters.* (*Recent tobacco quitters may include women who used tobacco before the pregnancy, and who have either spontaneously quit or stopped using tobacco in the pre-conception period or in early pregnancy, before their first antenatal visit*) [MODERATE] • **Offering pharmacological support:** ○ USPSTF blanket statement - concludes that the current evidence is insufficient to assess the balance of benefits and harms of pharmacotherapy interventions for tobacco cessation in pregnant women." (LOW) **NRT:** ○ New Zealand: "Pregnant women can use NRT in pregnancy and during breastfeeding. Discuss with them the risks versus benefits of using NRT during pregnancy." [MODERATE]	Prior to implementation of NICE guidelines in the UK, healthcare staff expressed concerns that BCO testing would unjustly accuse women who did not smoke of doing so, and that it would affect their relationship with the women. Following implementation of the guidelines, they found that it had little effect on their relationship with women and that staff had a unique opportunity to address SHS, smoke-free homes and the effects of smoking around children with non-smokers who may be regularly exposed to passive smoke *(Lit review by G Martin & KI Quintyne)* • There is no consensus regarding cut-off score; and raising or lowering the cut-off level of the test requires a trade-off between sensitivity and specificity. *(Lit review by G Martin & KI Quintyne)* • HIQA HTA - See Appendix D • HIQA HTA – note small study bias and definitions of interventions were very heterogeneous. • HIQA HTA: "Pregnant women who smoke should be offered a psychological intervention in the first instance. The psychological intervention with the

		○ Canada: "If counselling is found ineffective, intermittent dosing nicotine replacement therapies (such as lozenges, gum) are preferred over continuous dosing of the patch after a risk-benefit analysis." [LOW**]** ○ HIQA HTA: 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). Caveats re safety profile. ○ WHO:The panel cannot make a recommendation on use or non-use of nicotine replacement therapy to support cessation of tobacco use in pregnancy. [MODERATE] **Bupropion:** ○ HIQA HTA: Use of Bupropion is contraindicated among pregnant women in Ireland ○ WHO: The panel does not recommend use of bupropion or varenicline to support cessation of tobacco use in pregnancy. [VERY LOW] **Varenicline:** ○ HIQA HTA: Varenicline is not recommended during pregnancy, as the currently available studies of varenicline use in pregnancy are insufficient to provide evidence for safety. ○ WHO: The panel does not recommend use of bupropion or varenicline to support cessation of tobacco use in pregnancy. [VERY LOW]	largest body of evidence to support its evidence is counselling." • The concept of financial incentives is not currently in use in Ireland. • HIQA HTA - See Appendix E • Note: efficacy of NRT in pregnancy appears to be lower than in non-pregnant smokers. • **Summary of Product Characteristics re pregnancy**: • NRT: ○ Smoking during pregnancy is associated with risks such as intra-uterine growth retardation, premature birth or stillbirth. Stopping smoking is the single most effective intervention for improving the health of both pregnant smoker and her baby. The earlier abstinence is achieved the better. ○ Nicotine passes freely to the foetus and affects its breathing movements and circulation. The effect on the circulation is dose-dependent. Therefore, the pregnant smoker should always be advised to stop smoking completely without the use of nicotine replacement therapy. The risk of continued smoking may pose a greater hazard to the foetus as compared with the use of nicotine replacement therapy products in a supervised cessation programme. Use of Nicorette Invisi Patch should only be initiated after advice from a physician. • Varenicline:

			○ A moderate amount of data on pregnant women indicated no malformative or foetal/neonatal toxicity of varenicline. Animal studies have shown reproductive toxicity. As a precautionary measure, it is preferable to avoid the use of varenicline during pregnancy. • <u>Bupropion:</u> ○ Some epidemiological studies of pregnancy outcomes following maternal exposure to bupropion in the first trimester have reported an association with increased risk of certain congenital cardiovascular malformations specifically ventricular septal defects and left outflow tract heart defects. These findings are not consistent across studies. Animal studies do not indicate direct or indirect harmful effects with respect to reproductive toxicity (see section 5.3). Zyban should not be used in pregnancy. Pregnant women should be encouraged to quit smoking without the use of pharmacotherapy.
5.	**Values** Is there important uncertainty about or variability in how much people value the main outcomes? *(How much do individuals value each of the main outcomes? Is uncertainty about how much they value each of the outcomes or variability in how much different individuals value the outcomes large enough that it could lead to different decisions?*		
	JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
	○ Important uncertainty or variability ○ Possibly important uncertainty or variability ○ Probably no important uncertainty or variability ● **No important uncertainty or variability**	Healthy Ireland survey's from 2015-2018 indicates the majority of smokers want to quit, valuing the outcome of smoking cessation. Results show a high percentage of smokers are trying to, planning to or are considering quitting: - 63% (2015), 59% (2016), 57% (2017 and 2018) - Therefore in 2018, just 43% of current smokers are <u>Not</u> thinking about quitting smoking.	The introduction of **Making Every Contact Count** attempts to instigate a culture whereby patients will expect healthcare professionals to ask about health behaviours Ireland has a long tradition in tobacco control. The following table details **Key milestones in Tobacco Control In Ireland, 1998-2018** (source: SOTC)

