NICE Guidance title: Tobacco: harm-reduction approaches to smoking

Short title: Tobacco: harm reduction

Review 3: The effectiveness of long-term harm reduction approaches without the prior intention of quitting

November 2021: NICE guidelines PH45 (June 2013) PH48 (November 2013) have been updated and replaced by NG209.
The recommendations labelled [2013] or [2013, amended 2021] in the updated guideline were based on these evidence reviews.
See www.nice.org.uk/guidance/NG209 for all the current recommendations and evidence reviews.

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Date 22 January 2013

Version 4

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EXECUTIVE SUMMARY

1 INTRODUCTION

1.1 Aims of the review

To determine the effectiveness of long-term harm reduction approaches without the prior intention of quitting (ie reducing consumption without the aim of quitting), with and without assistance.

1.2 Research questions

- How effective are pharmacotherapies in helping people cut down or abstain from smoking, temporarily or indefinitely without the aim of quitting?
- How effective are different combinations of nicotine replacement therapy (NRT) products in helping people cut down or abstain from smoking, temporarily or indefinitely without the aim of quitting?
- How effective are 'nicotine-containing products' in helping people cut down or abstain from smoking, temporarily or indefinitely without the aim of quitting?
- How effective are behavioural support, counselling, advice or self-help (with or without pharmacotherapy) in helping people to cut down or abstain from smoking, temporarily or indefinitely, without the aim of quitting?
- Is there an optimal period to help people cut down or abstain (temporarily or indefinitely) from smoking without the aim of quitting?
- Is it more or less effective to draw up a schedule to help people cut down or abstain from smoking, temporarily or indefinitely, without the aim of quitting?
- Do some tobacco harm-reduction approaches have a differential impact on different groups (for example, people of different ages, gender, socio-economic status (SES) or ethnicity)?
- Are there any unintended consequences from adopting a tobacco harm-reduction approach; for example, does it deter people from trying to cut down or abstain from smoking, temporarily or indefinitely?

1.3 Background

Although smoking rates have declined sharply in the last 30 years, this decline has slowed in recent years. In the past, public health strategies have focused on discouraging people from starting to smoke and helping smokers to quit the habit completely. There remains a group of smokers who either want to quit but feel unable to stop abruptly or otherwise are not willing or able to quit but may be prepared to reduce the amount they smoke. The healthiest course of action for all smokers is to stop smoking but *harm reduction measures* attempt to limit the risks by reducing exposure to the toxic chemicals found in tobacco smoke (Royal College of Physicians, 2007). NICE has been asked by the Department of Health to develop guidance on 'Tobacco – harm reduction approaches to smoking'. The guidance will be underpinned by five evidence reviews. Review 1 considered the safety, risk and pharmacokinetics of tobacco harm reduction (THR) technologies (Jones et al, 2011). The second reviewed the effectiveness of

interventions for 'cutting down to quit'. This review is the third in the series and considers interventions for long term smoking reduction without the intention of quitting. Review 4 will be a companion to reviews two and three; looking at barriers and facilitators to harm-reduction approaches and the series will be completed with a health economic analysis of THR approaches.

2 METHODS

A systematic review of effectiveness evidence to address the above review question has been undertaken. A wide range of databases and websites was searched systematically, supplemented by grey literature[1] searches. Searches were carried out in August 2011 to identify relevant studies in the English language published between 1990 and 2011. A follow-up database search was conducted in November 2011.

All populations of all ages were included other than pregnant women; with a particular focus on those who have been identified as being more likely to smoke, at increased health risk from smoking and/or experiencing health inequalities.

Interventions considered were:

- Pharmacotherapies that are licensed for cutting down, temporary abstinence or harm reduction (currently only nicotine replacement therapy is licensed for these indications)
- Other non-tobacco nicotine containing products (e-cigarettes and topical gels)
- behavioural support, counselling, advice or self help.

All smoking-related outcomes were considered.

Study selection was conducted independently in duplicate. Quality assessment was undertaken by one reviewer and checked by a second, with 20% of papers being considered independently in duplicate. Both processes were tested for inter-rater reliability and monitoring. Data was extracted by one reviewer and checked by a second.

A narrative summary of the evidence was completed along with a meta-analysis of findings where feasible.

3. RESULTS

61 papers were included, comprising 45 individual studies and 1 systematic review.

The quality of the included studies was variable although there was a good body of consistent evidence in some areas. Five of the included randomised controlled trials (RCTs) were deemed to be of high quality (**Bolliger 2000 ++, Chan 2011 ++, Glasgow 2009 ++, Hovell 2000 ++, Warner 2005 ++**). Of the remaining studies there were 2 RCTs, 5 partial RCTs, 17 quasi-RCTs (unclear or inappropriate allocation concealment), 3 non-RCTs, 2 controlled before and after (CBA) studies, 10 uncontrolled before and after (UBA) studies and 1 secondary analysis. The UBAs and secondary analysis were all considered to be of low quality.

Five studies were carried out in the UK (**Foulds 1992 +, Gray 2005 –, Irvine 1999 +, McCambridge 2005 +, Munday 1993 –, Walker 2009 –**) and six in countries with smoking treatment programmes similar to those in the UK: three in Australia (**Borland 1999 +, Kelly 2006 +, Wakefield 2002 +**), two in Denmark

[1] Technical or research reports, doctoral dissertations, conference papers and official publications.

(**Pisinger 2005 –, Wennike 2003 +**) and one in Spain (**Jimenez-Ruiz 2002 –**). Twenty three of the remaining studies were conducted in the USA. Of these 11 were community based and feasible in the UK.

In general there was little information on specific socio-economic groups with only three studies looking at lower SES populations (**Hovell 2000 ++, Kelly 2006 +, Wakefield 2002 +**).

See Table 1 and Appendix A for details of all the included studies.

4. EVIDENCE STATEMENTS

Q1. How effective are pharmacotherapies in helping people cut down or abstain from smoking temporarily or indefinitely without the aim of quitting?

Evidence Statements:

1.1 There is strong to moderate evidence from nine studies - two RCTs, five quasi-RCTs and two UBAs - (**Bolliger 2000 ++**, **Etter 2007 +**, **Batra 2005 +Hatsukami 2005 –**, **Jiménez-Ruiz 2002 –**, **Kralikova 2009 +, Rennard 1990 –**, **Rennard 2006 +**, **Wennike 2003 +)** that NRT (gum or inhaler) versus placebo is effective in reducing cigarette consumption across multiple outcome measures and in eventual abstinence in smokers not looking to quit.

1.2 There is strong to moderate evidence from a meta-analysis of three RCTs and one quasi-RCT (**Bolliger 2000 ++**, **Chan 2011 ++**, **Etter 2007 +**, **Wennike 2003 +**) looking at ≥50% point prevalence reduction in CPD compared to baseline, that NRT, with or without a brief MI component, is more effective than placebo with a relative risk (RR) = 1.46 (95% CI 1.20, 1.78), with a number needed to treat (NNT) of 13 (95% CI 10, 20). A sensitivity analysis excluding **Chan 2011 ++** (which added a brief MI component to NRT) resulted in RR=1.35 (95% CI: 1.10, 1.65) and an NNT of 17 (95% CI 10, 50). Smoking reduction was verified by CO except in **Etter 2007 +**.

1.3 There is moderate evidence from a meta-analysis of one RCT and 2 quasi-RCTs (**Bolliger 2000 ++**, **Batra 2005 +**, **Wennike 2003 +**) that NRT is more effective than placebo in percentage reduction in cigarettes per day from baseline with a risk difference (RD) of −13.85 (95% CI: −25.5, −2.45).

1.4 There is unclear evidence from a meta-analysis of one RCT and three quasi-RCTs (**Bolliger 2000 ++**, **Batra 2005 +**, **Kralikova 2009 +**, **Wennike 2003 +**) for the efficacy of NRT for any sustained CPD reduction compared to baseline with an RR=2.45 (95% CI: 0.9, 6.4). In a sensitivity analysis that excluded **Kralikova 2009 +** for significant heterogeneity, NRT increased the chance of a sustained smoking reduction RR=3.38 (95% CI 1.7, 6.6), with an NNT of 17 (95% CI 13, 34), and no evidence of between-study statistical heterogeneity.

1.5 There is strong evidence from a meta-analysis of nine studies (three RCTs and six quasi RCTs) investigating cessation in populations not looking to quit (**Bolliger 2000 ++**, **Chan 2011 ++**, **Etter 2007 +**, **Batra 2005 +** , **Carpenter 2004 +**, **Joseph 2008 +**, **Kralikova 2009 +**, **Rennard 2006 +**, **Wennike 2003 +**) that NRT with or without associated behavioural interventions has a statistically significant effect: RR=1.96 (95% CI 1.36, 2.80) with an NNT of 20 (95% CI 13, 34). A sensitivity analysis excluding studies with a behavioural

component (**Carpenter 2004 +**, **Chan 2011 ++**, **Joseph 2008 +**), found a similar result for NRT alone: RR=1.93 (95%CI 1.26, 2.96) and an NNT of 20 (95% CI 13, 34).

1.6 There is moderate evidence from one RCT (**Warner 2005 ++**) that nicotine patch versus placebo is effective in reducing post-operative smoking consumption, a statistically significant self-reported reduction was observed 30 days post-operation but this was not maintained at 6 months.

1.7 There is weak evidence from five studies (**Benowitz 1998 –, Fagerström 1997 –, Foulds 1992 +, Hatsukami 2007 –, Pickworth 1994 –**) that a nicotine patch may help reduce *ad libitum* cigarette smoking. In the only controlled study (**Foulds 1992 +**) the result was not statistically significant.

The majority of the evidence is applicable to the UK as the studies are community based and feasible in UK settings, although **Batra 2005 +** involved participants making several clinic visits and **Foulds 1992 +** was in a laboratory setting. **Warner 2005 ++** was conducted within a specific population (patients undergoing elective surgery).

Q2. How effective are different combinations of NRT products in helping people cut down or abstain from smoking, temporarily or indefinitely without the aim of quitting?

Evidence Statement:

2.1 No studies were found that looked at combinations of NRT products for helping people to cut down or abstain from smoking, temporarily or indefinitely without the aim of quitting.

Q3. How effective are 'nicotine-containing products' in helping people cut down or abstain from smoking, temporarily or indefinitely without the aim of quitting?

For the purposes of this review 'nicotine containing products' were defined as 'electronic nicotine delivery systems' (sometimes known as 'electronic cigarettes' or 'e-cigarettes') and topical gels. Currently these products are not regulated by the Medicines and Healthcare products Regulatory Agency (MHRA).

Evidence Statement:

3.1 Very weak evidence from one UBA (Polosa 2011−) suggests that e-cigarette availability can help smokers reduce.

This evidence may be applicable to the UK as it is community based and feasible in a UK setting.

Q4. How effective are behavioural support, counselling, advice or self-help (with or without pharmacotherapy) in helping people to cut down or abstain from smoking, temporarily or indefinitely, without the aim of quitting?

Evidence Statements:

4.1 There is consistent evidence from seven studies (2 RCTs, 4 quasi-RCTs and 1 CBA) (**Horn 2007 +**, **McCambridge 2005 +**, **Kelly 2006 +**, **Audrain-McGovern 2011 +**, **Davis 2011 +**, **Gulliver 2008 +**, **Gray 2005 –**) that motivational interviewing compared with other behavioural methods or with no support and whether provided in single or multiple sessions, is not effective in helping people to reduce smoking levels. This evidence applies to healthy adolescents and adults, with no statistically significant between group differences reported across any of the studies reviewed. Weak evidence also exists for the lack of effectiveness of motivational interviewing for adolescent drug users (**McCambridge 2005 +, Gray 2005 –**) and military veterans with psychiatric problems (**Gulliver 2008 +**), with these studies again finding no significant between group differences for the outcomes reported.

4.2 There is strong evidence from a meta-analysis of two RCTs and three quasi-RCTs (**Horn 2007 +**, **McCambridge 2005 +**, **Audrain McGovern 2011 +**, **Davis 2011 +**, **Kelly 2006 +**) that motivational interviewing, compared with other behavioural methods or with no support and provided in single or multiple sessions, is not effective for smoking cessation in populations unable or unwilling to stop smoking: RR 1.34 (95% CI 0.75, 2.39; p=0.32). This is at variance with findings of a Cochrane systematic review of MI for smoking cessation (Lai 2010). The addition of NRT to a motivational component (**Chan 2011 ++**, **Carpenter 2004 +**) may improve the likelihood of abstinence: RR 3.09 (95% CI 1.06, 9.01; p=0.04).

4.3 There is moderate evidence from a large well-conducted RCT (**Chan 2011++**) that NRT combined with a motivational component is effective, with a significant CO-validated ≥50% 7-day point prevalence reduction rate.

4.4 There is strong to moderate evidence from four studies (1 RCT, 1 quasi-RCT, one non-RCT and a CBA) designed to reduce the impact of environmental tobacco smoke on children (**Hovell 2000 ++**, **Irvine 1999 +**, **Wakefield 2002 +**, **Fossum 2004 –**) of no effect for a variety of behavioural methods versus standard care in reducing parental smoking. This evidence applies to parents of children with asthma (**Irvine 1999 +**, **Wakefield 2002 +**) as well as to parents of healthy children (**Hovell 2000 ++**, **Fossum 2004 –**).

4.5 There is moderate evidence from two RCTs (**Hanson 2008 +, Joseph 2008 +**) and one UBA (**Hurt 2000 –)** that counselling combined with nicotine replacement therapy is not effective in helping adolescents (**Hanson 2008 +**) or adults (**Hurt 2000 –, Joseph 2008 +**) to reduce their cigarette consumption or to ultimately quit. There were no differences at follow-up between intervention and control groups for any smoking related oumes.

4.6 There is moderate evidence from one RCT (**Glasgow 2009 ++**) that telephone counselling is an ineffective approach to reducing cigarette consumption. At the 12 month follow-up

there were no significant differences between intervention and control groups in terms of numbers reducing their daily cigarette consumption by ≥50% or in carbon monoxide levels.

4.7 There is moderate evidence from one quasi-RCT (**Riley 2002 +**) that computer-aided and manual-aided approaches to assist with reduction had similar effect sizes. Twelve months after the start of the study there were no differences between groups in smoking reduction, and although more participants in the computer-aided group had made a quit attempt than in the manual-aided group, this difference was not statistically significant.

4.8 There is moderate evidence from one systematic review of pre-operative smoking interventions (**Thomsen 2010 +**) that counselling combined with NRT increases smoking cessation at the time of surgery for both brief and intensive interventions. However only intensive interventions were effective at 12 month follow-up. RR 2.96 (95% CI 1.57, 5.55) for two trials.

4.9 There is weak evidence from one quasi-RCT (**Carpenter 2004 +**) that both NRT aided reduction and motivational treatment are more effective than no treatment both in terms of reducing smoking and ultimately quitting. There were no significant differences between the two intervention groups on any outcomes (all self-reported). This finding is at odds with those reported in the other behavioural studies.

4.10 There is weak evidence from one RCT (**Schleicher 2010 +**) and one small UBA (**Roll 1998–**) that cognitive behavioural therapy is not effective in helping smokers to reduce their cigarette consumption or to reduce and ultimately quit.

4.11 There is weak evidence from one quasi-RCT (**Cunningham 2006 +**) that providing safer smoking tips can have a marginal effect on reduction. At three months follow-up those who received safer smoking tips self-reported a small reduction in the number of cigarettes smoked compared to those in the control condition (p=0.05). Overall levels of change in cigarettes per day were small, however, and the mean number of cigarettes per day remained high in both groups at follow-up.

4.12 There is weak evidence from one quasi-RCT (**Borland 1999 +**) that a self-help programme to assist smokers in coping with workplace smoking bans may not be effective. At the six month follow-up there were no differences between groups on any of the outcomes assessed.

4.13 There is weak evidence from one non randomised study and one UBA (**Munday 1993 –**, **Walker 2009 –**) that brief advice alone for pre-operative smoking cessation is not effective in achieving pre-operative abstinence.

4.14 There is very weak evidence from a UBA (**Carpenter 2007–**) that knowledge of alpha-1-antitrypsin (AAT) deficiency is effective in influencing quit attempts and cigarette consumption.

4.15 There is very weak evidence from two UBAs (**Griffiths 2010 –**, **Tidey 2002 –**) that behavioural support combined with NRT is effective in reducing smoking among adults with mental illness.

4.16 There is very weak evidence from one quasi-RCT (**Riggs 2001 –**) of no difference between NRT and hierarchical reduction versus NRT and increased inter-cigarette interval in reducing smoking.

4.17 There is very weak evidence from one small UBA (**Beard 2012)** that a personal CO monitor is not effective in reducing CPD and encouraging abstinence.

The majority of evidence is applicable to the UK as the studies are feasible in UK settings. However **Carpenter 2007 –**, **Griffiths 2010 –**, **Hanson 2008 +**, **Tidey 2002 –** are noted to have issues regarding applicability. Studies of specific populations included **Kelly 2006 +**, **Audrain-McGovern 2011 +**, **Hanson 2008 +**, **Horn 2007 +** (adolescents); **Gray 2005 –**, **McCambridge 2005 +** (adolescent drug users); **Gulliver 2008 +** (military veterans); **Griffiths 2010 –**,**Schleicher 2010** and **Tidey 2002 –** (mental health); **Munday 1993 –, Thomsen 2010 +**, **Walker 2009 –** (patients undergoing elective surgery); **Hovell 2000 ++**, **Fossum 2004 –**, **Irvine 1999 +**, **Wakefield 2002 +** (parents).

Q5. Is there an optimal period to help people cut down or abstain (temporarily or indefinitely) from smoking without the aim of quitting?

Evidence Statement:

5.1 No studies were found that looked at the effect of different reduction periods in helping people to cut down or abstain (temporarily or indefinitely) from smoking.

Q6. Is it more or less effective to draw up a schedule to help people cut down or abstain from smoking, temporarily or indefinitely, without the aim of quitting?

Evidence Statements:

6.1 Weak evidence from 2 quasi-RCTs and 2 UBAs (**Riggs 2001 –**, **Riley 2002 +**, **Hatsukami 2005 –**, **Hurt 2000 –**) suggests the use of a schedule may assist in reducing smoking. Schedules included week on week reduction (**Hatsukami 2005 –**, **Hurt 2000 –**), increased inter-cigarette interval or selective elimination (**Riggs 2001 –**, **Riley 2002 +**).

6.2 There is limited evidence from 2 quasi-RCTs (**Riggs 2001 –**, **Riley 2002 +**) of no difference in effect between different types of schedule (increasing inter-cigarette intervals or selective elimination).

The evidence is partially applicable to people in the UK since all four studies were community based (in the USA) and are feasible in UK settings.

Q7. Do some tobacco harm-reduction approaches have a differential impact on different groups (for example, people of different ages, gender, socio-economic status or ethnicity)?

Evidence Statements:

7.1 There is moderate evidence from five studies (2 RCTs, 2 quasi-RCTs, 1 CBA) (**Horn 2007 +**, **McCambridge 2005 +**, **Audrain McGovern 2011 +**, **Kelly 2006 +**, **Gray 2005 –**) of no effect for motivational interviewing interventions in reducing smoking in adolescents.

7.2 There is weak evidence from one quasi-RCT (**Hanson 2008 +**) that cognitive behavioural therapy (CBT) plus NRT is not effective in reducing smoking among adolescents.

7.3 Weak evidence from one quasi-RCT in the USA (**Audrain McGovern 2011 +**) comparing a multi-session intensive MI intervention to multiple sessions of brief structured advice, suggests that white adolescents are significantly less likely than black adolescents to attempt to reduce or quit smoking.

7.4 Moderate evidence from one high quality RCT (**Chan 2011 ++**) indicates that MI plus NRT was effective in reducing smoking in adult Chinese smokers who had previously failed to quit.

7.5 There is weak evidence from one quasi-RCT (**Kelly 2006 +**) of no effect of MI on Australian adolescents from lower SES families.

7.6 Moderate evidence from 1 RCT and 1 non-randomised study (**Hovell 2000 ++**, **Wakefield 2002 +**) found no evidence of effect for behavioural interventions in reducing parental smoking in low income families.

7.7 There no evidence of sustained effect of behavioural interventions from 4 studies (1 RCT and 3 UBAs) (**Schleicher 2010 +**, **Tidey 2002 –**, **Roll 1998 –**, **Griffiths 2010 –**) in mental health populations.

7.8 There is very weak evidence from two small UBAs (**Tidey 2002 –**, **Roll 1998 –**) of a 'during treatment effect' on carbon monoxide-verified reduction in mental health populations for contingency management with or without NRT.

The evidence is partially applicable to people in the UK. **McCambridge 2005 +** and **Gray 2005 –** were both based in the UK, and **Kelly 2006 +** and **Wakefield 2002 +** were based in Australia where there is a similar smoking treatment service to the UK. Of the remaining studies, **Chan 2011 ++**, **Griffiths 2010 –** and **Hovell 2000 ++** were based in the community and interventions may be feasible for the UK.

Q8. Are there any unintended consequences from adopting a tobacco harm-reduction approach; for example, does it deter people from trying to cut down or abstain from smoking, temporarily or indefinitely?

Evidence Statements:

8.1 There is strong evidence from eight studies reporting usage of NRT for periods between six months and five years (**Batra 2005 +**, **Bollinger 2000 ++**, **Etter 2007 +**, **Jiménez-Ruiz 2002 –**, **Joseph 2008 +**, **Kralikova 2009 +**, **Rennard 2006 +**, **Wennike 2003 +**) to suggest

that NRT is generally well tolerated long term with severe side effects being relatively rare.