		In depth analysis of the Healthy Ireland survey 2015 identified that over 40% of smokes are more likely to report poorer health (both physical and mental health) compared to people who do not smoke, independent of age, gender and social class. Ex-smokers report better health than current smokers and report similar levels of mental ill-health as never smokers. (The State of Tobacco Control in Ireland 2018) The profile of people who smoke with a positive intention to quit does not vary between male and female, however there is a significant difference across age group: positive intention to quit is more common across increasing age groups, peaking in 35-44 year age group. Attempts to quit is similar among males and females; however, across age groups, making a quit attempt was more common among younger people, for example those aged 25-34 years had made an attempt compared to 43% of those aged 55-64 years (The State of Tobacco Control in Ireland 2018).	✓ 2017 – Standardised (Plain) Packaging of Tobacco ✓ 2014 – EU Tobacco Products Directive ✓ 2013 – Launch of Tobacco Free Ireland ✓ 2011 – Graphic warnings on Tobacco ✓ 2010 – HSE Tobacco Control Framework ✓ 2009 – restrictions on sale, removal of point-of-sale tobacco displays ✓ 2005 – WHO Framework Convention on Tobacco Control ratified ✓ 2004 – Workplace Smoking Ban ✓ 2002 – Office of Tobacco Control established. Prohibition on advertising & sponsorship ✓ 2000 – Towards a Tobacco Free Society ✓ 1999 – Joint committee on Health & Children: A National Anti-Smoking Strategy ✓ 1991 – Certain regulations on tobacco advertising ✓ 1988 – Smoking banned in public buildings • Pregnancy is a unique opportunity to change behaviour – with heightened awareness/motivation among women to change risky health behaviours for the benefit of their health and future health of their baby.

6.	**Balance of effects** Does the balance between desirable and undesirable effects favour the intervention or the comparison? *(What is the balance between the desirable and undesirable effects , taking into account how much individuals value the main outcomes, how substantial the desirable and undesirable effects are , the certainty of those estimates, discount rates, risk aversion and risk seeking?*		
	JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
	○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ● **Favours the intervention** ○ Varies ○ Don't know	• Two-thirds of those who attempted to quit in the last 12 months did so due to concerns about their health. *(HI Survey 2018)* • Stopping smoking results in immediate health benefits, and stopping smoking before age 40 years avoids more than 90% of the excess mortality caused by continuing smoking, while stopping before 30 years avoids more than 97% of the excess mortality. (*Pirie et al, Lancet, 2013 & Jha et al, N Engl J Med, 2013*) • Ex-smokers report better health than current smokers and report similar levels of mental ill-health as never smokers. (*The State of Tobacco Control in Ireland 2018)* • 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. *(HIQA HTA 2018)* • BCO testing is safe, quick, non-invasive, inexpensive and yields immediate results at the point of care. *(Lit review by G Martin & KI Quintyne)* • Smoking cessation interventions reduced low birth weight and pre-term birth and there was a 53.9 gramme increase in mean birthweight. *(Lit review by G Martin & KI Quintyne)*	A national audit of smoking cessation services in Irish maternity units: (*Reynolds et al, 2017*)

7.	**Resources required** How large are the resource requirements (costs)? *(How large is the cost of the difference in resource use between the intervention and the comparison?)*		
	JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
	● **Large costs** ○ Moderate costs ○ Negligible costs and savings ○ Moderate savings ○ Large savings ○ Varies ○ Don't know	**A Budget Impact Analysis (BIA) informs this section of the guideline.** The HIQA HTA provides some information in that it details the costs of smoking cessation interventions, and offers various scenarios and related costs. 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 If BCOT is to be recommended, this will be included in the BIA.	Chapter 6 of HIQA HTA: Economic Analysis HSE budget allocation for 2019 is €16.05 billion. **Smoking in Pregnancy:** • No data/costs specific to this population in HIQA HTA – this will be informed by the planned Budget Impact Assessment.