8.2 There is moderate evidence from two quasi-RCTS (**Carpenter 2004 +**, **Wennike 2003 +**) that harm reduction interventions do not deter smokers from wishing to quit.

8.3 There is weak evidence from a single UBA (**Polosa 2011 –**) that frequent adverse events are reported by e-cigarette users. This finding supports the conclusions from Review One (Toxicity) that more evidence is required concerning the safety of e-cigarettes.

Adverse event studies are likely to be applicable to the UK.

5. DISCUSSION

This review contains a large body of evidence of relevance to long term harm reduction without the prior aim of quitting.

Five studies were conducted in the UK, and six in countries with similar smoking treatment programmes. In general, applicability to the UK was good with many other studies based in the community.

The quality of the included studies was variable with a wide variation in time periods and outcomes. There was a good body of consistent evidence for some topics and outcomes for NRT studies (measures of CPD, ≥50% reduction and continuous or point-prevalent abstinence) were generally consistent. By contrast, reduction outcomes for behavioural studies varied considerably and it was not possible to conduct meta-analyses other than for abstinence. Reduction outcomes were generally self-reported so there is little information on reduction in exposure. However, where studies identify abstinence at follow-up and report this outcome, it is generally biochemically verified.

Participant motivations were difficult to ascertain in some studies. Thus, the scope of the review included studies that were designed as long term harm reduction studies, as well as those where the included participants did not wish to quit smoking.

All six randomised/quasi-randomised studies investigating the use NRT in the general population were either industry sponsored (**Bolliger 2000 ++**, **Batra 2005 +**, **Kralikova 2009 +**, **Rennard 2006 +**, **Wennike 2003 +**), or the authors had financial ties to industry (**Etter 2007 +**). As noted in Review 2, authors declared sources of funding and any potential conflicts of interest. However, a 2003 meta-analysis of RCTs included in a Cochrane review of smoking cessation interventions concluded that "Compared with independent trials, industry-supported trials were more likely to produce statistically significant results and larger odds ratios. These differences persisted after adjustment for basic trial characteristics." (Etter 2003) The authors suggested that this difference may be the result of publication bias.

By contrast, potential conflicts of interest were only identified in one behavioural study (**Riley 2002 +**) in which the computerised scheduled reduction intervention had been developed and was being marketed by a company employing the authors.

Nine of the behavioural studies (three RCTs, five quasi-RCTs and one CBA) included a 'motivational interview' component as part of the intervention (**Chan 2011++**, **Horn 2007 +**, **McCambridge 2005 +**, **Audrain-McGovern 2011 +**, **Carpenter 2004 +**, **Davis 2011 +**, **Gulliver 2008 +**, **Kelly 2006 +**, **Gray 2005 –**); two studies combining that component with NRT (**Chan 2011 ++**, **Carpenter 2004 +**). The component ranged from a single brief interview to multiple intensive sessions. There appeared to be little difference in outcome between brief and intensive interventions. Fidelity to the principles and practice of motivational interviewing (Miller 2002) was also considered. Six of the seven studies looking at motivational interviewing alone identified key elements of principles and practice. Fidelity was unclear in both studies combining a motivational component with NRT.

Overall, the evidence within the review suggests that:

- Across all studies of NRT versus placebo where reduction is an intended outcome, meta-analyses indicate significant benefits from NRT.
- NRT may also be effective for abstinence in the longer term in populations not looking to quit.
- NRT supplementation may help reduce *ad libitum* smoking (where there is no instruction to reduce) but the evidence base is weak.
- No evidence comparing combinations of NRT was found but it appears that there are no clear differences in effectiveness between different types of medication and some modest evidence that offering smokers a choice of medication may enhance efficacy.
- Nicotine patch is effective in reducing post-operative smoking consumption in the short term but this is not maintained long term.
- Evidence for the value of e-cigarettes to date is available only from a single UBA study and, although suggestive of benefit, no conclusions can be drawn as yet. We note that the MHRA is currently considering whether to regulate e-cigarettes and other nicotine-containing products.
- Two studies suggest NRT combined with a brief motivational component may be effective for abstinence in populations not looking to quit. However, the impact of the motivational component is unclear.
- There is consistent evidence that motivational interviewing, either in single or multiple sessions, is not effective as a long-term harm reduction strategy.
- MI does not appear to be effective for abstinence in populations unable or unwilling to quit. This is at variance with the evidence from a Cochrane systematic review looking at the effect on abrupt cessation (Lai 2010); which found some evidence that MI may assist abstinence. The reason for this variance is not clear, although it may reflect the impact of the two statistically significant studies - Hollis 2007 and Soria 2006. In the first, which contributed considerable weight to pooled analyses, study participants had to be motivated to quit. In the second study bupropion was provided to a small proportion of the MI group, which may have skewed the results.
- The evidence available for other types of behavioural intervention is weaker but it is also suggestive of no benefit.
- Both brief and intensive pre-operative smoking interventions, combining counselling with NRT, increase smoking cessation at the time of surgery. However only intensive interventions were effective long term.

- There is no evidence of effect on parental smoking levels from interventions to reduce environmental tobacco smoke. Results do not appear to vary between parents of asthmatics and those with generally healthy children.
- No evidence was found to suggest an optimal reduction period.
- Limited weak evidence suggests that scheduled smoking reduction may be more effective than non-scheduled smoking reduction; although there do not appear to be differences in effect between types of scheduled reduction.
- There is very little evidence to distinguish the effectiveness of interventions across socio-economic groups.
- The small amount of evidence available suggests that harm reduction interventions do not deter smokers from wishing to quit. More evidence of smokers' views is likely to be provided within the barriers and facilitators review (Review 4).
- Longer-term NRT use appears to be well tolerated over periods between six months and five years with severe side effects being relatively rare.

Further research is needed in a number of areas: the differential effects for socio-economic and ethnic groups, the impact of different NRT combinations and the efficacy of e-cigarettes, the effect of intensity of the intervention.

ABBREVIATIONS

AAT	alpha-1-antitrypsin
BI	Instruction in deep breathing
BP	Blood pressure
C	Control group
CES-D	Center for Epidemiological Studies-Depression Scale
CBA	Controlled before and after study
CM	Contingency management
CO	Carbon monoxide
CPD	Cigarettes per day
CPW	Cigarettes per week
CSGR	Computerised schedule gradual reduction
DH	Department of Health
DSM	Diagnostic and Statistical Manual of Mental Disorders
ED	Emergency Department
ETS	Environmental tobacco smoke
FTND	Fagerström Test for Nicotine Dependence
FTQ	Fagerstrom Tolerance Questionnaire
GEE	Generalised estimating equation
GP	General Practitioner
HMO	Health management organisation
HR	Hierarchical Reduction
HR-E	Hierarchical reduction – easiest first
HR –H	Hierarchical reduction – hardest first
I	Intervention group
ICI	Increased Inter-cigarette interval
ITT	Intention to treat
MANOVA	Multiple analysis of variance
MET	Motivational enhancement therapy
MHRA	Medicines and Healthcare products Regulatory Agency
MI	Motivational interviewing OR myocardial infarction
MNWS	Minnesota Nicotine Withdrawal Scale
NA	Nicotine Anonymous
NCP	Nicotine containing product
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NIDA	National Institute of Drug Abuse
N-P	Nicotine placebo difference
NNT	Number needed to treat
NRT	Nicotine replacement therapy
NS	Not significant

NTIS	National Technical Information Service
OR	Odds ratio
QFL	Quit for Life
QSU	Questionnaire on Smoking Urges
POD	Post-operative day
PPM	Parts per million
RBC	Red blood cell
RT	Randomised trial (all intervention arms, no control)
RCT	Randomised controlled trial
SA	Secondary analysis
SBA	Structured brief advice
SC	South Carolina
SER	Selective elimination reduction
SES	Socio-economic status
IS	incentive spirometer
SR	Scheduled reduction
ST	Standard treatment
UBA	Uncontrolled before and after study
VAS	Visual Analogue Scale
WBC	White blood cell
WHO	World Health Organisation

1 INTRODUCTION

1.1 Aims of the review

To determine the effectiveness of long-term harm reduction approaches without the prior intention of quitting (ie reducing consumption without the aim of quitting), with and without assistance.

1.2 Research questions

- How effective are pharmacotherapies in helping people cut down or abstain from smoking, temporarily or indefinitely without the aim of quitting?
- How effective are different combinations of nicotine replacement therapy (NRT) products in helping people cut down or abstain from smoking, temporarily or indefinitely without the aim of quitting?
- How effective are 'nicotine-containing products' in helping people cut down or abstain from smoking, temporarily or indefinitely without the aim of quitting?
- How effective are behavioural support, counselling, advice or self-help (with or without pharmacotherapy) in helping people to cut down or abstain from smoking, temporarily or indefinitely, without the aim of quitting?
- Is there an optimal period to help people cut down or abstain (temporarily or indefinitely) from smoking without the aim of quitting?
- Is it more or less effective to draw up a schedule to help people cut down or abstain from smoking, temporarily or indefinitely, without the aim of quitting?
- Do some tobacco harm-reduction approaches have a differential impact on different groups (for example, people of different ages, gender, socio-economic status or ethnicity)?
- Are there any unintended consequences from adopting a tobacco harm-reduction approach; for example, does it deter people from trying to cut down or abstain from smoking, temporarily or indefinitely?

1.3 Background

Although smoking rates have declined sharply in the last 30 years, this decline has slowed in recent years with prevalence rates levelling off at 21% in England in 2008 (Robinson and Bugler, 2010) and 24% in Wales in 2009 (Welsh Assembly Government, 2010). Fourteen percent of adults in managerial and professional households in England reported that they currently smoked, compared with 29% in routine and manual households; the corresponding figures for Wales were 15% versus 31%.

People from routine and manual occupational groups take in more nicotine from cigarettes than more affluent people (Jarvis 2010). This increases their exposure to the other toxins in tobacco smoke and, thus, increases their risk of smoking-related disease. Higher nicotine exposure can also make it harder for them to quit and they are more likely to cut down first rather than quit smoking 'abruptly' (Siahpush et al. 2010). Exposure to increased levels of nicotine, carbon

monoxide and other toxins can also result from 'roll-your-own' as compared to manufactured cigarettes (UK Department of Health Tobacco Policy Team 2003).

In the past, public health strategies have focused on discouraging people from starting to smoke and helping smokers to quit the habit completely. There remains a group of smokers who either want to quit but feel unable to stop abruptly or otherwise are not willing or able to quit but may be prepared to reduce the amount they smoke. The healthiest course of action for all smokers is to stop smoking but *harm reduction measures* attempt to limit the risks by reducing exposure to the toxic chemicals found in tobacco smoke (Royal College of Physicians, 2007).

Harm reduction is defined as 'policies, programmes, services and actions which aim to reduce the harm to individuals, communities and society that are associated with the use of drugs'. Such measures are pragmatic, recognising that the reduction of harms may be more feasible than complete elimination of drug use (UK Harm Reduction Alliance).

In relation to tobacco use specifically a product is considered harm reducing 'if it lowers total tobacco-related mortality and morbidity, even though use of that product may involve continued exposure to tobacco related toxicants' (Stratton et al, 2001). Harm reduction can refer both to those who want to quit but feel unable to do so abruptly, and those who smoke and do not feel willing or able to quit but who want to reduce the harm that smoking is doing to their health, or to the health of those around them (Royal College of Physicians, 2007).

Smokers continue to smoke predominantly due to nicotine addiction, but in so doing expose themselves to a large number of chemicals, many of which are established carcinogens. Tobacco smoke contains over 4,000 chemicals, including carbon monoxide, nitrosamines, polycyclic aromatic hydrocarbons, nitrogen oxides, hydrogen cyanide and heavy metals. Furthermore, exposure to second-hand smoke in the home causes an estimated 11,000 deaths a year in the UK from lung cancer, stroke and ischaemic heart disease (Jamrozik 2005).

The Royal College of Physicians estimate that if only 0.4% of the population of smokers in the UK switch from smoking to less harmful nicotine sources each year, this would save approximately 25,000 lives in 10 years. In addition, the Department of Health's (DH) publication *'Drug Misuse and dependence: UK guidelines on clinical management'* states that: 'Given the high rates of smoking and the low quit rates in drug misusers, it may be reasonable to consider harm reduction approaches to smoking such as replacing cigarettes with clean nicotine in the form of patches for some of the day. This may be particularly useful in alleviating the symptoms of tobacco withdrawal while a patient is within a residential or inpatient drug treatment facility' (DOH, 2007).

A systematic review of the evidence (Pisinger 2007) found that the limited data available suggest that a substantial reduction in smoking (defined in many studies as ≥50% reduction in baseline smoking) improves several cardiovascular risk factors and respiratory symptoms. In addition, smoking reduction is associated with a 25% decline in biomarkers and incidence of lung cancer and a small, non significant, increase in birth weight.

Although harm reduction strategies have been successful in other areas, when applied to tobacco they are controversial. For example there may be unintended consequences of adopting harm reduction measures such as ex-smokers relapsing to the harm reduction option and young people starting off with the harm reduction option in the belief that it is safer. In such

cases it is possible the benefits may be overwhelmed by more widespread uptake of harm reduction measures. Another criticism levelled against harm reduction measures is that they represent an admission of defeat and still leave the smoker exposed to harm (Bates, 2002).

The National Institute for Health and Clinical Excellence (NICE) has been asked by the Department of Health to develop guidance on 'Tobacco – harm reduction approaches to smoking'. This guidance will provide recommendations for good practice based on the best available evidence of effectiveness, including cost effectiveness. It is aimed at professionals, commissioners and managers with public health as part of their remit. It is especially aimed at those involved in smoking cessation services within the NHS, local authorities and the wider public, private, voluntary and community sectors. It will also be of interest to members of the public, especially people who want to stop or cut down the amount they smoke.

The guidance will make recommendations on approaches to help smokers of all ages who:

- want to quit smoking but feel unable to do so 'abruptly' (that is, they want to cut down before quitting)
- are not willing or able to quit, but want to reduce the harm that smoking is doing to their health (or to the health of those around them)
- want to quit smoking but are not willing or able to stop using nicotine
- want to stop smoking temporarily, for example, while at work.

2. METHODS

2.1 Literature search

A comprehensive literature search was undertaken to identify evidence in the English language that is:

- of the highest quality available, considering the hierarchy of evidence ;
- applicable to the UK, from world-wide studies;
- of high methodological quality, as assessed by critical appraisal;
- publicly available, including trials in press ("academic in confidence").

The following study designs were included:

- systematic reviews, guidelines, randomised controlled trials (RCTs); controlled trials; [Systematic reviews and guidelines were identified and 'unpicked' for relevant studies to avoid any risk of double-counting.]
- controlled before and after studies, interrupted time series and uncontrolled before and after studies were considered for potential relevance, especially where evidence from controlled trials was limited.

2.1.1 Electronic sources (databases and websites)

The following sources were searched in August 2011 to identify relevant evidence/studies in the English language published between 1990 and 2011. In November 2011, update searches were conducted in the databases marked * and Globalink and ASH Scotland newsletters were checked on a weekly basis for additional research.

The search strategy was developed for Ovid Medline [Appendix C] and translated for use in all other sources detailed below. A full set of search strategies are available from the authors.

Databases:

- AMED (Allied and Complementary Medicine)*
- ASSIA (Applied Social Science Index and Abstracts)
- British Nursing Index
- CINAHL (Cumulative Index of Nursing and Allied Health Literature)
- Cochrane Central Register of Controlled Trials*
- Cochrane Database of Systematic Reviews*
- Cochrane Public Health Group Specialized Register [based at SURE]
- Database of Abstracts of Reviews of Effectiveness (DARE)*
- Database of promoting health effectiveness reviews (DoPHER), EPPI-Centre
- Current Contents
- EMBASE*
- HMIC (or King's Fund catalogue and DH data)*
- Medline and Medline in Process*
- UK Clinical Research Network Portfolio Database

- PsycINFO*
- Sociological Abstracts
- Social Policy and Practice
- Web of Knowledge (Science and Social Science Citation Indexes)*
- WHO Tobacco Control Database

Web sites:

- Smoke free http://smokefree.nhs.uk
- NHS Centre for Smoking Cessation and Training http://www.ncsct.co.uk/
- Action on Smoking and Health (ASH) http://www.ash.org.uk
- Treat tobacco.net http://www.treatobacco.net/en/index.php
- Society for Research on Nicotine and Tobacco http://www.srnt.org
- International Union against Cancer http://www.uicc.org
- WHO Tobacco Free Initiative (TIF) http://www.who.int/tobacco/en
- International Tobacco Control Policy Evaluation Project http://www.itcproject.org
- Tobacco Harm Reduction http://www.tobaccoharmreduction.org/index.htm
- Current controlled trials www.controlled-trials.com
- Association for the treatment of tobacco use and dependence (ATTUD) http://www.attud.org
- National Institute on drug abuse- the science of drug abuse and addiction http://www.nida.nih.gov/nidahome.html
- NICE http://www.nice.org.uk/
- OpenGrey http://www.opengrey.eu/
- Public health observatories http://www.apho.org.uk/
- Scottish Government http://home.scotland.gov.uk/home
- Welsh Government http://wales.gov.uk/?lang=en
- NHS Evidence http://www.evidence.nhs.uk/
- Joseph Rowntree Foundation http://www.jrf.org.uk/
- The Centre for Tobacco Control Research (University of Stirling) http://www.management.stir.ac.uk/research
- UK Centre for Tobacco Control Studies http://www.ukctcs.org/ukctcs/index.aspx
- Tobacco Control Research Group (University of Bath) http://www.bath.ac.uk/health/tobacco/
- Health Evidence Canada http://health-evidence.ca/articles/search
- ASH Scotland news digest http://www.ashscotland.org.uk/ash/4782
- American Association of Public Health Physicians http://www.aaphp.org/tobacco
- Health NZ News http://www.healthnz.co.nz/News2010.htm
- Globallink http://www.globalink.org
- Cancer Research UK http://www.cancerresearchuk.org

2.1.2 Additional searches

Following database and web site searching, the contents pages of the 'top' journals (ie the journals that contain the greatest number of papers that meet inclusion criteria) were hand searched – *Addiction, Nicotine & Tobacco Research* and *Preventive Medicine* - for the previous twelve months. Citation searches via Web of Science were also carried out for included papers.

NICE issued a call for evidence from registered stakeholders in August 2011.

In addition, first authors of all the studies that met the inclusion criteria and other topic specialists identified by the Expert Advisory Group and NICE were contacted to request information on additional published studies, unpublished work or research in progress.

Information on studies in progress, unpublished research or research reported in the grey literature was sought through searching a range of relevant databases including OpenGrey, Conference Proceedings Citation Index: Science (Thompson Reuters), Inside Conferences, National Technical Information Service (NTIS) and Clinical Trials.gov

Results of the literature searches were imported into Reference Manager and de-duplicated.

2.2 Inclusion/Exclusion criteria:

	Inclusion	Exclusion
Population	People of all ages who: • are not willing or able to quit, but want to reduce smoking. (ie, reduce the harm that smoking is doing to their health or the health of those around them); • want to quit smoking but are not willing or able to stop using nicotine and who take part in a study examining a tobacco harm reduction approach; • want to stop smoking temporarily, for example, while at work or for surgery; • participate in interventions designed to reduce the number of cigarettes smoked per day; • participate in pre-operative interventions designed to ensure abstinence on day of operation. With a particular focus on those who	Pregnant women [but the post partum population was included] Interventions to reduce the effects of second hand smoke on children where it is not possible to determine the effect on the parents' cigarette consumption

	have been identified as: • at increased health risk from smoking, • from more disadvantaged groups and, thus, vulnerable to health inequalities.	
Interventions	• Pharmacotherapies that are licensed for cutting down, temporary abstinence or harm reduction: ○ All nicotine replacement therapy (NRT) products (gum, transdermal patches, inhalers, microtabs, mouth/nasal sprays and lozenges[2]) • Other non-tobacco 'nicotine-containing products', such as 'electronic nicotine delivery systems' (sometimes known as 'electronic cigarettes' or 'e-cigarettes') and topical gels. • Behavioural support, counselling or advice for individuals/groups. • Self help.	• Pharmacotherapies that are not licensed for cutting down, temporary abstinence or harm reduction; including nicotine agonists (eg varenicline) and antidepressants (eg bupropion). • Any products containing tobacco. This includes products that claim to deliver reduced levels of toxicity (such as 'low tar' cigarettes), or that reduce exposure to tobacco smoke, for example, by warming instead of burning it. • Products that are smoked that do not contain tobacco, such as herbal cigarettes. • Smokeless tobacco products such as gutka, or paan. • 'Snus' or similar oral snuff products as defined in the European Union's Tobacco Product Directive (European Parliament and the Council of the European Union 2001). • Alternative or complementary therapies, such as hypnotherapy or acupuncture.
Comparison	All comparators	
Outcomes	All types of outcomes (validated and unvalidated)	

[2] Nicotine replacement therapy preparations are licensed for adults and children over 12 years, with the exception of Nicotinell® lozenges which are licensed for children under 18 years only when recommended by a doctor (BNF accessed online 28 July 2011)

Where interventions of interest were compared to/used in combination with excluded interventions, studies were included if the data for the interventions of interest could be disaggregated. Where disaggregation was not possible they were excluded.

Studies that were designed as smoking cessation interventions were excluded, as were interventions designed to reduce the effects of second hand smoke on children where it is not possible to determine that parents were reducing their overall cigarette consumption.