8.	**Certainty of evidence of required resources** What is the certainty of the evidence of resource requirements (costs)? *(How certain is the evidence of a difference for each type of resource used (e.g. drugs, hospitalisations) and the cost of the resources?)*		
	JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
	○ Very low ○ Low ● **Moderate** ○ High ○ No included studies	**A Budget Impact Analysis (BIA) informs this section of the guideline.** The HIQA HTA provides some information in that it details the costs of smoking cessation interventions, and offers various scenarios and related costs. 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, 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 BCOT is to be recommended, this will be included in the BIA. In UK, the additional cost per delivery was £31 and the incremental cost per delivery was £952.	**Smoking in Pregnancy:** • No data/costs specific to this population in HIQA HTA – this will be informed by the planned Budget Impact Assessment.

This section relies on Section 7 - resources

9.	**Cost effectiveness** Does the cost-effectiveness of the intervention favour the intervention or the comparison? *(Is the intervention cost-effective taking into account uncertainty about or variability in the costs, uncertainty about or variability in the net benefit, sensitivity analyses, and the reliability and applicability of the economic evaluation?)*		
	JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
	○ Favours the comparison ○ Probably favours the comparison ○ Does not favour either the intervention or the comparison ○ Probably favours the intervention ● **Favours the intervention** ○ Varies ○ No included studies	HIQA HTA: 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. Table 6.2 (HIQA HTA – *See Appendix C*) 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.. HIQA HTA concluded that all cessation interventions included in the analysis would be considered cost-effective when compared with unassisted quitting. 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. 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. Breath Carbon Monoxide Tests are inexpensive and yield immediate results. *(Lit review by G Martin & KI Quintyne)*	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%). 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.

10.	**Equity** What would be the impact on health equity? *(Are there plausible reasons for anticipating differences in the relative effectiveness of the intervention for disadvantaged subgroups or different baseline conditions across disadvantaged subgroups that affect the absolute effectiveness of the intervention or the importance of the problem?)*		
	JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
	○ Reduced ● **Probably reduced** ○ Probably no impact ○ Probably increased ○ Increased ○ Varies ○ Don't know	Potential to reduce – but need to target plan (price and marketing) carefully and track. SOTC: Gap, potentially widening. Poor visibility of equity impact with routine information but some "pro-equity" evidence with face to face services. NPS Research: Results: There was no association between area based deprivation and the likelihood of making a quit attempt. While use of smoking cessation aids was generally low, smokers in more deprived areas had higher odds of using aids in a quit attempt (adjusted OR 1.06, 95% CI 1.02 to 1.11 for every 10% increase in area-based deprivation). The odds of being successful in a quit attempt decreased as deprivation increased (adjusted OR 0.92, 95% CI 0.88 to 0.97 for every increase in deprivation decile), and this was remained significant after controlling for the use of help, age and gender were controlled for. HIQA HTA: "Some tobacco control policies, not limited to cessation interventions, may contribute to increasing cessation inequalities. 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."	Bosdriesz JR, Willemsen MC, Stronks K, Kunst AE. Socioeconomic inequalities in smoking cessation in 11 European countries from 1987 to 2012. Journal of epidemiology and community health. 2015;69(9):886-92. Low A, Unsworth L, Low A, Miller I. Avoiding the danger that stop smoking services may exacerbate health inequalities: building equity into performance assessment. BMC Public Health. 2007;7:198. Hill S, Amos A, Clifford D, et al Impact of tobacco control interventions on socioeconomic inequalities in smoking: review of the evidence Tobacco Control 2014;23:e89-e97. ***Institute of Public Health – A Tobacco Free Future _ An all-island report on Tobacco, Inequalities & Childhood*** **-** Smoking in pregnancy is strongly socially patterned across the island with age and socioeconomic factors including employment, social class and deprivation status acting as key determinants of smoking prevalence. Socioeconomic inequalities in smoking during pregnancy have persisted against a background of overall declines in prevalence of smoking during pregnancy. • A national audit of smoking cessation services in Irish maternity units: (*Reynolds et al, 2017*)

11.	**Acceptability** Is the intervention acceptable to key stakeholders? *(Are key stakeholders likely not to accept the distribution of the benefits, harms and costs; or the costs or the undesirable effects in the short term for desirable effects (benefits) in the future? Are they likely to disagree with the values attached to the desirable or undesirable effects , or not to accept the intervention because of ethical concerns?)*		
	JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**
	○ No ○ Probably no ● **Probably yes** ○ Yes ○ Varies ○ Don't know	• The Healthy Ireland survey 2017 reports: - 35% of smokers who saw their GP - 25% of those who saw a hospital doctor - 22% of those who saw a nurse - 20% of smokers who saw a dentist - 10% of smokers who saw a pharmacist in the past 12 months discussed ways of quitting smoking Those aged 25 to 34 (where smoking rates are higher) were less likely to discuss with their GP ways of quitting, 30% of this age group who saw their GP discussed ways of quitting. (Healthy Ireland 2017) Prior to implementation of NICE guidelines in the UK, healthcare staff expressed concerns that BCO testing would unjustly accuse women who did not smoke of doing so, and that it would affect their relationship with the women. Following implementation of the guidelines, they found that it had little effect on their relationship with women and that staff had a unique opportunity to address SHS, smoke-free homes and the effects of smoking around children with non-smokers who may be regularly exposed to passive smoke *(Lit review by G Martin & KI Quintyne)*	• Cultural issues within some different staff subgroups • Variability in prioritisation • Ability to release staff for training ***Request to Maria O'Brien (MECC) for additional information re acceptability*** • Initial findings on the acceptability of MECC among patients and clients is that MECC is well accepted by clients and patients, and there is an expectation that they will be asked about their lifestyle & behaviour change e.g. smoking cessation. The routine use of breath carbon monoxide testing is routine in 2 maternity units in Ireland, with plans to introduce it in a 3rd unit shortly. The test is optional to women in these units.

12	**Feasibility** Is the intervention feasible to implement? *(Is it feasible to sustain use of the intervention and to address potential barriers to using it?)*		
	JUDGEMENT	**RESEARCH EVIDENCE**	**ADDITIONAL CONSIDERATIONS**

	○ No
	○ Probably no
	● **Probably yes**
	○ Yes
	○ Varies
	○ Don't know
		An integral part of this guideline will be an accompanying implementation plan with time-frame of 2-3 years. This plan will include all expected outcomes and details of how these outcomes will be verified.
		
		The implementation plan also details the identified barriers and enablers for the implementation of each recommendation, and actions to address same are also included.
			• MECC Policy
			• New Undergraduate Curriculum for Chronic Disease Prevention and Management
			• Healthcare Utilisation by adults (aged 15+) in Ireland in 2018:
			  ○ 74% of adults in Ireland have visited a GP, with an average of 3.8 visits per person (6.2 visits for those with a full medical card);
			  ○ 12% of adults have been admitted to hospital as an inpatient;
			  ○ 10% have used an ED in a public hospital.
			• Tom Sharpe,1 Ali Alsahlanee,1 Ken D. Ward,2 and Frank Doyle1. Systematic Review of Clinician-Reported Barriers to Provision of Smoking Cessation Interventions in Hospital Inpatient Settings. Journal of Smoking Cessation. 2018. doi:10.1017/jsc.2017.25

SUMMARY OF JUDGEMENTS

	JUDGEMENT						
PROBLEM	No	Probably no	Probably yes	**Yes**		Varies	Don't know
DESIRABLE EFFECTS	Trivial	Small	Moderate	**Large**		Varies	Don't know
UNDESIRABLE EFFECTS	Large	Moderate	Small	Trivial		**Varies**	Don't know
CERTAINTY OF EVIDENCE	Very low	Low	Moderate	**High**			No included studies
VALUES	Important uncertainty or variability	Possibly important uncertainty or variability	**Probably no important uncertainty or variability**	No important uncertainty or variability			
BALANCE OF EFFECTS	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	**Favours the intervention**	Varies	Don't know
RESOURCES REQUIRED	**Large costs**	Moderate costs	Negligible costs and savings	Moderate savings	Large savings	Varies	Don't know
CERTAINTY OF EVIDENCE OF REQUIRED RESOURCES	Very low	Low	**Moderate**	High			No included studies
COST EFFECTIVENESS	Favours the comparison	Probably favours the comparison	Does not favour either the intervention or the comparison	Probably favours the intervention	**Favours the intervention**	Varies	No included studies
EQUITY	Reduced	**Probably reduced**	Probably no impact	Probably increased	Increased	Varies	Don't know
ACCEPTABILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know
FEASIBILITY	No	Probably no	**Probably yes**	Yes		Varies	Don't know

TYPE OF RECOMMENDATION

Strong recommendation against the intervention	Conditional recommendation against the intervention	Conditional recommendation for either the intervention or the comparison	Conditional recommendation for the intervention	**Strong recommendation for the intervention**
○	○	○	○	●

CONCLUSIONS

Draft Recommendations

See Final guideline document.

Justification

See Final guideline document.

Subgroup considerations

See Final guideline document.