2.3 Study selection

Titles and abstracts were screened independently by two reviewers using the inclusion/exclusion parameters. Any disagreement was resolved by discussion with a third reviewer and, if in doubt, included. Full paper screening was also undertaken independently by two reviewers, with recourse to a third to resolve any disagreements. Inter-rater reliability testing produced a Kappa score of 0.79.

During the screening process records were tagged for relevance to specific questions and populations of interest. Final inclusion was agreed by the review team. Excluded papers were retained with reasons for exclusion. Papers of potential relevance to review teams undertaking associated reviews were identified and forwarded to those teams.

2.4 Quality assessment

Quality assessment was conducted using the GATE checklist for quantitative studies [NICE 2009]. Studies were assessed by one reviewer and checked by a second. Twenty percent of papers were assessed independently in duplicate. Any disagreement was resolved by discussion. The review team assessed each study's internal and external validity; where external validity measured how far the findings of the study might be generalised beyond the participants to a wider population from which the participants were drawn (eg from one community setting in the US to all US communities) but not to other populations. These ratings are included in the evidence tables. In addition, Appendix B provides a summary of the quality ratings for each element of the included studies that was assessed. Where randomisation methods were unclear or methodologically insufficient, the study is described as quasi-randomised. Inter-rater reliability scores were explored and resulted in an overall kappa score of 0.72.

2.5 Applicability to the UK

Based on advice from members of the Expert Advisory Group, it was agreed that research from settings where the smoking reduction programmes are sufficiently similar to those in the UK (including Spain, Norway, Denmark, Australia and New Zealand) would be assessed as having high applicability to the UK.

2.6 Data extraction

Data were extracted as specified in Appendix K of the NICE Public Health Methods Manual and are presented in the Evidence Tables with study characteristics, quality scores and outcome measures

reported by the authors (with associated 95% confidence intervals (CI) and p-values where available).

2.7 Data synthesis

The key findings of evidence have been summarised in concise narrative summaries and evidence statements and are supported by evidence tables (Appendix A). The statements indicate:

- the message given by the evidence;
- the strength of the evidence (based on a quality assessment of the source studies);
- the applicability of the results to the UK.

A meta-analysis was conducted if at least two studies were sufficiently homogeneous in design and the intervention under investigation. Similarity between study design and interventions was explored using sub-group analyses. Treatment estimate and precision were used to determine if studies and interventions were suitable for pooling. Both clinical and statistical heterogeneity were assessed using the I^2 statistic. (Higgins 2011). Where heterogeneity was found to be at least moderate to substantial ($I^2 > 50\%$) the clinical characteristics of the studies were examined to explore the cause of the heterogeneity. In the presence of substantial heterogeneity ($I^2 > 60\%$) the cause was excluded in an additional sensitivity analysis.

For dichotomous outcomes, meta-analyses data were presented as relative risk ratios (RR) and continuous outcomes as mean difference. The dichotomous outcomes that were found to exhibit statistical evidence of an effect, were used to calculate the number of participants needed to treat to report at least one positive outcome (NNT, assuming the control arms were indicative of the underlying population prevalence. Meta-analyses were conducted using random effects models and all summarised data were provided with associated 95% CI.

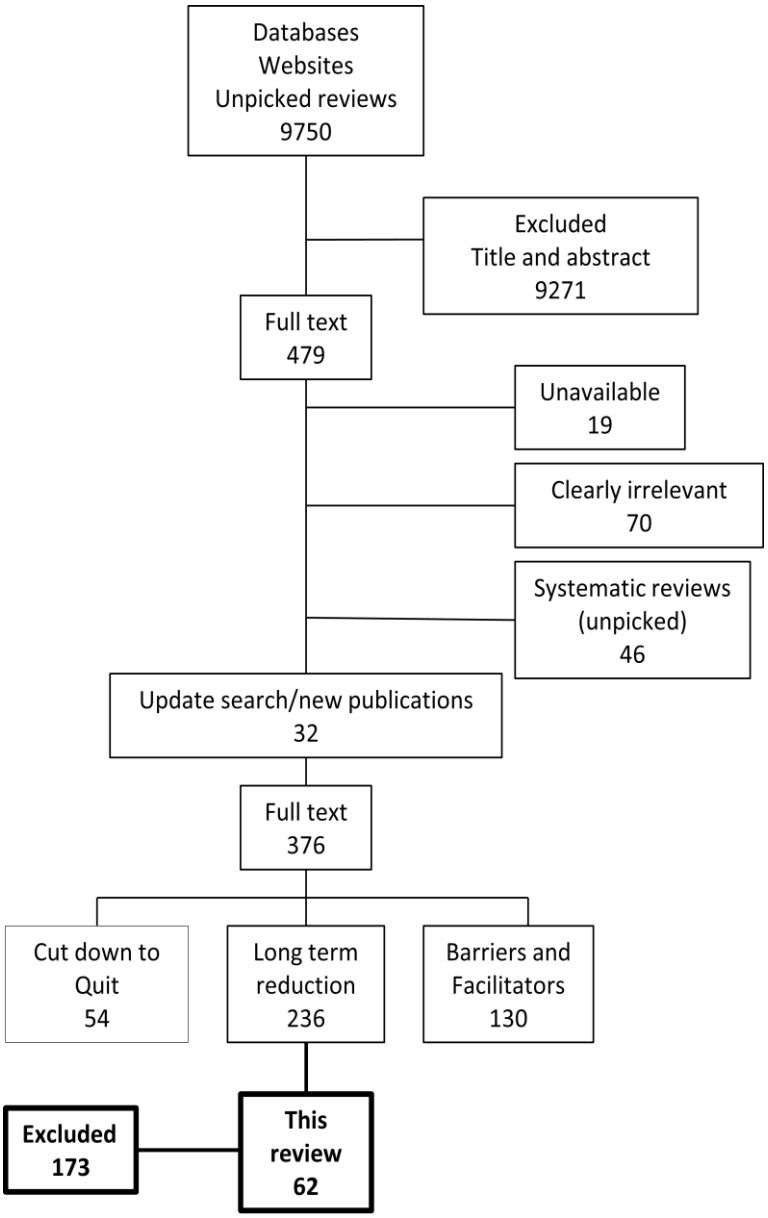
The strength of evidence assessment in the evidence statements is based on the most recent GRADE guidance (Guyatt 2010). The definitions used are broadly defined as follows with potential for moving up or down a grade as summarised in the guidance (Guyatt 2010):

GRADE low, very low quality	=	weak evidence (eg before and after studies graded –)
GRADE moderate quality	=	moderate evidence (eg RCTs/quasi RCTs graded +)
GRADE high quality	=	strong evidence (eg RCTs graded ++)

3. RESULTS

3.1 Search Results

The search strategy identified 9750 citations of which 9271 were excluded at title and abstract. Of the remaining papers to be considered in full text, 19 were unavailable, 70 were found to be clearly irrelevant and 46 were systematic reviews. Update searches identified an additional 30 papers; giving a total of 376 papers which were considered for inclusion in one or more of the three reviews. Two hundred and thirty six papers were considered for this review, of which 62 were included. These comprised 46 studies and one systematic review (the latter included four of the 62 identified papers). A full list of excluded papers with reasons for exclusion is provided in Appendix G



A brief summary of each of the included studies is provided in Table 1 and Appendix A.

3.2 Quality and applicability of studies

The quality of the included studies was variable although there was a good body of consistent evidence in some areas and five of the included studies, all RCTS, were deemed to be of high quality (**Bolliger 2000 ++, Chan 2011 ++, Glasgow 2009 ++, Hovell 2000 ++, Warner 2005 ++**). Of the remaining studies there were 2 RCTs, 5 partial RCTs, 17 quasi-RCTs (unclear allocation concealment), 3 non RCTs, 2 controlled before and after (CBA) studies, 10 uncontrolled before and after (UBA) studies and 1 secondary analysis. The UBAs and secondary analysis were all considered to be of low quality.

Five studies were carried out in the UK (**Foulds 1992 +, Gray 2005 –, Irvine 1999 +, McCambridge 2005 +, Munday 1993 –, Walker 2009 –**) and six in countries with similar smoking treatment programmes to the UK: three in Australia (**Borland 1999 +, Kelly 2006 +, Wakefield 2002 +**), two in Denmark (**Pisinger 2005 –, Wennike 2003 +**) and one in Spain (**Jimenez-Ruiz 2002 –**). 23 of the remaining studies were based in the USA, of which 11 were community based and feasible in the UK.

In general there was little information on specific socio-economic groups with only three studies looking at lower SES populations (**Hovell 2000 ++, Kelly 2006 +, Wakefield 2002 +**).

See Table 1 and Appendix A for details of all the included studies.

3.3 Outcomes

Data were extracted for all smoking-related outcomes. Reduction and abstinence data (both sustained and point prevalence) were extracted for all outcomes longer than six months from baseline, or the longest available period if these data were not available. Both self-report and verified reduction/abstinence - carbon-monoxide (CO) or cotinine - data were extracted.

Table 1: Brief summary of included studies

* Studies are complex and this table can only give a flavour of each intervention. See Appendix A for more detailed summaries.

Author and Year	Location and setting[3]	Population	Study outline	Internal validity[4]
Audrain McGovern 2011 Quasi-RCT	USA + (adolescent medical sites)	355 adolescents (aged 14-18) Attrition: 5.1%	Motivational interviewing versus brief structured advice over 12 weeks for smoking behaviour change. Self reported cigarettes per day (CPD), quit attempts and cotinine-validated 7 day abstinence to 24 weeks Participant motivations: Did not need to be interested in quitting	+ Participation required written parental consent, two issues with fidelity of MI intervention, no allocation method reported, no power calc.
Batra 2005 Quasi-RCT	Germany & Switzerland ++ (medical centres)	364 adults Attrition: 47% (I), 62% (C)	Ad lib nicotine gum (4 mg) versus placebo for up to 12 months with goal of smoking reduction. Smoking reduction ≥ 50%, CO verified, to 13 months. Participant motivations: Willing to change behaviour but not to quit.	+ High attrition, desired sample size not achieved, no allocation method, 3/5 authors from pharmaceutical co.
Benowitz 1998 Controlled study (cross over)	USA – (clinical study centre)	12 adult males Attrition: 8%	Nicotine patches (up to 63 mg/d) on ad lib smoking over 5 d per dose. Cigarette consumption, plasma nicotine, blood carboxy-haemoglobin during treatment Participant motivations: No desire to quit smoking	– Research ward study, no details of randomisation, no inclusion criteria, 5 day intervention periods only, no wash out, no power calc.
Bolliger 2000 RCT	Switzerland + (hospital pulmonary clinics)	400 adults Attrition: 22%	Nicotine inhaler (10 mg+ 1 mg menthol) vs placebo inhaler at 6-12 cartridges per day for 18 months – encouraged to decrease use at 4 mths. Smoking reduction ≥ 50% to 24 months, CO verified to 4 months. Participant motivations: Willing to reduce but unable/unwilling to stop immediately	++ Baseline differences in % women, pharma funded and part authored (but double blind).
Borland 1999 Cluster Quasi-RCT	Australia + (workplace)	41 workplaces (736 adults) Attrition: not provided.	Self help manual plus four one hour facilitated sessions (time frame unclear) versus self help manual only. Reduction in cigarette consumption, changes in workday CPD, urges to smoke, addiction level to 6 months. Participant motivations: No information but whole workforce recruited.	+ Recruitment problems, low interest and adherence to facilitated sessions, self reported outcomes only.
Carpenter 2004 Quasi-RCT	USA + (community based)	616 adults Attrition: 6%	Proactive reduction support plus nicotine gum (4mg) or patch (7, 14 or 21 mg) vs motivational calls vs no treatment. In intervention groups brief advice to quit plus NRT offer at 6 weeks.	+ Free NRT may have encouraged false reporting, no biochemical verification, outcome assessment not blinded, no

[3] The symbols (++ + –) in this column refer to the external validity; where ++ indicates an intervention that is applicable to all members of the population for which the study was designed. As external validity decreases, it is measured by + and then –.

[4] The symbols in this column provide a summary rating for quality; where ++ indicates that the study has been conducted so as to minimise risk of bias. As quality decreases/risk of bias increases, it is measured by + and then –.

			CPD, 7-day point prevalent abstinence to 24 weeks. Participant motivations: Not currently interested in quitting	power calc.
Carpenter 2007 Secondary analysis of UBA	USA – (genetic testing)	729 adults Attrition: 72.6%	Testing for alpha-1-antitrypsin (AAT) deficiency followed by a 3-months post test questionnaire to assess smoking status. CPD, ≥50% CPD reduction, quit attempts and steps towards quitting at 3-months. Participant motivations: Actively sought AAT testing	– No control group, low response, self reported outcomes, not generalisable since so few with AAT deficiency, secondary analysis, motivations uncertain, no power calc.
Chan 2011 RCT	China + (community-based)	1154 adults Attrition: 22.4% (CO validation)	Smoking reduction counselling plus NRT (gum or patch [no dosage information] with/without adherence advice) versus cessation advice, with self help quitting pamphlet to all participants. Smoking reduction ≥50% CPD, self reported and CO validated cessation, to 6 months. Participant motivations: Interested in reducing but no intention to quit in near future	++ Large difference between self reported and CO validated outcomes, Groups with/without adherence advice merged, high % male vs female, high attrition re CO validation despite payment offered
Cunningham 2006 Quasi-RCT	Canada + (community-based)	54 adults Attrition: 20%	Safer smoking tips versus requests (control group) to share harm reduction activities. CPD, type of cigarette and quit attempts to 3 months. Participant motivations: 81% reported at least one serious quit attempt	+ No biochemical validation, compensatory smoking a possibility, small sample size, high attrition, no power calc.
Davis 2011 Quasi RCT	USA – (lab based GP visit simulation)	218 adults Attrition: 44%	15 min motivational interviewing vs prescriptive interview. Smoking reduction ≥50% CPD and abstinence (both cotinine verified), intentions to quit or reduce, to 6 months. Participant motivations: Not ready to quit.	+ High attrition
Etter 2007 RCT	Switzerland ++ (community-based)	923 adults Attrition: 8% (2y); 27% (5y)	Choice of NRT versus placebo versus no intervention. All received an educational booklet. Smoking reduction ≥50% CPD, CPD, depth of smoking to 5 years. Participant motivations: No intention to quit during next 6 months	+ No biochemical validation (but deliberate to limit attrition), some pharmaceutical funding to authors, no power calc.
Fagerstrom 1997 Partial RCT	Sweden + (community-based)	170 adults Attrition: 16%	Familiarisation with NRT medications (2mg gum, 2mg tablet, patch, vaporiser or nasal spray [no dosage info]) followed by 2 weeks own choice, and 2 weeks randomised to specific medication. CPD, CO, cotinine, withdrawal score, views, adverse effects over 5 weeks. Participant motivations: Did not want to or could not give up smoking	– No control, large reduction in run in week, results from groups merged, no wash out period, no power calc.
Fossum 2004 CBA	Sweden + (child health centres)	37 child health nurses (41 mothers)	Training of child health nurses via 'smoke free children' versus no training. Maternal CPD verified by cotinine to 3 months.	– Small sample, potential selection bias, two control groups and unclear how matched, no information on counselling

		Attrition: 27% (mothers)	Participants motivations: No information	content/duration, No ITT, discrepancy in control numbers reported in table/text, no power calc.
Foulds 1992 Quasi-RCT	UK – (research centre)	34 adults Attrition: 11.8%	One week baseline, followed by week each of nicotine (15 mg) patches crossed over to placebo patches Nicotine placebo CO difference, CPD, plasma nicotine, cotinine, thiocyanate, subjective views, side effects Participant motivations: No information	+ Normal cues not likely to be present in lab, small trial, no information on participant recruitment/motivation, no allocation information
Glasgow 2009 RCT	USA ++ (community-based)	320 adults Attrition: 37% (I), 18% (C)	Telephone counselling and tailored newsletters versus enhanced usual care over 6 months. Smoking reduction ≥50% CPD, CO validated and abstinence to 12 months Participant motivations: Not interested in quitting	++ Exclusion of Spanish speaking smokers, high attrition, single setting only (Kaiser Permanente Colorado), no power calc.
Gray 2005 CBA	UK + (community-based)	162 adolescents Attrition: 13%	Single motivational interview versus no intervention. Smoking prevalence, cigarettes per week, cut down/quit attempts self-reported at 3 months Participant motivations: No information	– Self reported data only, non equivalent groups, little information and potential variation in delivery of MI, motivations of participants and researchers unknown, no power calc.
Griffiths 2010 UBA	Canada – (community-based)	56 adults with severe & persistent mental illness Attrition: 39%	12 weeks counselling sessions (Tobacco Addiction Recovery Programme). CPD, tobacco dependence, use of NRT at end of intervention Participant motivations: No information	– Self reported data only, no control, small sample, no follow up period, no ITT, no power calc.
Gulliver 2008 Quasi-RCT	USA + (community-based)	208 military veterans Attrition: 60.2%	Single motivational interview plus deep breathing versus MI plus incentive spirometer versus MI alone. Abstinence verified by CO, CPD to 6 months Participant motivations: Had not presented for smoking cessation or expressed any motivation to quit.	+ No (non MI) control, unknown therapist adherence to MI procedures, participant adherence to techniques unknown, almost entirely male population, high attrition at 6 months, no allocation information,
Hanson 2008 Quasi-RCT	USA ++ (high schools)	103 adolescents Attrition: 28.7%	NRT patch (up to 14 mg) or NRT gum (multiples of 2 mg) versus control (400 mg folic acid), plus weekly meetings for all participants for 4 weeks. CPD, expired CO, urinary cotinine to 6 months. Participant motivations: Not interested in quitting.	+ No placebo patch/gum, not blinded, high levels of co-morbidity in participants, (authors concerned that smoking reduction programme may give wrong message re health effects of smoking), no power calc.

Hatsukami 2005 Quasi-RCT	USA + (community-based)	151 adults Attrition: 35.1% (12 weeks)	6 week planned reduction schedule plus gum (4 mg) versus wait list control. Blood measures including cotinine, CPD, abstinence, respiratory symptoms to 26 weeks. Participant motivations: Interested in reducing but not quitting.	– Short time scale, results for intervention and wait list controls merged, high attrition over short period, no power calc.
Hatsukami 2007 UBA	USA – (community-based)	64 adults Attrition: 69%	Escalation, de-escalation of NRT patch (45 mg max.) over 7 weeks CPD, CO, urinary cotinine, withdrawal, physiological measures to 7 weeks. Participant motivations: Not immediately interested in quitting.	– No placebo control, some variations in way patches applied, no ITT, no post treatment follow up, no power calc.
Horn 2007 RCT	USA ++ (emergency department)	75 adolescents Attrition: 65%	Motivational intervention over 6 months plus workbook versus standard care with quit advice. Self reported CPD, abstinence to 6 months. Participant motivations: No information.	+ Recruitment difficulties, largely white sample, high attrition, no power calc.
Hovell 2000 RCT	USA ++ (community-based)	108 low income mothers Attrition: 11%	Individualised counselling over 3 months to reduce young children's exposure to environmental tobacco smoke versus nutritional counselling and brief smoking advice. CPD, cotinine verified, and abstinence to 12 months from baseline. Participant motivations: No information.	++ No limitations identified.
Hurt 2000 UBA	USA – (community-based)	23 heavy smokers Attrition: 30%	12 weeks behavioural counselling for scheduled reduction with NRT inhaler (up to 16 per day; 5 mg per cartridge). CPD, CO, cotinine, withdrawal symptoms, inhaler usage to 24 weeks. Participant motivations: Wanted to reduce but not stop smoking.	– Very small sample, no control group, no power calc.
Irvine 1999 Quasi-RCT	UK ++ (community-based)	501 families with an asthmatic child Attrition: 13.2%	Advice on passive smoking and asthma and reducing child's exposure plus commercial leaflet on smoking versus commercial leaflet only. CPD (parents), [also children's cotinine levels] at 12 months. Participant motivations: No information	+ No ITT, concerns that study was underpowered (though power calc. for primary outcome of child cotinine reported)
Jimenez-Ruiz 2002 UBA	Spain + (smokers' clinic)	17 adults with severe COPD Attrition: None	Nicotine gum (4 mg) for *ad libitum* use to 18 months. CPD, nicotine use, spirometric tests, CO, adverse events to 18 months. Participant motivations: Unable to quit.	– Very small uncontrolled study, no power calc.
Joseph 2008 RCT	USA + (community-based)	152 adults with cardiovascular disorder Attrition: 31.5 – 35.9% (18 mths)	Smoking reduction counselling with nicotine gum (4 mg) over 18 months. CPD, abstinence, CO, cotinine,other biomarkers, heart disease symptoms, QoL, walk test, adverse events to 18 months. Participant motivations: Unwilling and uninterested in setting a quit date over next 30 days.	+ Sub-optimal power for some outcomes, mainly male heavily dependent smokers limit generalisability, reduction not CO verified, assessment unblinded

Kelly 2006 Quasi-RCT	Australia ++ (high schools)	56 adolescents from lower SES families Attrition: 25%	Single motivational interview versus standard advice. Self reported days per week smoking, CPD, smoking refusal self efficacy at 6 months. Participant motivations: No information.	+	Small sample, self reported data, high attrition, no allocation information, no power calc.
Kralikova 2009 Quasi-RCT	Czech Republic + (medical centres)	314 adults Attrition: 38.9%	Nicotine gum (4 mg) or inhaler (10 mg) versus placebo for 6 months plus 3 months voluntary tapering. Smoking reduction ≥ 50%, short-term and sustained abstinence verified by CO, intention to quit, adverse events to 12 months. Participant motivations: Wanted to reduce smoking and had made ≥ 1 quit attempts but did not need to be motivated to quit.	+	Some reduction between screening and baseline visits, significant attrition
McCambridge 2005 RCT	UK ++ (further education colleges)	200 young people Attrition: 19%	Single motivational interview versus education as usual. CPD, other drug and alcohol use, health problems, behaviours and attitudes to drugs, state of change at 12 months. Participant motivations: No information.	+	No, no intervention, control; No biochemical validation of outcomes.
Munday 1993 Non-RCT	UK + (teaching hospital)	233 patients awaiting surgery Attrition: unclear	Leaflet advising ≥ 6 weeks pre-surgery cessation versus no advice. Pre-operative abstinence for ≥3 days, CPD at surgical admission. Participant motivations: No information	–	When receiving the leaflet patients did not know date of surgery, may not have understood leaflet, outcomes self reported, no randomisation, little baseline information, no power calc.
Pickworth 1994 UBA	USA – (residential research ward)	10 adults Attrition: None	Escalating nicotine patches (up to 44 mg) for 7 days periods in random double blind order plus ad lib smoking during 30 day stay. CPD, CO, puff measure, plasma cotinine and nicotine. Participant motivations: No current interest in quitting.	–	Close involvement of pharmaceutical company, uncontrolled study in tiny population group (some with extensive drug abuse history), no power calc.
Pissinger 2005 Partial RCT/secondary analysis	Denmark + (community-based)	39 adults Attrition: 51.3% overall for intervention group	Subgroup receiving lifestyle consultation and 6 smoking reduction group sessions over 6 months versus no intervention CO to 6 months. Participant motivations: Unable or unwilling to quit.	–	No biochemical validation, poor compliance with smoking reduction groups, lack of clarity since appears to be a predominantly smoking cessation intervention, some baseline differences, no power calc.
Polosa 2011 UBA	Italy – (hospital)	40 hospital staff Attrition: 32.5%	E-cigarette kit and maximum of 4 cartridges per day to 24 weeks. Product use, ≥50% CPD reduction, CO, adverse events to 24 weeks. Participant motivations: Not wishing to quit.	–	Small uncontrolled study, high attrition, lead author is consultant for e-cigarette supplier
Rennard 1990 UBA	USA – (setting unclear)	15 adult heavy smokers Attrition: None	≥ 20mg nicotine gum daily and payment to 2 months; subjects agreed to reduce CPD by ≥ 50%. CPD, CO, respiratory tract inflammation.	–	Study not designed as an efficacy study but to examine respiratory tract effects, no control group, short term follow up,

			Participant motivations: Not currently interested in quitting.	small population and no description, pharma company funding, no power calc.
Rennard 2006 Quasi-RCT	USA + (community-based)	429 adults Attrition: 64%	Nicotine (10 mg) versus placebo inhaler with instruction to reduce smoking as much as possible; smoking cessation recommended at mth 6. ≥50% CPD reduction & abstinence, verified by CO, intentions to quit, QoL, cardiovascular risk markers, adverse events to 15 months. Participant motivations: Wanted to reduce but unwilling to quit.	+ High attrition, no information on study funding (and four authors employees for pharma company)
Riggs 2001 Quasi-RCT	USA + (community-based)	20 adult volunteers Attrition: unclear	One week hierarchical reduction (easiest cigarettes first) versus one week increased inter-cigarette interval in cross over design, with ad lib nicotine gum (2 or 4 mg). CPD, CO, salivary thiocyanate, ease of reduction, adverse events to end of treatment Participant motivations: Not currently interested in quitting but wishing to reduce.	– Small self selected sample, short duration, no follow up, CO measures not linked to CPD
Riley 2002 Quasi-RT	USA ++ (community-based)	93 adults Attrition:32% (CSGR) 45% (SER)	Computerised scheduled gradual reduction (CSGR) versus selective elimination reduction (SER) to 5 weeks. ≥50% CPD reduction, abstinence validated by CO to 12 months. Participant motivations:	+ Smoking rates by self report only, lack of no treatment control, high attrition, no allocation method information, authors worked for organisation with commercial interest in CSR products, no power calc.
Roll 1998 UBA	USA – (mental health setting)	11 adults with schizophrenia/ Schizoaffective disorder Attrition: 9%	Regular visits over 3 weeks with cash payments for smoking reduction – intensive during week 2. CO to 8 weeks post intervention. Participant motivations: Not considering quitting.	– Short term, small scale, uncontrolled, no power calc.
Schleicher 2010 RCT	USA + (university)	58 students with elevated depressive symptoms Attrition: 39.7%	6 cognitive behavioural sessions over 8 weeks for smoking change versus 6 sessions to increase fruit/vegetable consumption. ≥50% CPD reduction, abstinence, salivary cotinine (no results provided), motivation, psychological outcomes, product use to one month post intervention. Participant motivations: Not seeking treatment for smoking.	+ Small scale pilot, short follow up, self report outcomes only, significant attrition (though ITT used)
Thomsen 2010 Systematic review	World wide + (literature review)	8 RCTs of smokers scheduled for elective surgery Attrition: N/A	Any pre-operative brief or intensive intervention to assist abstinence at time of surgery. Abstinence at time of surgery and 12 months post-operatively. Participant motivations: Unclear	Small sample sizes, various smoking policies introduced over period covered by studies, limited information on search strategy and motivations of participants.

Tidey 2002 UBA	USA – (outpatient mental health centre)	14 adults with schizophrenia/ Schizoaffective disorder Attrition: 21.4%	Contingency management (CM; cash payments) plus 21 mg nicotine patch for reduction versus CM plus placebo versus non contingency monetary reinforcement plus placebo; 5 day spells of treatment with washout weeks. CO, nicotine withdrawal scores, salivary cotinine, other drug use, adverse effects to 2 weeks post study. Participant motivations: Not actively trying to quit.	– Author concerns that 21 mg patch not strong enough for this group, small sample size, no randomisation to treatments, no CPD reports
Wakefield 2002 Non-RCT	Australia ++ (paediatric outpatients)	292 families with child with asthma Attrition: 9.6%	Formal letter providing child's cotinine-to-creatinine ratio with minimally tailored feedback and booklets versus usual care. (Smoking ban in home), CPD, abstinence, (child's cotinine, reduction in smoking in front of child, smoking ban in car) Participant motivations: No information but does not appear that parents needed to be motivated to quit.	+ No randomisation, low power.
Walker 2009 UBA	UK + (hospital)	25 forefoot surgery patients Attrition: None	Outline of risks and advice to stop smoking pre-surgery approx 6 months in advance of surgery. Reduction (not defined), abstinence at time and 12 months post surgery. Participant motivations: No information.	– No biochemical validation, no control group, single surgeon's intake only, small sample, no power calc.
Warner 2005 RCT	USA + (surgical clinic)	116 elective surgery patients Attrition: ca 15%	NRT patch (21, 35 or 42 mg/d) on morning of surgery and 30 days post op. Self reported CPD and abstinence, nicotine withdrawal, psychological stress and pain, patch adherence to 6 months post op. Participant motivations: Mixed but more than 80% at action stage of change.	++ Participants likely to be motivated, limited time for acclimatisation to patch pre surgery, high short term attrition
Wennike 2003 Quasi-RCT	Denmark + (community-based)	411 adults Attrition: Unclear but circa 59%	Nicotine gum (2 or 4 mg) up to 12 months versus placebo gum. ≥50% CPD reduction and abstinence, both CO verified, changes in attitudes to 24 months. Participant motivations: Wanted to reduce smoking with nicotine gum.	+ High attrition rate

4. FINDINGS

Q1. How effective are pharmacotherapies in helping people cut down or abstain from smoking, temporarily or indefinitely without the aim of quitting?

Nicotine replacement therapy (NRT) products are the only pharmacotherapies with a UK marketing authorisation for cutting down, temporary abstinence or harm reduction.[5] NRT is available in the following formulations: chewing gum, transdermal patches, inhalers, microtabs, mouth/nasal sprays and lozenges.

Nine studies, one RCT (**Bolliger 2000 ++**), five quasi- RCTs (**Batra 2005 +**, **Etter 2007 +**, **Kralikova 2009 +**, **Rennard 2006 +**, **Wennike 2003 +**) and three uncontrolled before and after designs (**Hatsukami 2005 –**, **Jiménez-Ruiz 2002 –**, **Rennard 1990 –**) explored the effect of NRT versus placebo on smoking reduction. One RCT **(Warner 2005 ++)** investigated NRT versus placebo on the effect of pre and post-operative smoking behaviour. Five studies (**Benowitz 1998 –, Fagerström 1997 –**, **Foulds 1992 +**, **Hatsukami 2007 –**, **Pickworth 1994 –**), of which only one was controlled (**Foulds 1992 +**), looked at the effect of nicotine on the suppression of *ad libitum* smoking. The latter are largely small exploratory studies with low quality ratings, and are considered at the end of this section.

Six studies were conducted in the USA (**Benowitz 1998 –**, **Hatsukami 2007 –**, **Pickworth 1994 –**, **Rennard 1990 –**, **Rennard 2006 +**, **Warner 2005 ++**), three in Switzerland (**Batra 2005 +**, **Bolliger 2000 ++**, **Etter 2007 +**) with **Batra 2005 +** also including populations from Germany, two in Sweden (**Fagerström 1997 –** and **Kralikova 2009 +**), one in Denmark (**Wennike 2003 +**) and one in the UK (**Foulds 1992 +**).

Of the six studies discussed below that were rated as high or moderate quality (**Bolliger 2000 ++**, **Rennard 2006 +**, **Batra 2005 +**, **Wennike 2003 +**, **Etter 2007 +**, **Kralikova 2009 +**) all compared NRT with placebo. In all six studies any advice or information was provided to both NRT and placebo groups.

Nine studies in which NRT was combined with a behavioural intervention are summarised in section 4.4 (**Chan 2011 ++**, **Carpenter 2004 +**, **Hanson 2008 +**, **Joseph 2008 + Griffiths 2010 –**, **Hurt 2000 –**, **Pisinger 2005a –**, **Riggs 2001 –**, **Tidey 2002 –**).

NRT versus placebo for reduction

Inhaler versus placebo

One RCT (**Bolliger 2000 ++)** and one quasi RCT (**Rennard 2006 +**) looked the efficacy of NRT inhaler vesus placebo. **Bollinger 2000 ++** examined the efficacy of 10mg nicotine/1mg menthol inhaler for long term reduction of smoking. The intervention group were instructed to use the inhaler as needed and recommended to use 6-12 cartridges over 24 hours and encouraged to decrease use of the inhaler after 4 months but continue treatment for 18 of the 24 months, participants in the placebo group received a matched placebo inhaler. All participants received information on the implications of smoking and its effects on health and were willing to reduce smoking but unable or unwilling to stop smoking immediately. A significantly greater sustained reduction in number of cigarettes smoked was observed for the intervention group versus the placebo group as verified

[5] Nicotine replacement therapy preparations are licensed for adults and children over 12 years, with the exception of Nicotinell® lozenges which are licensed for children under 18 years only when recommended by a doctor (BNF accessed online 28 July 2011)

by expired CO measurements at 4, 12 and 24 months, OR 3.55 (95% CI: 2.04, 6.19) p<0.001, 3.59 (95% CI: 1.65, 7.80) p=0.002 and 3.39 (95% CI: 1.39, 8.29) p=0.012 respectively. Abstinence as verified by expired CO measurements was only significant at 4 months, ORs for 4, 12 and 24 months: 3.41 (1.16, 10.01) p=0.044; 1.36 (0.63, 2.95) p=0.557; 1.26 (0.65, 2.47) p=0.609. A secondary analysis, (**Bolliger 2002–)**, found that at 2 years successful reducers had a significantly greater decrease in plasma cotinine measurements than unsuccessful reducers (60% vs. 1%, p<0.001). **Rennard 2006 +** investigated the effect of an *ad libitum* 10 mg NRT inhaler versus placebo inhaler, plus reduction advice, on healthy adults within a 12 month intervention. At 12 months the mean CPD reduction from baseline was 14.5 for the intervention and 12.6 for the placebo group. Self reported results were validated by expired CO. At 15 months point prevalent abstinence was 7.9% versus 1.4% (p=0.002).

Gum versus placebo

Two quasi-RCTs examined to efficacy of nicotine gum versus placebo, **Batra 2005 +** and **Wennike 2003 +**. **Batra 2005 +** investigated the efficacy of 4mg of nicotine gum for reducing cigarette consumption among smokers not ready to quit but willing to change their behaviour. Participants were instructed to use gum on urge to smoke and to chew 6-12 pieces daily for up to 12 months, participants in the placebo group received matched placebo gum. They were all told to reduce smoking as much as possible. At the 13 month assessment 7.1% of the intervention group had a significant sustained reduction in cigarette consumption (≥50% reduction in CPD compared to baseline) versus 2.8% of the placebo group (p=0.088). At 13 months the 7-day point prevalence abstinence was 12% for the intervention group and 2.2% for the placebo group (p=0.015).

Wennike 2003 + investigated the effect of 2mg and 4mg of nicotine gum for reducing cigarette consumption and smoking cessation in smokers not motivated or not able to quit smoking. Gum was provided for *ad libitum* use for up to 12 months. Participants in the placebo group received matched placebo gum. All participants received moderate behavioural smoking reduction information. Sustained smoking reduction (≥50% reduction in CPD compared to baseline) was significantly greater at all time points with active gum versus the placebo. 6.3% and 0.5% respectively, OR 13.9 (95% CI: 1.80, 107, p<0.001) at 24 months and 8.8% and 1.5% respectively, OR 6.51 (95% CI: 1.89, 22.5, p<0.001) at 12 months. Point prevalence cessation rates were significantly greater at all time points with active gum versus placebo at 24 months, 9.3% and 3.4% respectively, OR 2.90 (95% CI: 1.19, 7.07, p=0.015) and at 12 months, 11.2% and 3.9% respectively, OR 3.13 (95% CI: 1.36, 7.7, p=0.005).

Self-reported reduction and abstinence were verified by expired CO measurement in both studies

Three lower quality studies (effectively all UBAs) also explored the effect of NRT gum on reduction (**Hatsukami 2005 –**, **Jiménez-Ruiz 2002 –**, **Rennard 1990 –**). **Hatsukami 2005 –** was designed as a quasi RCT but the authors merged the study groups. Adult smokers were given 4 mg gum and reduction advice for a 6 week period. Those who found it difficult to achieve ≥ 50% reduction in CPD versus baseline goals were offered a 14 mg nicotine patch to be used with the gum. At 26 weeks 27% achieved ≥ 40% reduction in CPD and 7% achieved cotinine verified abstinence. **Jiménez-Ruiz 2002 –** explored the effect of 4 mg nicotine gum and reduction advice in a UBA of heavy smokers (> 30 CPD) with severe chronic obstructive pulmonary disease. At 18 months, the patients (29%; n=5) who had continued to use the gum had substantially reduced their CPD to 6±7

versus 39±11 at baseline. The remaining patients (71%) had stopped using gum and relapsed to their baseline CPD levels. **Rennard 1990 –** examined the effect of ≥ 20 mg nicotine gum daily plus payment (amount unstated) and advice to reduce CPD by 50%, on healthy volunteers. After 2 months, self reported CPD decreased from 50.7±2.3 to 18.8±1.5 (p<0.001) and expired CO decreased from 48.5±2.5 to 27.3±2.5 ppm (p<0.001).

Gum or inhaler versus placebo

A quasi-RCT,(**Kralikova 2009 +**), evaluated the efficacy of 4mg nicotine gum or 10mg nicotine inhaler to aid smokers to reduce or quit smoking in a population of smokers who wanted to reduce smoking. Participants were recommended to use gum (maximum 24 pieces/day) or inhaler (6-12 cartridges not exceeding 12 in 24 hours,) *ad libitum* for 6 months followed by up to 3 months voluntary tapering. Participants in the placebo group received a matched placebo product. All participants received brief behavioural smoking reduction/cessation information. There was no significant difference for smoking reduction between groups at 4 or 12 months follow-up. Significantly more smokers in the intervention group than in the placebo group had sustained abstinence at 12 months, 18.7% and 8.6% p=0.019.

Gum, patch, inhaler or combination versus placebo and control

A quasi-RCT, **Etter 2007 +**, looked at whether the reduction in cigarette consumption obtained after 6 months of NRT (choice of 15mg patch, 4mg gum, 10mg inhaler or combination) was maintained 5 years after the end of treatment in smokers who were not motivated to quit. After testing samples of each product, participants ordered the amount and type of product they needed and received products by mail every other week for 6 months. Participants in the placebo group received matched placebo products. All participants received an educational booklet. At five years, reduction in CPD was similar for all 3 groups (NRT 7.9, placebo 6.6 and control 6.3) all p≥.43 (excludes quitters). The proportion of participants who had reduced their cigarette consumption by ≥50% compared with baseline was similar in all 3 groups (NRT 20.9%, placebo 21.4% and control 18.3%) all p≥.48 (excludes quitters). Continuous abstinence rates (no smoking in previous 5 years) were also similar across groups (NRT 7.2%, placebo 6.3% and control 4.6%, drop-outs counted as smokers) all p>0.16. At two years, mean reduction in CPD was 9.8, 7.7 and 7.7 in NRT, placebo and control groups respectively (all p ≤ .02). Overall, 31.3% in NRT group versus 21.9% in placebo (p=0.014) and 24.4% in control (p=0.052) had decreased CPD by at least 50% compared with baseline.

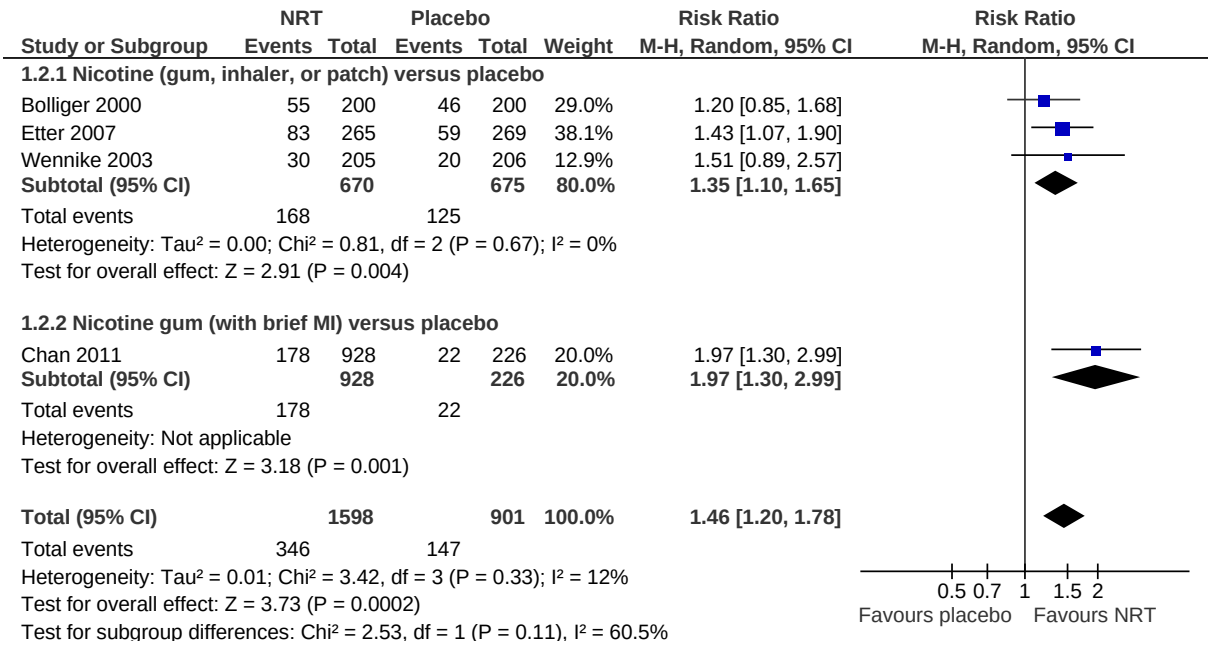
Examining NRT usage at 5 years showed that fewer participants were using NRT than at 2 years but the same proportion of participants were using NRT across the groups (daily + occasional use NRT: Nicotine, 12%; placebo, 9%; no treatment, 11%; p =.48). NRT users were more likely to be current smokers (82%) rather than former smokers (18%). During the previous 30 days, former smokers had used NRT for longer (median=30 days) than current smokers (median=10 days) p=0.003. Former smokers using NRT daily (n=11) abstained from smoking before those not using NRT (n=109), median: 123 days versus 826 days, respectively, p=0.003.

Meta-analyses: NRT and reduction outcomes

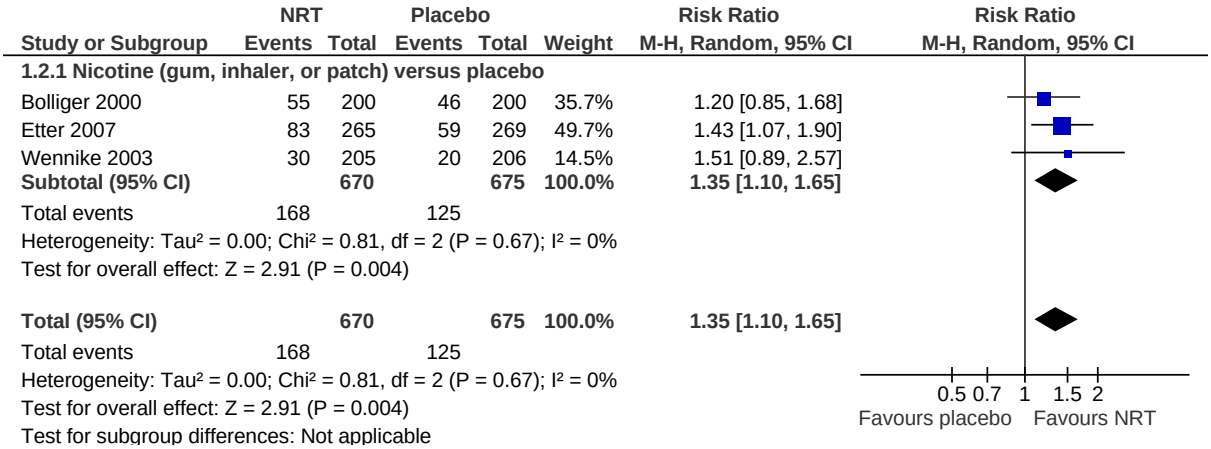
A series of meta-analyses were conducted to examine the effect of various forms of NRT on reduction outcomes.