Implementation considerations

See Final guideline document.

Monitoring and evaluation

See Final guideline document.

Research priorities

See Final guideline document.

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^2 (95% CI)
Individual counselling vs Nothing*[199]	1	155	0.85 (0.27 – 2.63)	0.772		NA
Telephone support vs Nothing*[275]	1	1821	1.11 (0.74 - 1.67)	0.621		NA
Internet-based vs Nothing*[242, 248, 249]	3	3671	1.46 (1.18 – 1.81)	0.001		0.61 (0.00 - 0.89)
Control vs Nothing[173, 215, 223, 240, 353, 462-469]	14	9720	1.67 (1.34 - 2.07)	<0.001	(0.97 - 2.85)	0.31 (0.00 - 0.64)
Intensive advice vs Nothing[187, 215, 224, 225, 229, 231, 233, 234, 240]	9	6707	1.74 (1.36 - 2.24)	<0.001	(0.96 - 3.15)	0.36 (0.00 - 0.71)
Acupuncture vs Nothing*[167, 173]	2	243	2.49 (1.23 – 5.02)	0.011		0.00
Group behaviour therapy vs Nothing[167, 173, 177, 182, 187, 190]	6	846	3.16 (1.26 - 7.90)	0.014	(0.19 - 53.03)	0.69 (0.28 - 0.87)
Acupuncture vs Control[164-166, 168-174]	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*[251-253]	3	1112	1.18 (0.88 - 1.60)	0.272		0.51 (0.00 - 0.86)
Intensive advice vs Control[210, 212-223, 226-228, 230, 232, 235-241]	25	16196	1.19 (1.05 - 1.35)	0.008	(0.84 - 1.67)	0.28 (0.00 - 0.56)
Telephone support vs Control[218, 235, 254-274, 276-293]	41	44218	1.35 (1.21 - 1.51)	<0.001	(0.78 - 2.35)	0.64 (0.49 - 0.74)
Internet-based vs Control[244-247, 250]	5	5128	1.43 (1.02 - 2.00)	0.041	(0.45 - 4.51)	0.70 (0.23 - 0.88)
Individual counselling vs Control[178, 192, 200-203, 207, 208]	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[168, 173, 175, 176, 178, 180, 184-186, 188, 189, 191-197]	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*[204, 206]	2	1226	1.02 (0.74 - 1.42)	0.884		0.22
Intensive advice vs Telephone support*[211, 218, 235]	3	2869	1.11 (0.77 - 1.59)	0.572		0.00 (0.00 - 0.88)
Mobile phone-based vs Internet-based*[243]	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*[178, 183, 192, 198]	4	2854	1.10	(0.87 - 1.40)	0.426	0.42	(0.00 - 0.81)
Intensive advice vs Individual counselling*[205, 209]	2	1028	1.40	(1.08 – 1.80)	0.010	0.85	
Intensive advice vs Group behaviour therapy*[179, 181, 187]	3	351	1.05	(0.63 - 1.75)	0.853	0.00	(0.00 - 0.33)
Acupuncture vs Group behaviour therapy*[167, 168, 173]	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.

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^2 (95% CI)
NRT vs Control[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]	116	53,066	1.59 (1.50 - 1.69)	<0.001	(1.12 - 2.25)	0.34 (0.16 - 0.47)
Bupropion vs Control[294-301, 303-311, 313, 314, 316-323, 325-327]	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*[311, 312, 320]	3	1,240	1.73 (1.39 – 2.15)	<0.001		0.31 (0.00 - 0.93)
Combination NRT vs Control*[312, 328, 330]	3	904	1.71 (1.30 – 2.25)	<0.001		0.00 (0.00 - 0.64)
E-cigarette vs Control*[340, 341]	2	662	2.29 (1.05 – 4.96)	0.037		0.00
Cytisine vs Control*[41, 337, 338]	3	2,151	1.87 (1.48- 2.38)	<0.001		0.68 (0.00 - 0.91)
Varenicline vs Control[295, 305, 318, 319, 327, 342, 396, 448-452, 454-458]	17	9,275	2.66 (2.25 - 3.15)	<0.001	(1.52 - 4.66)	0.58 (0.27 - 0.75)
Bupropion vs NRT[296, 302, 303, 312, 313, 320, 324, 327]	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*[340]	1	584	1.26 (0.68 - 2.34)	0.463		NA
Varenicline vs NRT[327, 335, 342, 345, 350, 395, 396, 441]	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[312, 313, 320, 324, 358, 398]	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[312, 313, 328-336, 395]	12	7,239	1.31 (1.16 - 1.47)	<0.001	(1.05 - 1.62)	0.13 (0.00 - 0.53)
Cytisine vs NRT*[339]	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^2 (95% CI)
NRT + bupropion vs Bupropion[311-313, 320, 324]	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*[312, 313, 315]	3	1,216	1.27 (1.08 – 1.50)	0.003		0.64 (0.00 - 0.90)
Varenicline vs Bupropion[295, 305, 315, 318, 319, 327]	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*[312, 313]	2	1,076	1.06 (0.89 - 1.26)	0.512		0.63
Varenicline vs Combination NRT*[315, 335, 395]	3	1,511	1.04 (0.88 - 1.23)	0.628		0.68 (0.00 - 0.91)
Varenicline + bupropion vs Varenicline*[453]	1	506	1.26 (0.95 - 1.68)	0.109		NA
NRT + varenicline vs Varenicline*[446]	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.