Figure 1.1 – Proportion of participants with ≥50% reduction in cigarettes per day

Plot A – Analysis of all NRT studies versus placebo



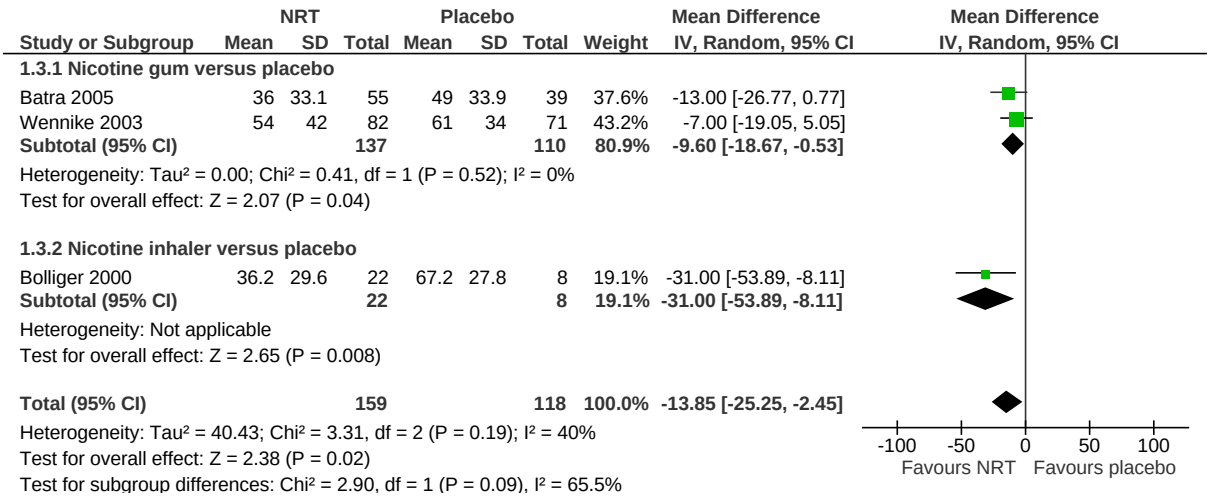
Plot B – Sensitivity analysis of NRT (without MI) versus placebo (excluding Chan 2011 ++)



A meta-analysis of three RCTs and one quasi-RCTs (**Bolliger 2000 ++**, **Chan 2011 ++**, **Etter 2007 +**, **Wennike 2003 +**) examined the effect of NRT with or without MI on point prevalence reduction in CPD of at least 50% (Figure 1.1. Plot A). As the **Chan 2011 ++** intervention included a brief motivational component and could be considered clinically diverse, a sensitivity analysis was conducted from which that study was excluded (Figure 1.1, Plot B).

Results from both analyses show that NRT increases the chance of a participant achieving a point prevalence reduction in cigarette usage of ≥50%. The initial meta-analysis resulted in a relative risk (RR) = 1.46 (95% CI 1.20, 1.78; p=0.0002; I^2=12%), with an NNT of 13 (95% CI 10, 20). The sensitivity analysis resulted in an RR=1.35 (95% CI 1.10, 1.65; p=0.004; I^2=0%) and an NNT=17 (95% CI 10, 50).

Figure 1.2 –Cigarettes per day (% reduction from baseline)

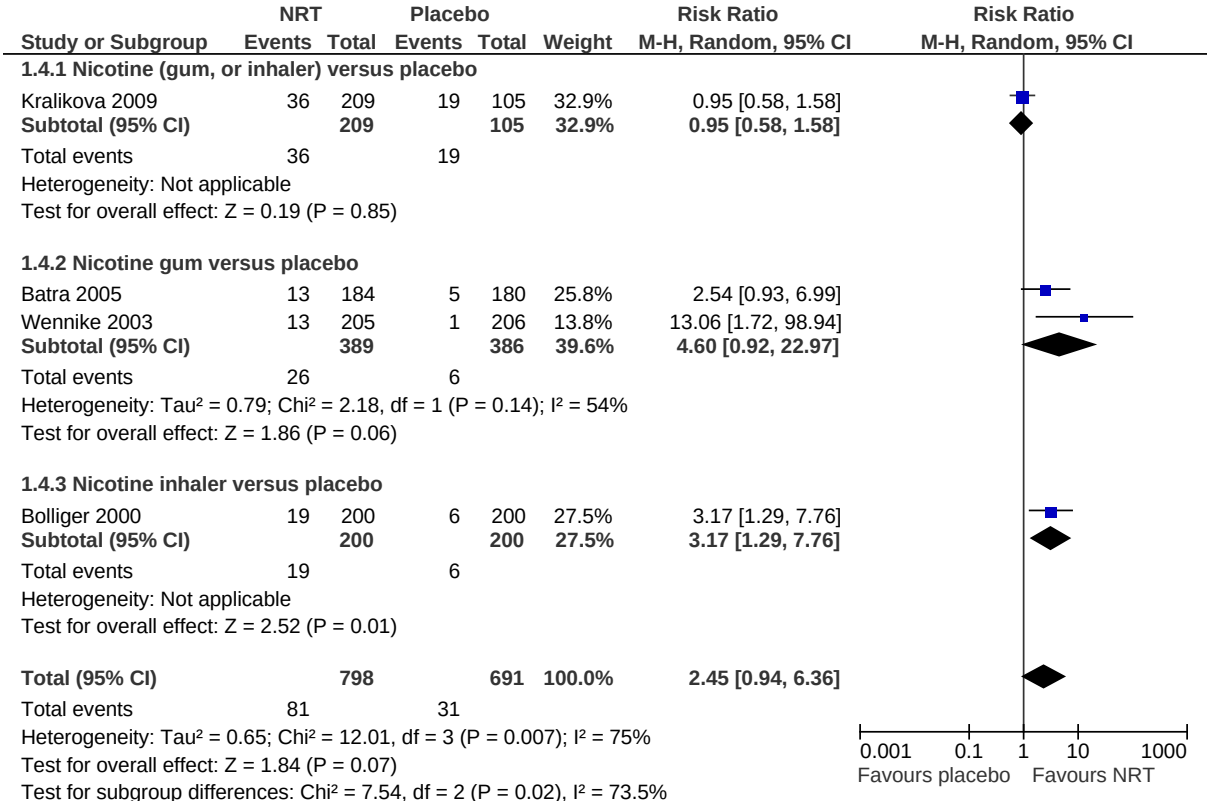


[*Note:* the axis on this Forest Plot is reversed in comparison with all other plots.]

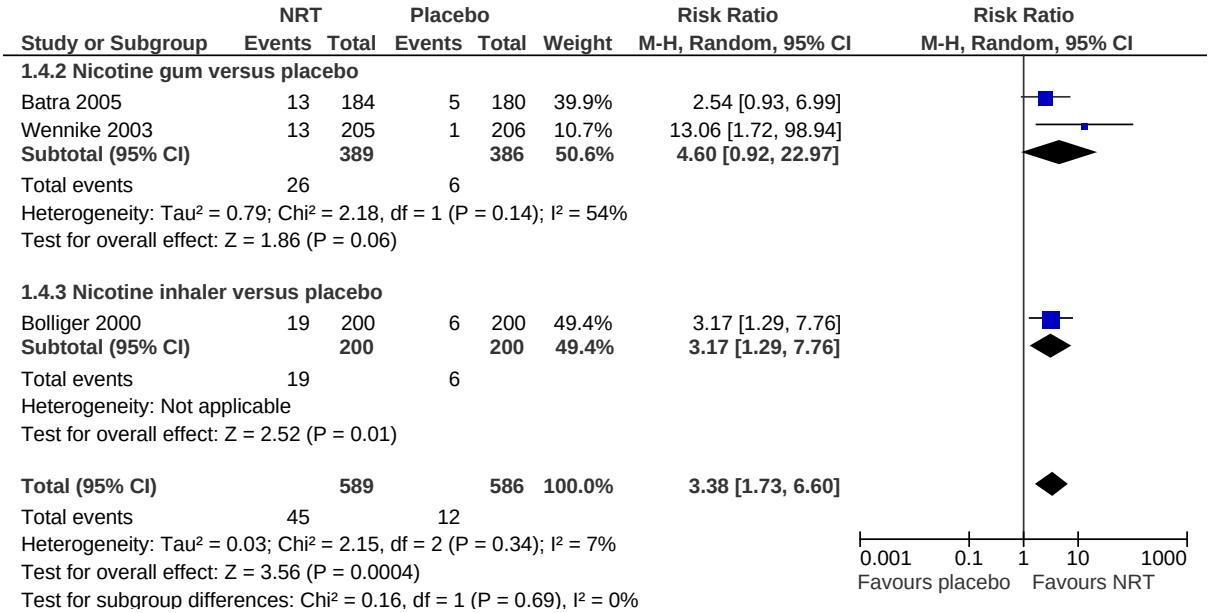
Three studies (one RCT and two quasi-RCTs) looked at the effect of NRT on percentage reduction in cigarettes per day from baseline (**Bolliger 2000 ++**, **Batra 2005 +**, **Wennike 2003 +**). The meta-analysis found that CPD reduction as a percentage of baseline was greater when using NRT compared to placebo resulting in a risk difference (RD) of -13.85 (95% CI: −25.25, −2.45; p=0.02; I^2=40%).

Figure 1.3 – Participants with a sustained CPD reduction (any reduction compared to baseline)

Plot A – All NRT studies versus placebo



Plot B – Sensitivity analysis [excluding Kralikova 2009 +]



Four studies (one RCT and three quasi-RCTs) investigating a variety of NRT methods versus placebo for any sustained CPD reduction compared with baseline (**Bolliger 2000 ++**, **Batra 2005 +**, **Kralikova 2009 +**, **Wennike 2003 +**) were included in a meta-analysis (Figure 1.3, Plot A) with

an RR=2.45 (95% CI: 0.9, 6.4; p=0.07; I^2=75%). However, severe statistical heterogeneity was found in this analysis. As outlined in the methods (see Section 2.7), the heterogeneity was investigated and was found to be due to a difference between **Kralikova 2009 +** and the other three studies. No clinical difference in study design was identified other than that **Kralikova 2009 +** offered a choice of NRT delivery method. In a sensitivity analysis excluding this study (Figure 1.3 Plot B), NRT increased the chance of a sustained smoking reduction RR=3.38 (95% CI 1.7, to 6.6; p=0.0004; I^2=7%), with an NNT of 17 (95% CI 13, 34) and no evidence of statistical heterogeneity between studies.

Meta-analyses: NRT and abstinence outcomes

Further meta-analyses were conducted to examine the effect of various forms of NRT on abstinence outcomes.

Figure 1.4 – Smoking cessation by delivery mechanism (gum +/- inhaler, and inhaler).
Plot A - Analysis of all NRT studies versus control

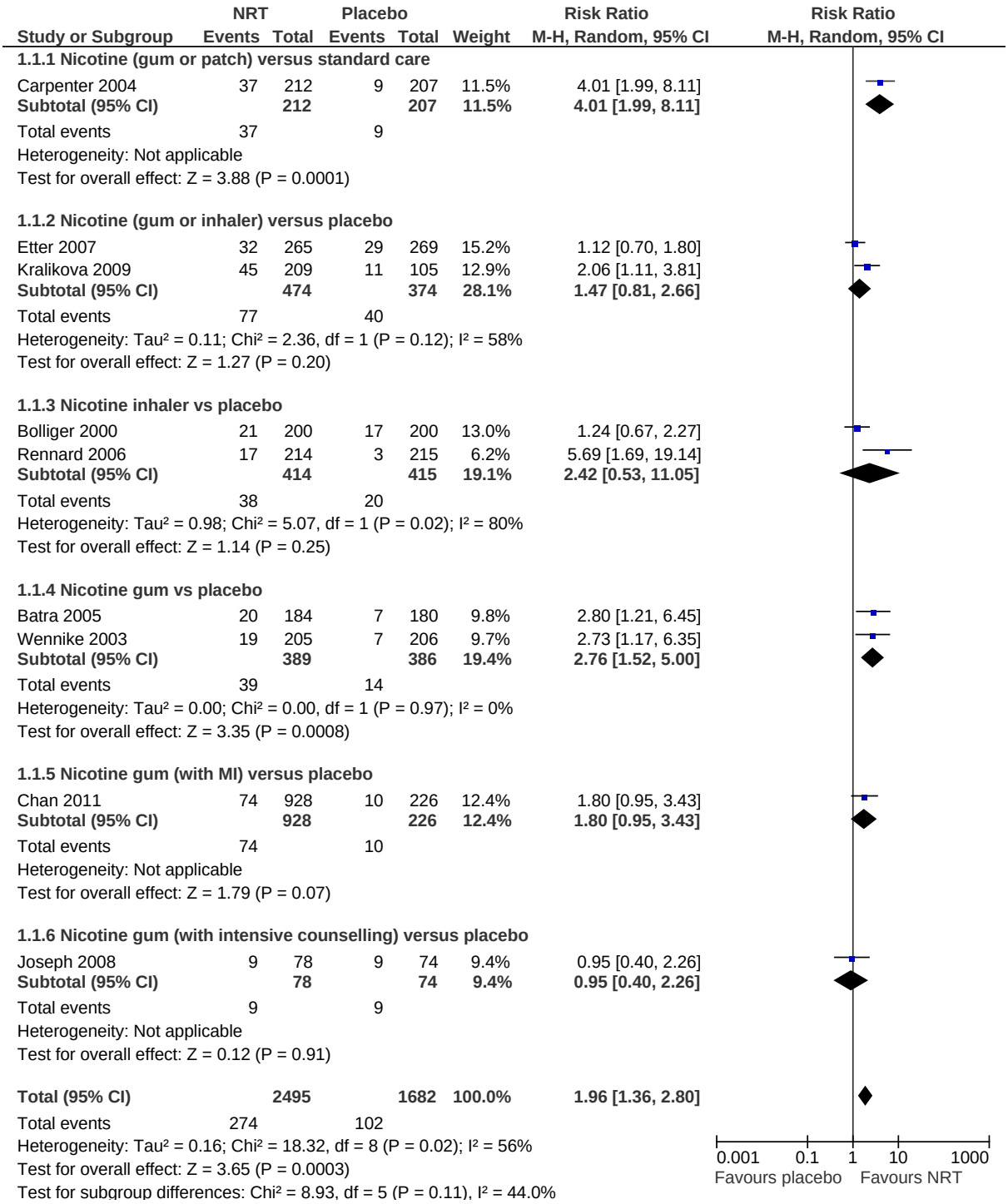
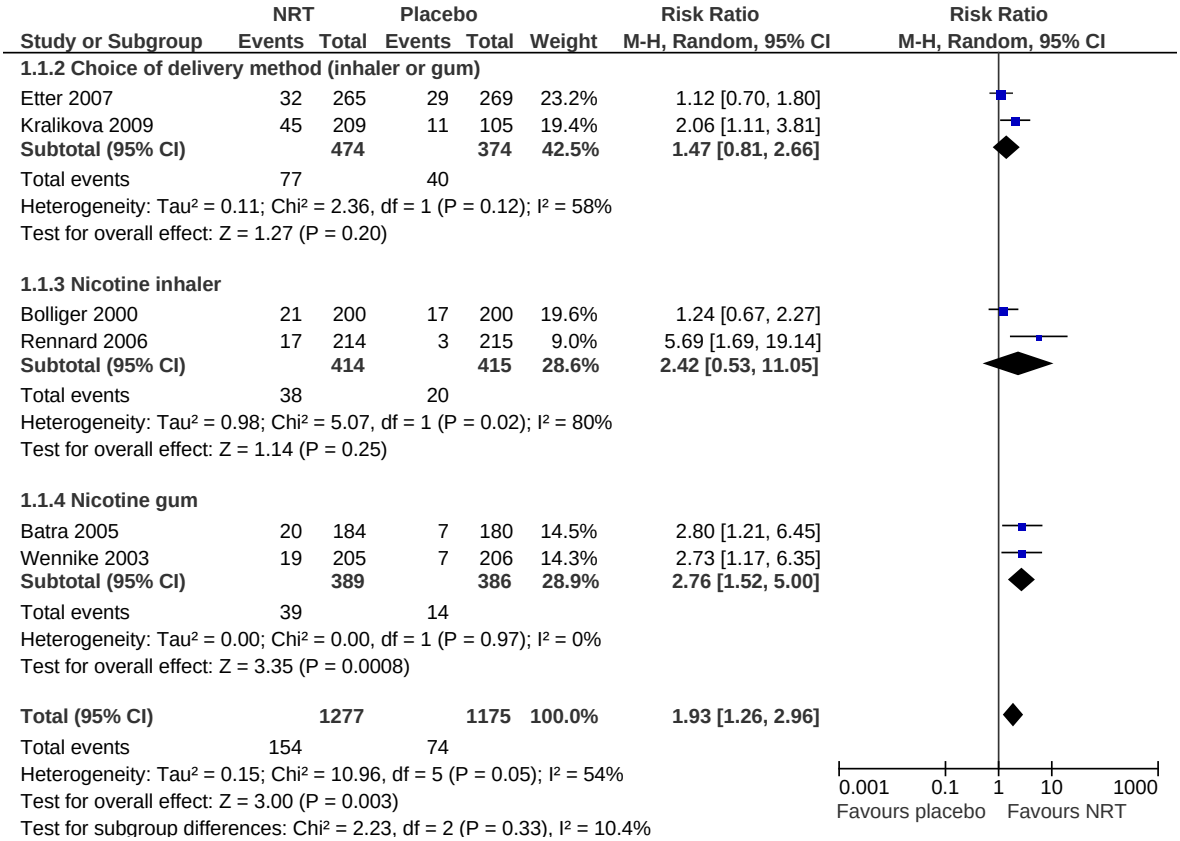


Figure 1.4 – Smoking cessation by delivery mechanism (gum +/- inhaler, and inhaler)
PLOT B – Sensitivity analysis (NRT versus placebo only)



A meta-analysis of nine studies – three RCTs and six quasi-RCTs – (**Bolliger 2000 ++**, **Chan 2011 ++**, **Etter 2007 +**, **Batra 2005 +**, **Carpenter 2004 +**, **Joseph 2008 +**, **Kralikova 2009 +**, **Rennard 2006 +**, **Wennike 2003 +**) was conducted to investigate whether NRT, with or without a behavioural intervention, versus control increased abstinence rates in smokers not looking to quit (Figure 1.4, Plot A). Additionally a sensitivity analysis was conducted excluding studies of NRT plus a behavioural intervention (**Carpenter 2004**, **Chan 2011 ++**, **Joseph 2008 +**) to examine differences (Figure 1.4, Plot B).

The results indicate that NRT, with or without associated behavioural interventions, has a statistically significant effect on smoking cessation in study populations not looking to quit: RR=1.96 (95% CI 1.36, 2.80; p=0.0003; I^2=56%) with an NNT of 20 (95% CI 13, 34). For the sensitivity analysis of NRT-only versus placebo the result was RR=1.93 (95%CI 1.26, 2.96; p=0.003; I^2=54%), again with an NNT of 20 (95% CI 13, 34).

NRT versus placebo in peri- and post-operative smoking behaviour

An RCT (**Warner 2005 ++**) analysed the effects of nicotine patch versus placebo patch on self-reported peri- and post-operative smoking behaviour in patients undergoing elective surgery with >80% of participants motivated to quit. Patients were provided with patches of 21, 35 or 42mg of nicotine/day (dose based on cigarette consumption) on the morning of surgery followed by a 30-day post-operative supply. Across both groups 99% patients maintained abstinence during hospitalisation. There was no significant difference between groups for continuous abstinence at

30 days or 6 months post-operation, intervention=29% versus placebo=15% (p=0.66) and intervention=9% and placebo=15% (p=0.32), respectively. Smokers in the intervention group 30 days post-operatively had significantly reduced the number of cigarettes smoked per day from baseline (mean ± SD: intervention = -9.7 ± 7.8, placebo = -6.1 ± 7.0, p=0.027) though this was not significant 6 months post-operation (mean ± SD: intervention = -5.0 ± 7.4, placebo = -5.3 ± 6.9, p=0.44).

NRT effect on *ad libitum* cigarette smoking

Five studies (**Foulds 1992 +**, **Benowitz 1998 –**, **Fagerström 1997 –**, **Hatsukami 2007 –**, **Pickworth 1994 –**), of which only one was controlled (**Foulds 1992 +**), looked at the effect of nicotine on the suppression of *ad libitum* smoking.

A quasi-RCT with a cross-over design (**Foulds 1992 +**) of one week nicotine patches (ca 15 mg released over 16h) and one week placebo patches suggested modest effects at most on CPD. The effect of the nicotine versus placebo patch on self-reported CPD over 6 days was not significant at -0.8 (95% CI -1.8 to 0.1).