Table 6.2 Summary of previous cost-effectiveness studies

Study	Comparison	Perspective (Country)	Time horizon (Discount rate)	Results
Fiscella 1996[779]*	Physician counselling plus NRT patch versus physician counselling alone	Payer (USA)	Lifetime (3%)	Cost per QALY ranged from €5,942 to €14,812 in men, and from €6,707 to €9,452 in women
Wasley 1997[780]*	NRT plus brief physician advice versus brief advice alone	Payer (USA)	Lifetime (5%)	Cost per LYG ranged from €2,377 to €3,902 for men and €4,023 to €5,810 for women
Song 2002[781]*	Counselling alone, counselling plus NRT or bupropion, counselling plus NRT and bupropion	Payer (UK)	Lifetime (0%)	Cost per LYG vs counselling alone ranged from €1,701 to €4,079 for NRT, €1,086 to €2,538 for bupropion and from €1,513 to €3,348 for NRT plus bupropion
Antonanzas 2003[782]*	Bupropion or NRT versus nothing	Payer (Spain)	20 years (NA)	Cost per LYG of €2,165 for bupropion and €5,524 for NRT
Gilbert 2004[783]*	Physician counselling plus NRT or bupropion versus physician counselling	Payer (Seychelles)	Lifetime (3%)	Cost per LYG ranged from €1,489 to €5,168
Feenstra 2005[784]*	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 €1,206 to €5,371
Bolin 2006[785]*	Bupropion versus NRT	Societal (Sweden)	20 years (3%)	Cost per QALY for bupropion of €740 for men, and €549 for women, versus NRT
Cornuz 2006[786]*	Brief physician advice plus NRT or bupropion versus brief advice alone	Payer (USA & Europe)	Lifetime (3%)	Cost per LYG ranged from €834 to €3,666 for men and from €3,078 to €9,165 in women
Bolin 2008[787]**	Varenicline versus bupropion	Societal (Sweden)	Lifetime (3%)	Varenicline dominated bupropion
Hoogendoorn 2008[788]*	Varenicline versus unassisted quitting or NRT	Payer (Netherlands)	Lifetime (4% on costs, 1.5% on effects)	Cost per QALY €281 versus unaided, €907 vs NRT

Study	Comparison	Perspective (Country)	Time horizon (Discount rate)	Results
Howard 2008[789]*	Varenicline versus bupropion, NRT and unaided quitting	Payer (USA)	Lifetime (3%)	Varenicline dominated all comparators
Thavorn 2008[790]*	Pharmacy-based intervention versus routine care	Payer (Thailand)	Lifetime (3%)	Intervention dominated usual care (cost saving and generated LYG)
Annemans 2009[791]*	Varenicline versus brief counselling, unassisted quitting or bupropion	Payer (Belgium)	Lifetime (3% on costs, 1.5% on effects)	Cost per QALY of €336 versus brief counselling, €2,315 versus unassisted quitting and cost saving versus bupropion
Bae 2009[792]**	Varenicline versus bupropion and NRT	Payer (South Korea)	Lifetime (5%)	ICER of €4,761 compared with bupropion and NRT
Bolin 2009[793]*	Varenicline versus NRT in Belgium, UK, Sweden and France	Payer (Europe)	Lifetime (3.5%)	Varenicline was cost saving in all countries except France, where the cost per QALY was €3,917
Bolin 2009[794]*	Extended varenicline versus placebo	Societal (Sweden)	50 years (3%)	Cost per QALY €7,345 for men and €7,389 for women
Iqarashi 2009[795]*	Physician counselling versus physician counselling plus varenicline	Payer (Japan)	Lifetime (3%)	Addition of varenicline dominated in men, and had a cost per QALY of €2,980 in women
Knight 2010[796]*	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 cost per QALY was €971
Linden 2010[797]**	Varenicline versus bupropion and unaided quitting	Payer (Finland)	20 years (5%)	ICER of €9,466/QALY and €8,389/QALY compared with bupropion and unaided cessation, respectively
Athanasakis 2012[761]	Varenicline versus bupropion, NRT and unaided cessation	Payer (Greece)	Lifetime (3%)	Varenicline dominates all comparators
Guerriero 2013[765]	Text message bases smoking cessation support versus usual care	Payer (UK)	Lifetime (3.5%)	Text message support dominated
Leaviss 2014[768]	Cytisine versus varenicline	Payer (UK)	Lifetime (3.5%)	Cytisine dominated varenicline, being more effective and less costly

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Study	Comparison	Perspective (Country)	Time horizon (Discount rate)	Results
VonWartburg 2014[772]	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 €3,602/QALY
Cantor 2015[762]	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 €2,784/QALY 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.

Figure 4.16 Forest plot of studies comparing counselling versus control

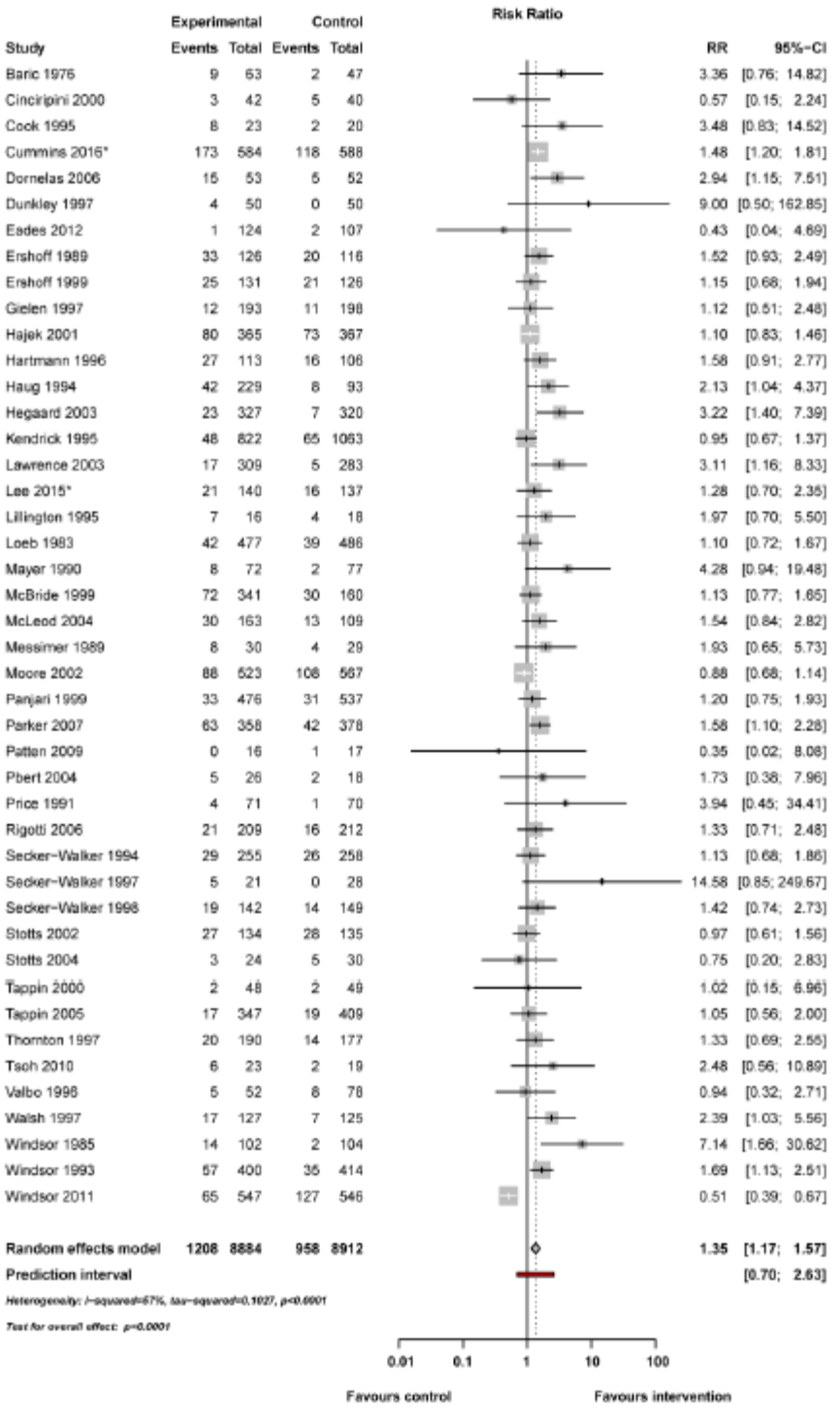


Figure 4.20 Forest plot of studies comparing financial incentives versus control[558-560]