A very small UBA (**Benowitz 1998 –**) found transdermal nicotine patches (up to 63 mg) suppressed *ad libitum* smoking in a dose dependent manner. During the 5 day laboratory based study suppression of nicotine intake from smoking averaged 3% (95% CI, -37% to 43%), 10% (95% CI, -31% to 50%) and 40% (95% CI, 6% to 74%) in the 21, 42 and 63mg conditions, respectively ($p<0.05$).

Another UBA (**Fagerström 1997 –**) explored the effect of NRT, and choice of NRT, on cigarette consumption and motivation to quit. Researchers found that a range of NRT formulations (2mg gum, 2mg tablet, patch, vaporiser, nasal spray) supported CPD reductions. Following a one week familiarisation period with the medications, subjects were randomised to a specific medication for two weeks, and then allowed free choice for two weeks. At 5 weeks, self reported CPD across all conditions declined from 22.6 (SD 7.0) to 10.4 (SD 1.0) ($p<0.001$); a 54% decrease, with the biggest drop (37%) during week 1. CO readings decreased from 22.7 (SD 8.5) to 14.8 (SD 8.4) ppm ($p<0.001$), confirming a 35% decrease in smoking. There was no significant effect between conditions on medication use. Cotinine levels remained steady, suggesting subjects were titrating nicotine to their original levels.

Results from another UBA (**Hatsukami 2007 –**) suggested that escalating the dosage of an NRT patch up to 45 mg led to CO verified reductions in smoking. CPD from week 3 to 4 (15 to 30 mg NRT) reduced by 5.81 ($p<0.0001$). For CO, significant reductions were noted from weeks 3 to 4 (15mg to 30 mg patch) (-3.36, p=0.0004) and weeks 4 to 5 (30 mg to 45 mg) (-3.25, p=0.0016). There was some evidence of greater inhalation per cigarette as CPD reduced.

Finally a very small laboratory study (**Pickworth 1994 –**) in 10 subjects found that, compared to smoking rates in the placebo condition each of the nicotine conditions significantly reduced average CPD (placebo: 18.1±1, 22 mg: 15.3±1, 44 mg: 13.4±1). Significant reductions in expired CO were noted from the use of a 44 mg nicotine patch versus placebo, but not with a 22 mg patch. The nicotine content of the patch did not significantly affect the average or total puff duration on the daily cigarette.

Evidence Statements:

1.1 There is strong to moderate evidence from nine studies - two RCTs, five quasi-RCTs and two UBAs - (**Bolliger 2000 ++**, **Etter 2007 +**, **Batra 2005 +Hatsukami 2005 −**, **Jiménez-Ruiz 2002 −**, **Kralikova 2009 +, Rennard 1990 −**, **Rennard 2006 +**, **Wennike 2003 +)** that NRT (gum or inhaler) versus placebo is effective in reducing cigarette consumption across multiple outcome measures and in eventual abstinence in smokers not looking to quit.

1.2 There is strong to moderate evidence from a meta-analysis of three RCTs and one quasi-RCT (**Bolliger 2000 ++**, **Chan 2011 ++**, **Etter 2007 +**, **Wennike 2003 +**) looking at ≥50% point prevalence reduction in CPD compared to baseline, that NRT, with or without a brief MI component, is more effective than placebo with a relative risk (RR) = 1.46 (95% CI 1.20, 1.78), with a number needed to treat (NNT) of 13 (95% CI 10, 20). A sensitivity analysis excluding **Chan 2011 ++** (which added a brief MI component to NRT) resulted in RR=1.35 (95% CI: 1.10, 1.65) and an NNT of 17 (95% CI 10, 50). Smoking reduction was verified by CO except in **Etter 2007 +**.

1.3 There is moderate evidence from a meta-analysis of one RCT and 2 quasi-RCTs (**Bolliger 2000 ++**, **Batra 2005 +**, **Wennike 2003 +**) that NRT is more effective than placebo in percentage reduction in cigarettes per day from baseline with a risk difference (RD) of −13.85 (95% CI: −25.5, −2.45).

1.4 There is unclear evidence from a meta-analysis of one RCT and three quasi-RCTs (**Bolliger 2000 ++**, **Batra 2005 +**, **Kralikova 2009 +**, **Wennike 2003 +**) for the efficacy of NRT for any sustained CPD reduction compared to baseline with an RR=2.45 (95% CI: 0.9, 6.4). In a sensitivity analysis that excluded **Kralikova 2009 +** for significant heterogeneity, NRT increased the chance of a sustained smoking reduction RR=3.38 (95% CI 1.7, 6.6), with an NNT of 17 (95% CI 13, 34), and no evidence of between-study statistical heterogeneity.

1.5 There is strong evidence from a meta-analysis of nine studies (three RCTs and six quasi RCTs) investigating cessation in populations not looking to quit (**Bolliger 2000 ++**, **Chan 2011 ++**, **Etter 2007 +**, **Batra 2005 +** , **Carpenter 2004 +**, **Joseph 2008 +**, **Kralikova 2009 +**, **Rennard 2006 +**, **Wennike 2003 +**) that NRT with or without associated behavioural interventions has a statistically significant effect: RR=1.96 (95% CI 1.36, 2.80) with an NNT of 20 (95% CI 13, 34). A sensitivity analysis excluding studies with a behavioural component (**Carpenter 2004 +**, **Chan 2011 ++**, **Joseph 2008 +**), found a similar result for NRT alone: RR=1.93 (95%CI 1.26, 2.96) and an NNT of 20 (95% CI 13, 34).

1.6 There is moderate evidence from one RCT (**Warner 2005 ++**) that nicotine patch versus placebo is effective in reducing post-operative smoking consumption, a statistically significant self-reported reduction was observed 30 days post-operation but this was not maintained at 6 months.

1.7 There is weak evidence from five studies (**Benowitz 1998 −, Fagerström 1997 −, Foulds 1992 +, Hatsukami 2007 −, Pickworth 1994 −**) that a nicotine patch may

help reduce *ad libitum* cigarette smoking. In the only controlled study (**Foulds 1992 +**) the result was not statistically significant.

The majority of the evidence is applicable to the UK as the studies are community based and feasible in UK settings, although **Batra 2005 +** involved participants making several clinic visits and **Foulds 1992 +** was in a laboratory setting. **Warner 2005 ++** was conducted within a specific population (patients undergoing elective surgery).

Q2. How effective are different combinations of NRT products in helping people cut down or abstain from smoking, temporarily or indefinitely without the aim of quitting?

No studies were found that looked at the efficacy of combinations of NRT products in helping people cut down or abstain from smoking without the intention of quitting. One quasi-RCT (**Etter 2007 +**) permitted a combination of products but did not provide an analysis of take up or effects**. Hatsukami 2005** –, a study designed as a quasi-RCT but which did not present results for participant groups separately, offered those who found it difficult to reduce CPD using gum, an additional 14mg patch. However data are not reported separately for this group. A UBA (**Fagerström 1997 –**) looked at the effect of choice of product on outcomes.

Etter 2007 + explored whether a reduction in cigarette consumption obtained after 6 months of NRT (choice of 15mg patch, 4mg gum, 10mg inhaler or combination), was maintained 5 years after the end of treatment in smokers who were not motivated to quit. However a separate analysis of those participants using a combination of products was not conducted.

Hatsukami 2005 – gave participants 4 mg gum and instructed them to reduce CPD from baseline levels to 75% in first 2 weeks, 50% in weeks 3-4 and 25% in weeks 5-6. Those who found it difficult to achieve 50% or 75% goals were offered 14mg nicotine patch to be used with gum. However, no separate data are provided for those who received the additional patch. Although designed as a quasi-RCT, the groups were merged.

Fagerström 1997 – found that a range of NRT formulations (2mg gum, 2mg tablet, patch, vaporiser, nasal spray – doses not described) supported CPD reductions. Following a one week familiarisation period with the medications, subjects were randomised to a specific medication for two weeks, and then allowed free choice for two weeks. Authors reported (though little data in paper) that the overall effect of free choice on self-reported CPD reduction was 3.1 vs 1.1 ($p<0.001$). For CO reduction the effect was 2.7 vs 0.9 ppm ($p<0.05$). The overall measures for cotinine were higher in the free choice than in the no choice groups (+1.6 vs -1.7 ng/ml) but the results were not significant. There was no significant effect between conditions on medication use. No clear medication preference emerged, though patch and vaporiser seemed not as good in reducing craving as gum and spray, and spray was rated as having the greatest "similarity to cigarettes".

Evidence Statement:

2.1 No studies were found that looked at the efficacy of combinations of NRT products in

helping people cut down or abstain from smoking without the intention of quitting.

Q3. How effective are 'nicotine-containing products' in helping people cut down or abstain from smoking, temporarily or indefinitely without the aim of quitting?

For the purposes of this review 'nicotine containing products' were defined as 'electronic nicotine delivery systems' (sometimes known as 'electronic cigarettes' or 'e-cigarettes') and topical gels. Currently these products are not regulated by the Medicines and Healthcare products Regulatory Agency (MHRA).

The only relevant intervention research identified was a proof of concept study designed as a UBA, (**Polosa 2011**−) where regular smokers of ≥ 15 factory-made CPD were provided with an e-cigarette kit for *ad libitum* use, up to 4 cartridges per day. At 24 weeks follow up there was self-reported 50% CPD reduction in 13/40 (32.5%) participants, with a reduction from a median of 25 CPD (IQR 20, 30) to 6 CPD (IQR 5, 6) ($p<0.001$). Results were validated by reduced CO levels. Product use varied greatly with a mean of 2.0 (±1.4) cartridges per day and a range of 0 to 4 per day over study period. There was no relationship between cartridges per day and sustained 50% reduction or abstinence.

Evidence Statement:

3.1 Very weak evidence from one UBA (**Polosa 2011**−) suggests that e-cigarette availability can help smokers reduce their self reported CPD and CO levels.

This evidence may be applicable to the UK as it is community based and feasible in a UK setting.

Q4. How effective are behavioural support, counselling, advice or self-help (with or without pharmacotherapy) in helping people cut down or abstain from smoking, temporarily or indefinitely without the aim of quitting?

Various types of behavioural support have been offered. The most common approach was motivational interviewing (MI), which was used in nine studies (**Chan 2011++**, **Audrain-McGovern 2011 +**, **Carpenter 2004 +**, **Davis 2011 +**, **Gulliver 2008 +**,**Horn 2007 +**, **Kelly 2006 +**, **McCambridge 2005 +**, **Gray 2005 −**). Five of these studies were carried out among adolescents – three in healthy adolescents (**Kelly 2006 +, Audrain-McGovern 2011 +**, **Horn 2007 +**) and two in adolescent drug users (**McCambridge 2005 +**, **Gray 2005 −**). Of the remaining studies carried out among adults, three involved healthy adults (**Chan 2011++**, **Carpenter 2004+**, **Davis 2011 +**) and one was carried out among "psychiatrically complex" military veterans (**Gulliver 2008 +**). Six studies were randomised controlled trials, five with randomisation at an individual level (**Chan 2011 ++**, **Audrain-McGovern 2011 +**, **Davis 2011 +**, **Horn 2007 +**, **Kelly 2006 +**) and one with randomisation clustered at the college level (**McCambridge 2005 +**). Two studies were quasi-randomised (**Carpenter 2004+**, **Gulliver 2008 +**), and one was a controlled before and after study (**Gray 2005 −**). Two studies were carried out in the UK (**McCambridge 2005 +, Gray 2005 −**), five in the USA

(**Audrain-McGovern 2011 +**, **Carpenter 2004+**, **Davis 2011 +**, **Gulliver 2008 +**, **Horn 2007 +**), one in Australia (**Kelly 2006 +**), and one in China (**Chan 2011 ++**).

Seven further behavioural studies utilised a range of techniques: one used cognitive behavioural therapy for college students with elevated depressive symptoms (**Schleicher 2010 +**); one explored the of effect intensive contingent positive reinforcement with cash payments for adults with schizophrenia (**Roll 1998 –**); one examined the effectiveness of telephone counselling among adults scheduled for outpatient surgery or a diagnostic procedure (**Glasgow 2009 +**); one compared computer-aided reduction with manual-aided reduction among adults (**Riley 2002 +**); one examined the effectiveness of safer smoking tips for adults (**Cunningham 2006 +**); one looked at the effectiveness of workplace self-help programmes (**Borland 1999 +**); one investigated if knowledge of alpha-1-antitrypsin (AAT) deficiency is effective in influencing quit attempts and cigarette consumption (**Carpenter 2007 –**). Of these seven studies three were randomised controlled trials, two being individually randomised (**Schleicher 2010 +**, **Glasgow 2009 +**) and one being cluster randomised (**Borland 1999 +**). One study was a randomised non-controlled trial (**Riley 2002 +**), and one was a quasi-randomised controlled trial (**Cunningham 2006 +**). Two studies were uncontrolled before and after studies (**Roll 1998 –**, **Carpenter 2007 –)**.

Five studies were carried out in the USA (**Carpenter 2007 –**, **Glasgow 2009 +**, **Riley 2002 +**, **Roll 1998 –**, **Schleicher 2010 +**), one in Australia (**Borland 1999 +**) and one in Canada (**Cunningham 2006 +**). Two studies were specific to subjects with mental health conditions (**Roll 1998 –**, **Schleicher 2010 +).**

Six studies examined behavioural therapy in combination with NRT. **Hanson 2008 +**, a randomised open-label trial, used cognitive behaviour therapy in combination with a nicotine patch or gum among adolescents. **Joseph 2008 +**, a RCT; **Hurt 2000** –, a UBA**;** and **Pisinger 2005a –**, a small sub-group analysis of a RCT, combined counselling and behavioural strategies with nicotine replacement therapy for reduction among adults. Two studies examined behavioural support with NRT among adults with mental illness (**Griffiths 2010** –, **Tidey 2002 –**)**. Hanson 2008 +**, **Hurt 2000 –**, **Joseph 2008 +** and **Tidey 2002 –** were conducted in the USA, **Pisinger 2005a –**, in Denmark and **Griffiths 2010 –** in Canada.

One quasi -RCT in the USA compared NRT and hierarchical reduction versus NRT and increased inter-cigarette interval (**Riggs 2001 –).**

One systematic review of RCTs (**Thomsen 2010 +**) which included trials from Denmark, Australia, Canada, Sweden and the UK, plus a controlled trial (**Munday 1993–**) and an uncontrolled before and after study (**Walker 2009 –**), both of which were conducted in the UK, reported on the effectiveness of pre-operative smoking cessation interventions. All studies should be applicable in a UK setting.

Motivational interviewing

Nine studies were identified that described a 'motivational interviewing' component as part of the intervention. The fidelity of this MI component was examined using the definition outlined in Lai 2010; a Cochrane systematic review of motivational interviewing for smoking cessation. The review required the intervention to comply with the MI principles and practice of Miller and

Rollnick (Miller 2002). Specifically, the study should make specific reference to MI principles and some form of monitoring of MI should be reported.

Six studies met Lai's definition (**Audrain McGovern 2011+**, **Davis 2011+**, **Gray 2005 −**, **Horn 2007 +**, **Kelly 2006**, **McCambridge 2005**). One (**Gulliver 2008+**) did not make any reference to monitoring. Two further studies combined a 'motivational' intervention with NRT (**Carpenter 2004+**, **Chan 2011 ++**). Although both studies made reference to motivational interviewing techniques, neither described the nature of the intervention nor did they discuss monitoring; so did not meet either of the criteria outlined in Lai 2010.

A brief summary of the MI interventions is provided below:

Author	**Intervention**	**Control group**	**Intervention delivery**
Audrain McGovern 2011 +	Five intensive MI sessions - mix of 3 face-to-face (f2f) and 2 telephone interviews	Five sessions of structured brief advice	Trained counsellors
Carpenter 2004 + [Note: fidelity to MI principles and practice unclear]	Reduction aided by NRT (R-NRT): Three telephone calls focusing on behavioural reduction strategies. Plus NRT gum or patch for six weeks with additional NRT from week 6 for those committing to quit. Motivational treatment (MT): Three telephone calls focusing on 5Rs, At week 6 those committing to quit given NRT.	No treatment	University researchers
Chan 2011 ++ [Note: fidelity to MI principles and practice unclear]	A1: 3 x 15 mins face-to-face counselling on smoking reduction based on MI techniques and 3 x 3 mins adherence to NRT. Free NRT (choice of patch or gum – no dosage information). Plus self-help quitting pamphlet, 'Tips for Quit Smoking' A2: as above without adherence to NRT info	Simple cessation advice at baseline. Plus self-help quitting pamphlet, 'Tips for Quit Smoking'	Trained smoking cessation counsellors.
Davis 2011 +	15-minute MI session	Prescriptive interview	University researchers trained MI deliverers but unclear who delivered.
Gray 2005 −	Single MI session	Nothing	Youth workers trained in MI
Gulliver 2008 + [Note: authors do not state whether MI component was monitored for practice	Single MI session 45-50 minutes	All three groups receive MI. One group also received instruction in deep	Psychologists with ≥3 years' experience treating addictions and trained using

fidelity]		breathing, instruction in how to use a spirometer	Motivational Interviewing Professional Training Series.
Horn 2007 +	15 to 30 minute patient-tailored f2f motivational interview. Stage matched self-help, take home workbook with audio. Handwritten personal postcard within 3 days. Follow-up "booster" phone calls at 1, 3, and 6 months.	Standard care (brief advice)	Researchers trained in MI
Kelly 2006 +	Single 60 minute f2f MI session	Standard care	Psychotherapist trained in MI
McCambridge2005 +	Single 60 minute f2f MI session	Nothing	Researcher trained in MI

MI in adolescents

Kelly 2006 + carried out a randomised controlled trial in which a motivational interviewing intervention was delivered to Australian adolescents caught smoking in high school. Intervention participants received a one hour MI session with reading materials also being provided. At three and six month follow-up there were no differences between the intervention and control groups in terms of number of smoking days and the number of cigarettes smoked on smoking days.

Audrain-McGovern 2011 + evaluated the efficacy of motivational interviewing (MI) compared with structured brief advice (SBA) for adolescent smoking behaviour change. In this randomised controlled trial intervention participants received three 45-minute office-based MI sessions and two 30-minute office or telephone sessions over 12 weeks. The intervention was based on motivational enhancement therapy (MET), which adds personalized feedback about assessment results and collaborative development of a formal change plan to the standard principles and techniques of MI. The control group received 5 sessions of structured brief advice, focusing on the "5 A's" for those interested in quitting and the "5 R's" for those not interested in quitting. In each session, the 5 A's/R's were followed by a review of self-help materials, followed by a brief check-in to see if the adolescent needed help in gaining access to services. Treatment group was not significantly associated with attempting to cut back at either week 12 or week 24 (both $p>0.05$), although adolescents who received MI showed a greater reduction in the number of cigarettes smoked daily than adolescents who received SBA (5.3 versus 3.3 fewer CPD respectively). Those receiving MI were around 60% less likely than those who received SBA to try to quit smoking (OR=0 .41, 95% CI 0.17–0.97).

In their randomised controlled trial, **Horn 2007 +** examined the efficacy of an emergency department based motivational teenage smoking intervention. The intervention consisted of one 15 to 30 minute patient-tailored face-to-face motivational interview including a readiness assessment, a reflection on smoking behaviours, and a health inventory. Participants were also given a stage matched self-help take home workbook with audio, they received a handwritten personal postcard within three days of the emergency department visit, and also received three

follow-up booster phone calls at one, three and six months post emergency department visit. Control group participants received no more than two minutes of generic advice, referral to a telephone helpline, and one follow-up telephone call six months after the emergency department visit. At the six month follow-up intervention participants showed a greater reduction in the number of cigarettes smoked than the control participants, although this difference was not significant (20.5% versus 6.1% reduced CPD compared to baseline; p=0.15). Among teenagers who reduced their smoking, the intervention group reduced more than the control group at the six month follow-up, although again this difference was not significant. There were also no differences in quit rates at six months between the two groups (2.5% versus 2.9%, p=0.55).

MI in adolescent drug users

McCambridge 2005 + carried out a cluster randomised controlled trial in which they assessed whether a single session of motivational interviewing, discussing alcohol tobacco, and illicit drug use, would lead to a reduction in use of these drugs or in perceptions of drug related risk and harm among young people who had current involvement with drug use. The intervention was adapted from the literature on MI and took the form of a topic-based 1 hour single session face-to-face interview. Although the number of cigarettes smoked per week three months post-intervention was lower in the intervention group than the control group (p=0.009), the differences between groups disappeared over time; being non-significant at 12 months (p>0.1). When restricting the analyses to only those who were smokers at study entry, the mean number of cigarettes smoked per week declined significantly in the intervention group (41.0 to 32.3, p=0.02), but not in the control group (41.0 to 38.9, p>0.01). At three month follow-up 25% of smokers at baseline in the intervention group quit compared to 8% in the control group (p=0.008). After adjusting for confounders though this result fell just short of significance (p=0.056). Twelve month data were not reported for this outcome.

Following on from this, **Gray 2005 –** undertook a controlled before and after study examining whether a single session of motivational interviewing focussing on drinking alcohol, and cigarette and cannabis smoking would successfully lead to reductions in use or problems. Participants were daily cigarette smokers, weekly drinkers or weekly cannabis smokers. The intervention group received one MI session, whilst the control group received no intervention. At three month follow-up there were no differences between the two groups in terms of the number of cigarettes smoked in the previous week. A greater proportion of the MI group than the control group reported trying to cut down or quit one or more times over the study period, however (73% vs 45%).

MI in adults

In a randomised controlled trial, **Chan 2011 ++**, examined the effectiveness of motivational interviewing based smoking reduction counselling plus free nicotine replacement therapy for smokers not willing to quit. Two intervention groups received three 15 minute face-to-face smoking reduction counselling session based on MI techniques and the 5R approach, although the fidelity of the MI is unclear. The first group also received three minutes of information on adherence to NRT whilst the second group did not. Free NRT was provided in both groups, with a choice of patch or gum being available. A control group received simple cessation advice at baseline. Results were presented for both intervention groups together. At six month follow-up

more participants in the intervention groups had achieved biochemically validated reductions of at least 50% than in the control group (OR 2.2, 95% CI 1.4,3.5; p=0.001). Differences between groups in self-reported quit rates were significant (p=0.01) but biochemically verified quit rates were not (OR 1.9, 95% CI 1.0, 3.7; p=0.07). The authors identified problems, however, in achieving biochemical verification among many of the participants.

Carpenter 2004 + carried out a quasi-RCT comparing the effects of motivational treatment and behavioural reduction aided by NRT with no treatment control. Participants in the motivational treatment group received three motivational and advice giving telephone calls over six weeks, with advice to quit being given in the final call. The fidelity of this MI intervention is unclear. Those in the reduction aided by NRT group also received three telephone calls with the focus being on behavioural reduction strategies and problem solving advice being given where necessary. Participants in this group could also choose to receive nicotine gum or patches, and again advice was given to quit at week six. At follow-up, 24 weeks post-baseline, participants in both experimental groups who continued to smoke were smoking less than those in the no treatment condition ($p<0.05$), although there were no differences between the two experimental groups. Higher numbers of participants in the intervention groups than in the no treatment group had cut their smoking in half (circa 20% vs 11%), although significance values were not reported. Over the six month study period both intervention groups were more likely than the no treatment group to make a 24 hour quit attempt (reduction group OR 4.2 95% CI=2.6-6.7, motivational group OR 5.6 95% CI=3.5-9.1). The reduction group were less likely than the motivational group to make a quit attempt, although this difference was not significant (OR 0.7 95% CI=0.5-1.1). A greater number of participants in both intervention groups also achieved seven day point prevalence abstinence than in the no treatment group ($p<0.01$).

In an RCT, **Davis 2011 +** compared the effectiveness of brief motivational interviewing versus prescriptive counselling among adult smokers who were not ready to quit. The intervention was a 15 minute MI session delivered in a laboratory setting, designed to match the time available in the average professional-patient interaction. The control group received a 15 minute prescriptive interview, also delivered in a laboratory setting. Outcomes were measured at one and six-months post-intervention and included intentions to quit or reduce smoking, verbal report of reducing cigarette consumption by 50% or quitting, and biologically verified quitting or reductions of 50%. At follow-up there were no differences between groups on any of the outcome measures.

MI in military veterans

Gulliver 2008 + carried out a quasi-randomised controlled trial in which they investigated the differential efficacy of three brief motivational interviewing interventions to yield changes in smoking behaviour among psychiatrically complex military veterans. No information is provided on whether the interventions were monitored for fidelity to MI practices. The three intervention groups were MI plus instruction in deep breathing (MI/BI), MI plus instruction in use of an incentive spirometer for practice in breathing/diaphragmatic control (MI/IS), and MI alone. Across all conditions the MI component consisted of one single session lasting 40 to 50 minutes. At six month follow-up there was no difference between treatment groups on either or cigarettes per day ($p>0.65$) or point prevalence abstinence ($p>0.30$). CO levels fell from baseline to 6-month follow-up in the MI/BI and MI/IS groups, but increased in the MI group. Those receiving MI/BI had

significantly lower CO levels during follow-ups than those receiving MI/IS (p=0.003; no useable data; graphical presentation only). Differences between MI/IS and MI were non-significant (p=0.12).

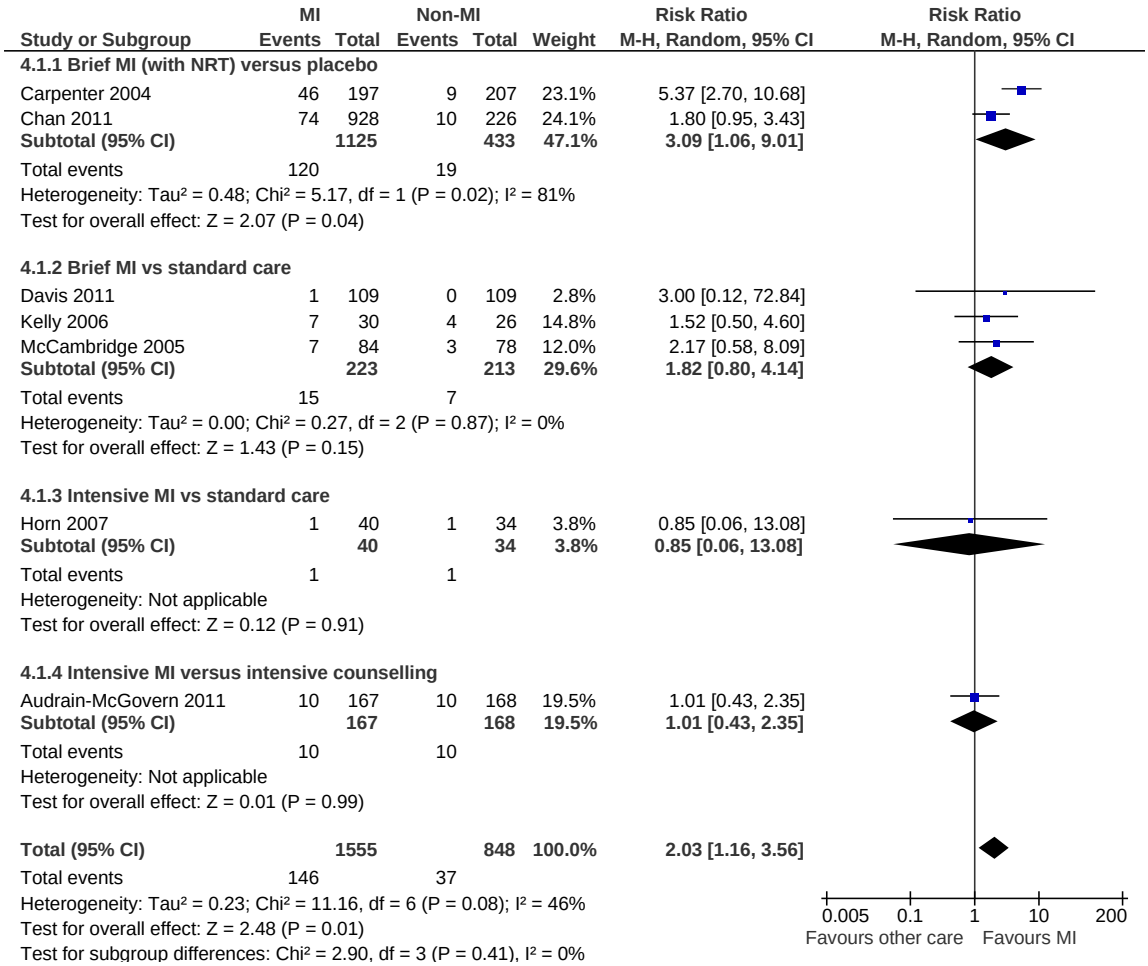
Meta-analysis of motivational interviewing interventions

The possibility of undertaking a meta-analysis to examine reduction-related outcomes for motivational interviewing interventions was explored. However, there was considerable clinical heterogeneity in reported outcomes for smoking reduction and no two studies used exactly the same measures.

Only one outcome (abstinence) was sufficiently homogeneous in terms of measures to allow pooling of data. A pragmatic meta-analysis was conducted, including all studies that reported a cessation measure (Figure 4.1 Plot A).

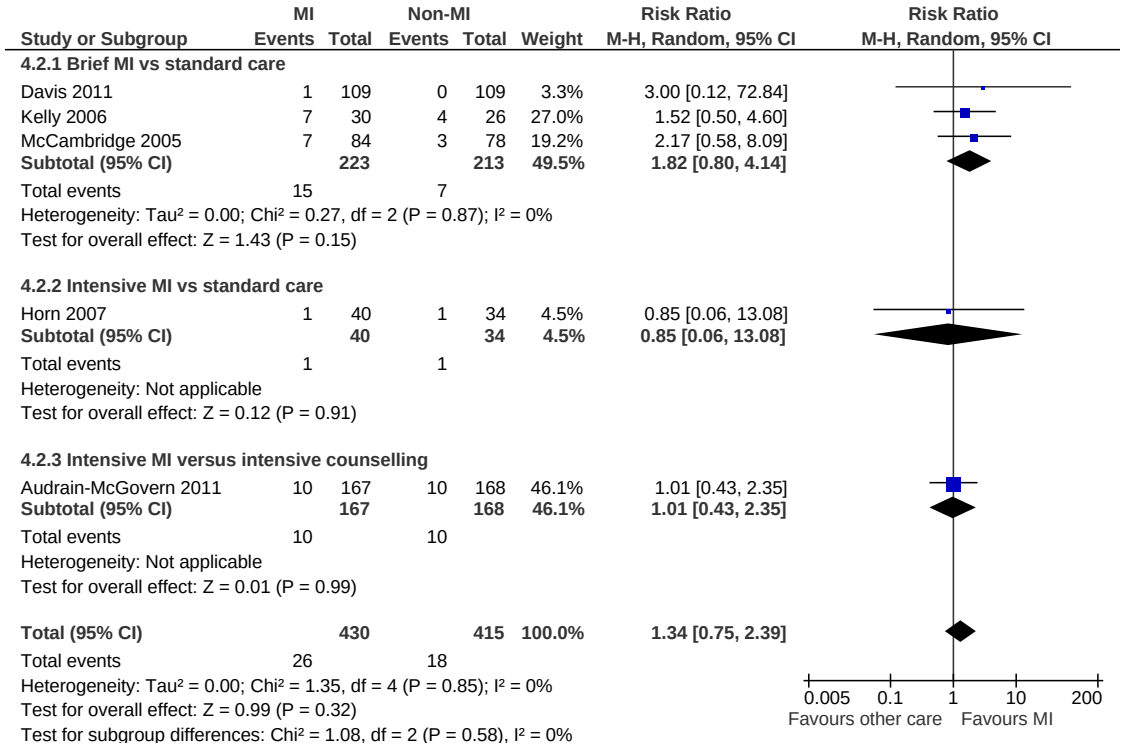
Figure 4.1 – Long term smoking cessation in motivational interviewing (MI) versus non-MI based interventions, split by composition of intervention

Plot A – Analysis of all MI studies compared to control

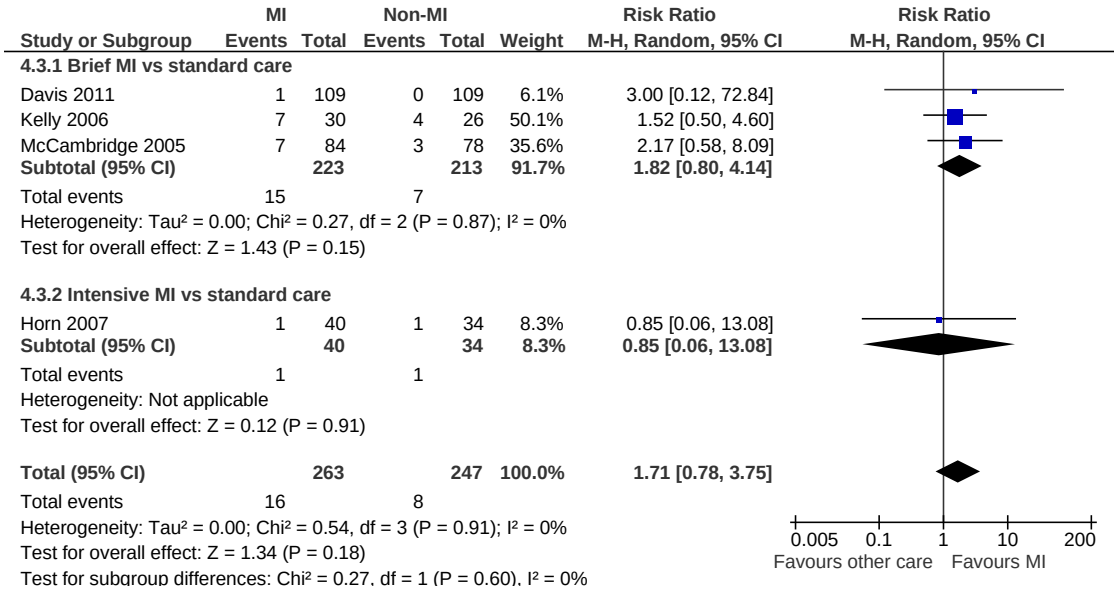


[Note: Brief = single session; Intensive = multiple sessions]

Plot B - Sensitivity analysis of MI (no NRT) compared to control



Plot C – Sensitivity analysis of MI compared to non-intensive control



Seven studies, three RCTs and four quasi-RCTs (**Chan 2011++**, **Horn 2007 +**, **McCambridge 2005 +**, **Audrain-McGovern 2011 +**, **Carpenter 2004 +**, **Davis 2011 +**, **Kelly 2006 +**,)[6] were pooled (Figure 4.1 Plot A) with a risk ratio of 2.03 (95% CI 1.2, 3.6; p=0.01; I^2=46%) and an NNT of 20 (95% CI 10, α[7]). The analysis indicated that MI interventions led to an increase in the number of abstinent participants. However, as identified in Question 1, NRT usage on its own increases the likelihood of smoking cessation even in study populations not looking to quit.

Two sensitivity analyses were conducted. The first (Figure 4.1 Plot B) excluded **Carpenter 2004 +** and **Chan 2011 ++**. These studies combined a motivational component with NRT which may have biased the estimate treatment effect upward. Additionally, the fidelity of the motivational component is unclear in both studies. This analysis indicates that motivational interviewing is not effective for abstinence: RR 1.34 (95% CI 0.75, 2.39; p=0.32).

The second sensitivity analysis (Figure 4.1 Plot C) also excluded **Audrain-McGovern 2011 +** which used an intensive control that could potentially cause a downward bias of the overall treatment effect. Excluding this study did not result in any significant difference: RR 1.71 (95% CI 0.8, 3.8; p=0.18).

Overall the analyses indicate that MI interventions are not effective in increasing abstinence in study populations not looking to quit smoking. However, adding NRT to a motivational component may improve the likelihood of a positive outcome: RR 3.09 (95% CI 1.06, 9.01; p=0.04)

Behavioural studies using other techniques

Behavioural interventions for subjects with mental health problems

One RCT **Schleicher 2010 +** and one small UBA (**Roll 1998 –**) looked at behavioural interventions for subjects with mental illness.

Schleicher 2010 + carried out an RCT examining smoking reduction and cessation among college smokers with elevated depressive symptoms. Participants took part in six group-based multi-component cognitive behaviour therapy based intervention including mood management, behavioural counselling, and motivational enhancement. Control group participants received six sessions designed to increase the consumption of fruit and vegetables. The follow-up period was one month after the end of treatment. No significant differences emerged between groups in terms of either the proportion who reduced their smoking levels by 50% or 30-day point prevalence abstinence.

Roll 1998 – explored the effect of intensive contingent positive reinforcement with cash payments for adults with schizophrenia. By the end of two weeks intensive therapy expired CO levels had dropped to an average of 15.9 ppm compared to the baseline measure of 37 ppm. However, by 8 weeks post participation the average level (36.8 ppm) had returned to baseline.

[6] Participant motivations were unclear for three studies (**Horn 2007 +**, **Kelly 2006 +**, **McCambridge 2005 +**). In the remaining studies participants did not have to be interested in quitting (**Audrain-McGovern 2011 +**) or they did not want to quit (**Carpenter 2004 +**, **Chan 2011 ++**, **Davis 2011 +**).

[7] α symbol indicates infinity

Telephone counselling among adults

In an individual randomised controlled trial, **Glasgow 2009 ++** examined the effectiveness of a smoking reduction programme relative to enhanced usual care among adult patients scheduled for outpatient surgery or a diagnostic procedure. Participants in the intervention group received a combination of telephone counselling sessions and tailored newsletters. At the 12 month follow-up there were no significant differences between intervention and control groups in terms of numbers reducing their daily cigarette consumption by ≥50% or in carbon monoxide levels.

Computer aided reduction versus reduction via manual instruction in adults

Riley 2002 + tested the feasibility of two self-help behavioural treatments for smoking reduction via a randomised non-controlled trial. The first approach was Computerised Scheduled Gradual Reduction (CSGR). In this approach a computer programme was used to schedule a reduction to 50% of baseline levels, prompting cigarettes at intervals to achieve this. After the two week reduction period, there was a two week maintenance period comprising a fixed schedule to maintain the 50% reduction. The second approach was Selective Elimination via manual instruction (SER). In this approach participants determined the daily reduction by using a table in the manual. Once the goal of 50% reduction was achieved, participants again completed a two week period at which this smoking level was maintained. Telephone follow-up interviews took place six and 12 months after the start of the study. The difference between groups in % reduction in smoking from baseline was not significant at 12 or six months. The numbers of subjects achieving ≥50% reduction in CPD compared to baseline was 18.2% for CSGR versus 18.4% for SER. More CSGR than SER participants were abstinent or had made a 24 hour quit attempts at 12 month follow-up, although the differences between groups were not statistically significant.

Effectiveness of providing safer smoking tips to adult smokers

Cunningham 2006 + carried out a quasi-randomised controlled trial testing the hypothesis that framing health information as safer smoking tips might motivate change in smoking behaviours. Adult smokers completed questionnaires. Those in the intervention condition were asked if they knew about a range of harm reduction techniques whilst those in the control group were simply asked to report their current harm reduction activities, with no information on harm reduction techniques being provided. At the three month follow-up point those who received safer smoking tips reported a small reduction in the number of cigarettes smoked compared to those in the control condition (p=0.05). Overall levels of change in cigarettes per day were small, however, and the mean number of cigarettes per day remained high in both groups at follow-up (C=21.1 +/- 12.2 CPD at baseline and 23.1 +/- 14.1 CPD at follow-up, I=23.2 +/- 8.1 CPD at baseline and 20.1 +/- 8.4 CPD at follow-up).

Workplace self-help programmes for adults

Borland 1999 + developed programs to assist smokers in coping with workplace smoking bans and, in a cluster randomised controlled trial, compared outcomes associated with two types of reduced smoking interventions to those of a control condition. The first intervention was a group programme in which weekday smokers who responded to the workplace survey were given a self-help manual and were offered four sessions in a facilitator led group programme. The second

intervention group received the manual only. There were no significant differences between groups on any outcomes at the six month follow-up.

Genetic testing and counselling

A secondary analysis of a UBA, **Carpenter 2007 –**, suggested that a smoker's knowledge that they had alpha-1-antitrypsin (AAT) deficiency, having volunteered for testing, could influence quit attempts and CPD. Odds of quit attempt were 3.3 x higher (95% CI 1.1, 10.0) among AAT deficient versus non deficient individuals. There were no group differences in abstinence at 3 months. 59% of severely AAT deficient smokers reduced their CPD by ≥50% compared with less than 20% in carriers and non-carriers.

Use of a personal CO monitor

Beard 2012, an uncontrolled before and after study in 10 participants, looked at whether use of a personal CO monitor would be effective in reducing CPD and in abstinence. Results at six weeks were not statistically significant for CPD reduction: baseline 14.1 CPD (SD 6.03); 6-week follow-up 9.5 (SD 5.50); (p=0.127).

Behavioural techniques in combination with nicotine replacement therapy (NRT)

Cognitive behavioural therapy (CBT) and NRT in adolescents

Hanson 2008 + examined via an individual randomised open-label trial whether adolescents not interested in quitting could reduce cigarette consumption. Participants were allocated to receive nicotine patch, nicotine gum, or a folic acid pill control condition. Nicotine patch (up to 21 mg) and gum doses (one 2 mg piece for each cigarette) were recommended according to participants' baseline smoking levels. Participants also met weekly for six weeks and received CBT designed to help reduce smoking. Participants were told to gradually reduce their smoking over the course of the weeks. After the reduction period participants were asked if they wanted to set a quit date within one week. If they chose to do so they received four additional weeks of their choice of medication and CBT sessions designed to help them quit. Follow-up took place at three and six months, and outcomes were measured in relation to reduction in number of cigarettes per day, expired carbon monoxide levels, urinary cotinine levels, and smoking cessation. Across all groups participants reduced the mean number of cigarettes smoked per day both at the end of treatment and at the follow-up visits. There were no differences across groups at either of the follow-up time points for any of the smoking related variables (all p>0.05).

Counselling combined with NRT among adults

Joseph 2008 + carried out a smoking RCT comprising counselling and adjunctive nicotine replacement therapy among adult smokers. Different behavioural strategies for reducing cigarette consumption were described to participants, who then chose the strategy that was most appealing to them. In addition participants substituted 4mg nicotine gum for each cigarette, switching to a patch if using more than six pieces of gum a day or if not reducing with gum alone. Control group participants had an initial visit to a counsellor to encourage the participant to seek cessation assistance but received no other counselling or pharmacotherapy. There were no significant differences between groups for reduction or abstinence at any of the three follow-up

points (6, 12 and 18 months). There were also no significant differences between groups in terms of changes in cotinine and expired carbon monoxide levels.

In a small subgroup of an RCT primarily aimed at smoking cessation (**Pisinger 2005a –**) the outcomes were explored for 39 adult smokers who did not wish to quit and who were provided with a lifestyle consultation, the opportunity to attend 6 smoking reduction group sessions and NRT of the participant's choice (patch, gum, inhaler, tablet). At six months, mean CO reduction was 10% for 39 eligible participants (no raw data presented). Authors state that data were too limited for further analyses.