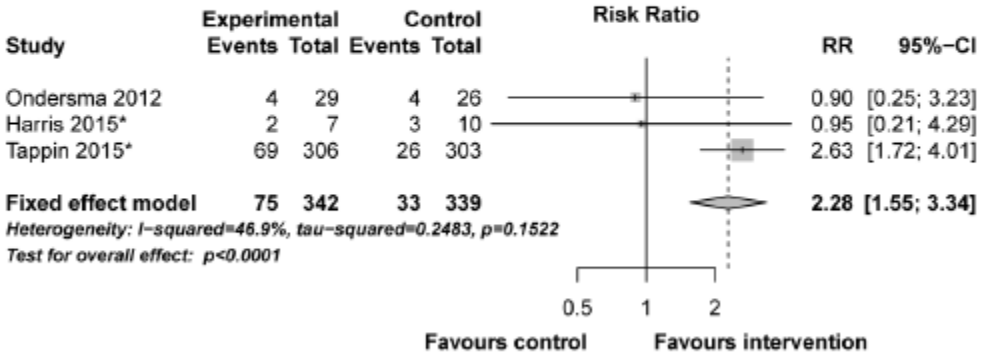
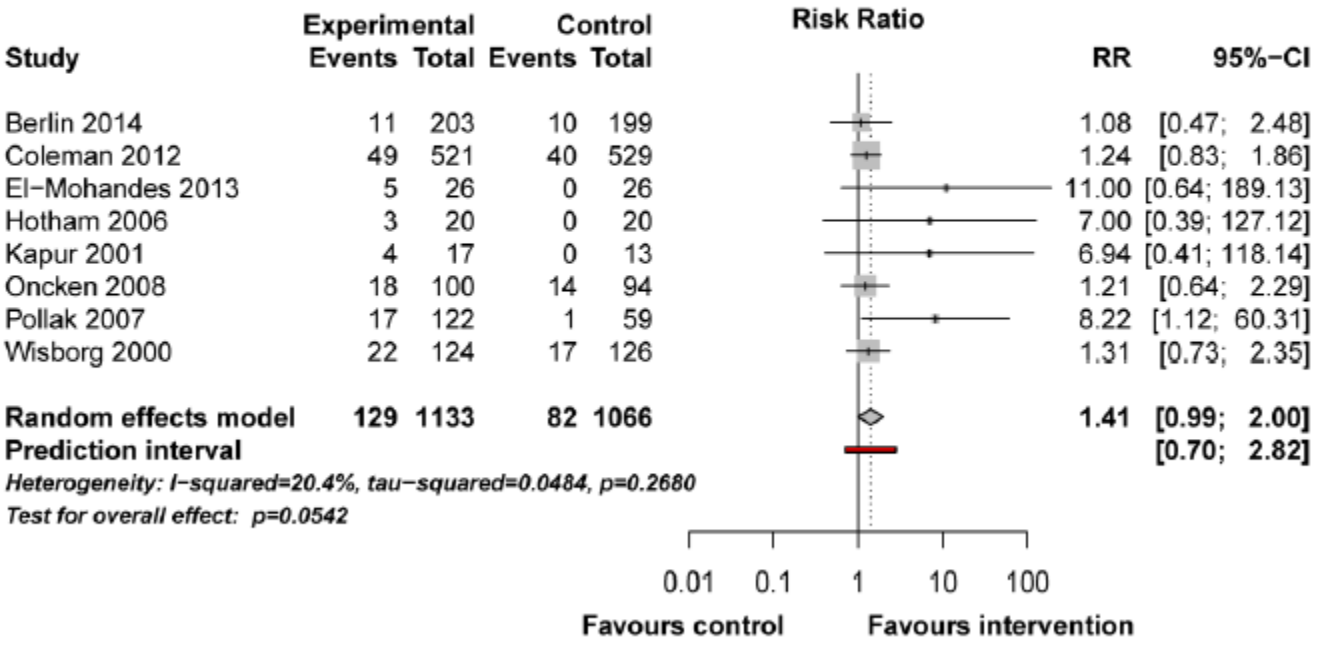


Figure 4.15 Abstinence in late pregnancy: forest plot of studies comparing NRT versus control



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