Finally, a weak UBA (**Hurt 2000 –**) looked at the effect of 6-16 nicotine inhaler cartridges per day (ca 5 mg NRT per cartridge) and 12 weekly behavioural counselling sessions with a smoking reduction schedule for heavy smokers (≥ 40 CPD at baseline). Inhaler use was inversely associated with smoking rate but across the study population, CO levels (ppm) were not significantly reduced from baseline at any measured time point. Baseline: 30.4 ± 9.0, 12 weeks: 24.1 ± 8.3, 24 weeks: 26.0 ± 8.0.

Behavioural support combined with NRT among adults with mental illness

A small UBA, **Griffiths 2010 –**, concluded that 12 weekly counselling sessions using the Tobacco Addiction Recovery Programme (TARP) with free NRT (no details) could help adults with severe and persistent mental illness reduce their smoking. From an analysis of the 38 completers only (61% of the original population) immediately following the intervention, 44% reported that they had quit smoking. Among the reducers, 78% reported that they had reduced smoking by ≥ 50%. There was no biochemical validation of these results.

A very small study examined sequential 5-day interventions in regular smokers with schizophrenia or schizoaffective disorder. **Tidey 2002 –**, explored contingency management (CM; payments for reduction) plus 21 mg nicotine patch (C+NIC), CM plus placebo patch (C+P) and non contingent monetary reinforcement plus placebo patch (NC). Average CO levels during NC condition were significantly higher than during C+P and C+NIC conditions; respectively 28.0 (SEM = 2.9), 20.5 (SEM = 3.7) and 19.4 (SEM = 2.9) ppm ($p<0.05$).

NRT + hierarchical reduction versus NRT + increased inter-cigarette interval

A very small crossover quasi RCT (**Riggs 2001 –**) compared hierarchical reduction (HR; eliminating easiest to give up cigarettes first) to increased inter-cigarette interval (ICI) with, in both groups, *ad libitum* access to nicotine gum at 2mg or 4mg doses based on baseline CPD for the reduction in smoking. Each treatment lasted two weeks before cross over to the alternate treatment. There was a significant reduction in CO at the end of each treatment period (19% reduction HR vs 20% ICI ($p<0.0001$ in each case) with no difference between treatments.

Pre-operative interventions, for abstinence on day of surgery

A systematic review (**Thomsen 2010 +**), reviewed eight trials; of which two initiated multi-session face to face counselling at least six weeks before surgery, and six used a brief intervention. NRT was offered or recommended to some or all participants in seven trials. Five trials detected significantly increased smoking cessation at the time of surgery, and one approached significance; although the trials were not consistent in the definition of "at the time of surgery" and there were variations in the intensity of the support provided. Subgroup analyses showed that both intensive

and brief intervention significantly increased smoking cessation at the time of surgery; pooled RR 10.76 (95% CI 4.55, 25.46) for two trials and RR 1.41 (95% CI 1.22, 1.63) for five trials respectively.

Four trials evaluating the effect on long-term smoking cessation found a significant effect; pooled RR 1.61 (95% CI 1.12, 2.33). However, when pooling intensive and brief interventions separately, only intensive intervention retained a significant effect on long-term smoking cessation; RR 2.96 (95% CI 1.57, 5.55) for two trials.

Munday 1993 –, a controlled clinical trial, evaluated the effectiveness of a leaflet outlining reasons for stopping smoking prior to elective surgery with the recommendation to stop smoking at least 6 weeks before their operation. The intervention group was compared with a control group who had not been given any specific advice. There was no significant difference between groups for reported abstinence of more than 3 days, intervention=7.4% (95% CI: 5.1, 9.6) and control=9.3% (95% CI 6.4, 12.2), p>0.5. There was a trend for the participants in the intervention group to decrease cigarette consumption but this did not reach statistical significance, intervention= 40/136 and control =20/97 (p>0.1).

A UBA (**Walker 2009 –**) evaluated the effectiveness of advice outlining the risks of smoking associated with forefoot surgery and advice to stop smoking prior to surgery. Advice was given to patients approximately 6 months before elective forefoot osteomy or arthrodesis and reiterated at pre-operative clinic. Based on self-reported outcomes sixteen (64%) of the smokers stopped smoking prior to surgery, four (16%) reduced smoking and 2 (8%) were not influenced.

Interventions to reduce children's exposure to environmental tobacco smoke

Four studies (1 RCT, 1 quasi-RCT, one non-RCT and a CBA) reported parental smoking reduction outcomes. Interventions ranged from brief information and advice to a series of individualised counselling sessions over several months. Two studies targeted parents of asthmatic children. Outcomes of interest (reduction or abstinence in parents) were generally secondary outcomes and only limited data were available.

An RCT (**Hovell 2000 ++**) evaluated the effectiveness of seven individualised counselling sessions over three months (three face to face and four by telephone) in low-income Californian mothers. The control group received one session of brief advice about smoking and child ETS exposure. At twelve months from start of treatment, there was a non-significant decrease (p=0.06) in counselled mothers' cotinine concentrations (80.6ng/ml) compared with the control group (112.9ng/ml). There was also no significant difference in the number of mothers who had ceased smoking (counselling = 6/53; brief advice = 4/55).

A quasi-RCT (**Irvine 1999 +**) investigated the effectiveness of advice and information to parents of asthmatic children. Parents in the intervention group were visited and given information on the impact of passive smoking on asthma, followed by a discussion and advice to quit smoking or, if this was not possible to reduce child's exposure. They were also provided with a general leaflet and another specifically designed to reinforce information. Specifically designed follow-up leaflets and letters were sent by post four and eight months after the initial meeting. A control group was provided with the general leaflet only. One year post-visit, based on self-reported CPD, 59 (28%) of the intervention group and 55 (25%) of the control group smoked less; 59 (28%) and 55 (25%) respectively smoked same amount; 58 (27%) and 47 (21%) respectively smoked more (p=65).

Twelve parents reported they had ceased smoking: seven in the intervention group and five in the control group. None of these differences was significant.

A non-randomised controlled trial (**Wakefield 2002 +**) also included parents of asthmatic children. The study compared written and verbal feedback on child urinary cotinine levels supplemented by information booklets and two telephone calls, to usual care for parents visiting an Australian hospital paediatric asthma outpatient clinic. The study population comprised 58% low-income families with a household income of less than Aus$20,000 per annum and the employment rate of fathers was 80% compared to an average of 90-95% in the general population. At six months, mean change reduction in cigarettes per day from baseline was not significant for mothers [intervention group -0.17 (95%CI: -1.62, 1.27), control group -0.94 (95%CI: -1.90, 0.02) p= .40] or fathers [Intervention group -1.51 (95%CI: -3.61, 0.59); control group -1.20 (95%CI: -3.28, 0.88) p= .80]. There was no significant impact on cessation with no parents in the intervention group and three parents in the control group biochemically verified as abstinent.

A CBA (**Fossum 2004 –**) evaluated the impact of training Swedish community health nurses (CHNs) working with post-partum mothers in a counselling method "Smoke-free children". Mothers' self-reported CPD consumption was cotinine-verified for 22 of 26 mothers receiving care from CHNs trained in the counselling method and 8 of 14 mothers receiving care from CHNs not trained in the method. There were no statistically significant differences between groups for measures from baseline (B) at one month before birth and follow-up (FU) three months after birth. Mean CPD (SD) for intervention: B = 12.7 (6.6); FU = 12.9 (6.2) and control: B = 8.4 (3.9); FU = 7.1 (2.8).

Evidence Statements:

4.1 there is consistent evidence from seven studies (2 RCTs, 4 quasi-RCTs and 1 CBA) (**Horn 2007 +**, **McCambridge 2005 +**, **Kelly 2006 +**, **Audrain-McGovern 2011 +**, **Davis 2011 +**, **Gulliver 2008 +**, **Gray 2005 –**) that motivational interviewing compared with other behavioural methods or with no support and whether provided in single or multiple sessions, is not effective in helping people to reduce smoking levels. This evidence applies to healthy adolescents and adults, with no statistically significant between group differences reported across any of the studies reviewed. Weak evidence also exists for the lack of effectiveness of motivational interviewing for adolescent drug users (**McCambridge 2005 +, Gray 2005 –**) and military veterans with psychiatric problems (**Gulliver 2008 +**), with these studies again finding no significant between group differences for the outcomes reported.

4.2 There is strong evidence from a meta-analysis of two RCTs and three quasi-RCTs (**Horn 2007 +**, **McCambridge 2005 +**, **Audrain McGovern 2011 +**, **Davis 2011 +**, **Kelly 2006 +**) that motivational interviewing, compared with other behavioural methods or with no support and provided in single or multiple sessions, is not effective for smoking cessation in populations unable or unwilling to stop smoking: RR 1.34 (95% CI 0.75, 2.39; p=0.32). This is at variance with findings of a Cochrane systematic review of MI for smoking cessation (Lai 2010). The addition of NRT to a motivational component (**Chan 2011 ++**, **Carpenter 2004 +**) may improve the likelihood of abstinence: RR 3.09 (95% CI 1.06, 9.01;

p=0.04).

4.3 There is moderate evidence from a large well-conducted RCT (**Chan 2011++**) that NRT combined with a motivational component is effective, with a significant CO-validated ≥50% 7-day point prevalence reduction rate.

4.4 There is strong to moderate evidence from four studies (1 RCT, 1 quasi-RCT, one non-RCT and a CBA) designed to reduce the impact of environmental tobacco smoke on children (**Hovell 2000 ++**, **Irvine 1999 +**, **Wakefield 2002 +**, **Fossum 2004 –**) of no effect for a variety of behavioural methods versus standard care in reducing parental smoking. This evidence applies to parents of children with asthma (**Irvine 1999 +**, **Wakefield 2002 +**) as well as to parents of healthy children (**Hovell 2000 ++**, **Fossum 2004 –**).

4.5 There is moderate evidence from two RCTs (**Hanson 2008 +, Joseph 2008 +**) and one UBA (**Hurt 2000 –)** that counselling combined with nicotine replacement therapy is not effective in helping adolescents (**Hanson 2008 +**) or adults (**Hurt 2000 –, Joseph 2008 +**) to reduce their cigarette consumption or to ultimately quit. There were no differences at follow-up between intervention and control groups for any smoking related oumes.

4.6 There is moderate evidence from one RCT (**Glasgow 2009 ++**) that telephone counselling is an ineffective approach to reducing cigarette consumption. At the 12 month follow-up there were no significant differences between intervention and control groups in terms of numbers reducing their daily cigarette consumption by ≥50% or in carbon monoxide levels.

4.7 There is moderate evidence from one quasi-RCT (**Riley 2002 +**) that computer-aided and manual-aided approaches to assist with reduction had similar effect sizes. Twelve months after the start of the study there were no differences between groups in smoking reduction, and although more participants in the computer-aided group had made a quit attempt than in the manual-aided group, this difference was not statistically significant.

4.8 There is moderate evidence from one systematic review of pre-operative smoking interventions (**Thomsen 2010 +**) that counselling combined with NRT increases smoking cessation at the time of surgery for both brief and intensive interventions. However only intensive interventions were effective at 12 month follow-up. RR 2.96 (95% CI 1.57, 5.55) for two trials.

4.9 There is weak evidence from one quasi-RCT (**Carpenter 2004 +**) that both NRT aided reduction and motivational treatment are more effective than no treatment both in terms of reducing smoking and ultimately quitting. There were no significant differences between the two intervention groups on any outcomes (all self-reported). This finding is at odds with those reported in the other behavioural studies.

4.10 There is weak evidence from one RCT (**Schleicher 2010 +**) and one small UBA (**Roll 1998 –**) that cognitive behavioural therapy is not effective in helping smokers to reduce their cigarette consumption or to reduce and ultimately quit.

4.11 There is weak evidence from one quasi-RCT (**Cunningham 2006 +**) that providing safer smoking tips can have a marginal effect on reduction. At three months follow-up those

who received safer smoking tips self-reported a small reduction in the number of cigarettes smoked compared to those in the control condition (p=0.05). Overall levels of change in cigarettes per day were small, however, and the mean number of cigarettes per day remained high in both groups at follow-up.

4.12 There is weak evidence from one quasi-RCT (**Borland 1999 +**) that a self-help programme to assist smokers in coping with workplace smoking bans may not be effective. At the six month follow-up there were no differences between groups on any of the outcomes assessed.

4.13 There is weak evidence from one non randomised study and one UBA (**Munday 1993 –**, **Walker 2009 –**) that brief advice alone for pre-operative smoking cessation is not effective in achieving pre-operative abstinence.

4.14 There is very weak evidence from a UBA (**Carpenter 2007–**) that knowledge of alpha-1-antitrypsin (AAT) deficiency is effective in influencing quit attempts and cigarette consumption.

4.15 There is very weak evidence from two UBAs (**Griffiths 2010 –**, **Tidey 2002 –**) that behavioural support combined with NRT is effective in reducing smoking among adults with mental illness.

4.16 There is very weak evidence from one quasi-RCT (**Riggs 2001 –**) of no difference between NRT and hierarchical reduction versus NRT and increased inter-cigarette interval in reducing smoking.

4.17 There is very weak evidence from one small UBA (**Beard 2012)** that a personal CO monitor is not effective in reducing CPD and encouraging abstinence.

The majority of evidence is applicable to the UK as the studies are feasible in UK settings. However **Carpenter 2007 –**, **Griffiths 2010 –**, **Hanson 2008 +**, **Tidey 2002 –** are noted to have issues regarding applicability. Studies of specific populations included **Kelly 2006 +**, **Audrain-McGovern 2011 +**, **Hanson 2008 +**, **Horn 2007 +** (adolescents); **Gray 2005 –**, **McCambridge 2005 +** (adolescent drug users); **Gulliver 2008 +** (military veterans); **Griffiths 2010 –**,**Schleicher 2010** and **Tidey 2002 –** (mental health); **Munday 1993 –, Thomsen 2010 +**, **Walker 2009 –** (patients undergoing elective surgery); **Hovell 2000 ++**, **Fossum 2004 –**, **Irvine 1999 +**, **Wakefield 2002 +** (parents).

Q5. Is there an optimal period for helping people cut down or abstain from smoking, temporarily or indefinitely without the aim of quitting?

None of the studies looked specifically at this issue. The supported reduction periods in the included studies varied greatly from a single behavioural session at baseline to 18 months support and designs were heterogeneous so it is not possible to draw conclusions based on the evidence available.

Evidence Statement:

5.1 No studies were found that looked at the effect of different reduction periods in helping people to cut down or abstain from smoking.

Q6. Is it more or less effective to draw up a schedule to help people cut down or abstain from smoking, temporarily or indefinitely without the aim of quitting?

Four studies of moderate to poor quality included some form of scheduled reduction; two quasi-RCTs (**Riggs 2001 –**, **Riley 2002 +**) and two UBAs (**Hatsukami 2005 –**, **Hurt 2000 –**). None of these studies compared scheduled with non-scheduled reduction. All four studies were conducted in the USA.

Riggs 2001 –, a quasi-randomised study of 20 participants used a within-subject crossover design. A baseline week of smoking as normal was followed by one of two scheduled reduction methods over the next two weeks. Either participants increased their inter-cigarette intervals (ICI), or they eliminated cigarettes by hierarchical reduction (HR). For ICI, the mean baseline inter-cigarette interval was calculated and participants increased intervals between cigarettes by 25% in the first week and doubled these in the second week; resulting in a 50% decrease in CPD. HR required eliminating the 25% of cigarettes rated easiest to give up during first week and the easiest remaining 50% during the second week. In weeks 4-5 a baseline of normal smoking was re-established with participants using the second reduction schedule. All participants given nicotine gum to be used *ad libidum*, and encouraged to chew one piece of gum for each cigarette eliminated. Self-reported CPD reductions were significant: 10/20 (50%) of participants reduced their smoking by at least 50% by the end of ICI treatment and 6/20 (30%) by the end of HR treatment ($p<0.0001$). There was also a significant reduction in CO for both treatments: 20% for ICI and 19% for HR ($p<0.0001$) with no difference between treatments. There was no significant difference in self-reported ease of reduction: ICI: 5.8 (±2.7); HR: 5.0 (±2.4).

Riley 2002 +, a quasi-RCT, compared Computerized Schedule Gradual Reduction (CSGR) with Selective Elimination Reduction via manual instruction (SER). Both conditions received a manual providing equivalent information - advice on relapse prevention techniques and condition-specific information. In week one, The CGSR group established baseline smoking by pressing a 'smoke' button when they smoked whilst the SER group recorded CPD manually in a smoking diary. Subsequently during the two-week reduction phase CGSR participants were given a computer program which scheduled a reduction to 50% of baseline; prompting cigarettes at intervals to achieve this. The program could be adjusted (and lengthened) if subjects were having difficulties. Once 50% reduction had been achieved, a two-week fixed schedule was provided to maintain 50% reduction. The SER group used a table in the manual to determine daily reduction during the two-week reduction phase. Once the goal of 50% reduction was obtained, subjects completed a 2 week period during which this smoking level was maintained. In those who completed all time points (45/93) there was no significant difference between groups on any measure: reduction in CPD by at least 50% at either 12 months (CSGR = 18.2%, SER = 18.4%) or six months (CSGR = 18.2%; SER = 12.2%); 11.4% of CSGR vs 6.1% of SER particpants were abstinent at 12 months. A

mean reduction of approximately 10 CPD from pre-treatment to post treatment occurred in both groups and was maintained over one year.

In what was reported essentially as an uncontrolled study (**Hatsukami 2005 –**) participants were given 4 mg gum and instructed to reduce CPD from baseline levels to 75% in first 2 weeks, 50% in weeks 3-4 and 25% in weeks 5-6 (the control group received treatment after a six week delay). Those who found it difficult to achieve 50% or 75% goals offered 14mg nicotine patch to be used with gum. Participants were instructed on various methods to achieve reduction (substitution, timed interval use and situational use). At 26 weeks from baseline 41 of the 151 participants (27%) had achieved a reduction in CPD of at least 40% and 11 (7%) had achieved biochemically verified 30 day abstinence.

A pilot study in 23 heavy smokers (**Hurt 2000 –**), provided short weekly counselling sessions (10-15 minutes) plus a nicotine inhaler for twelve weeks and instructed participants to reduce from 40 or more to 10 CPD using a schedule: weeks 1-4 to 30 CPD; weeks 5- 8 to 20 CPD; weeks 9-24 to 10 CPD. Subjects asked to use ≥6 but no more than 16 5 mg nicotine inhaler cartridges per day. For the sixteen who completed the study CPD fell from 41.9 ± 3.2 at baseline to 26.7 ± 10.8 at 24 weeks. CO levels were not significantly reduced from baseline at any measured time point (baseline: 30.4 ± 9.0; 24 weeks: 26.0 ± 8.0).

Evidence Statements:

6.1 Weak evidence from 2 quasi-RCTs and 2 UBAs (**Riggs 2001 –**, **Riley 2002 +**, **Hatsukami 2005 –**, **Hurt 2000 –**) suggests the use of a schedule may assist in reducing smoking. Schedules included week on week reduction (**Hatsukami 2005 –**, **Hurt 2000 –**), increased inter-cigarette interval or selective elimination (**Riggs 2001 –**, **Riley 2002 +**).

6.2 There is limited evidence from 2 quasi-RCTs (**Riggs 2001 –**, **Riley 2002 +**) of no difference in effect between different types of schedule (increasing inter-cigarette intervals or selective elimination).

The evidence is partially applicable to people in the UK since all four studies were community based (in the USA) and are feasible in UK settings.

Q7. Do some tobacco harm-reduction approaches have a differential impact on different groups (for example, people of different ages, gender, socio-economic status or ethnicity)?

Included studies looked at several relevant populations: adolescents, ethnic groups, low income families and those with mental health problems,.

Adolescents

Five moderate and one poor quality study had adolescent populations; four looking at healthy populations (**Audrain McGovern 2011 +**, **Hanson 2008 +**, **Horn 2007 +**, **Kelly 2006 +)** and two at drug/alcohol users (**Gray 2005 –**, **McCambridge 2005 +**). One of these studies (**Hanson 2008 +**)

used a combination of behavioural therapy and NRT; the other five used motivational interviewing techniques.

As noted in Question 4 above, no statistically significant between group differences were reported in any of the studies reviewed.

Two studies were carried out in the UK (**Gray 2005 –**, **McCambridge 2005 +**) and one in Australia (**Kelly 2006 +**). These studies are all applicable to a UK setting, although the UK studies are in a specific population of drug and alcohol users. The remaining three studies (**Audrain McGovern 2011 +**, **Hanson 2008 +**, **Horn 2007 +)** were conducted in the USA and their applicability is less certain.

Ethnicity

Two papers looked at ethnic populations. **Audrain McGovern 2011 +** was set in the USA and **Chan 2011 ++** in China. In a mixed race population of American adolescents (40% white, 45% black, 15% other/mixed race), a quasi RCT (**Audrain McGovern 2011 +**) found that regardless of allocated group, white adolescents were approximately 80% less likely to attempt to cut back (OR= 0.21, 95% CI 0.08, 0.53) and more than 80% less likely to attempt to quit than black adolescents (OR=0.17 95% CI 0.06, 0.46).

Chan 2011 ++, an RCT, examined the effectiveness of motivational interviewing based smoking reduction counselling plus free nicotine replacement therapy for smokers in Hong Kong who had previously failed to quit. At six months, more participants in the intervention groups had achieved biochemically validated reductions of at least 50% than in the control group (p=0.001). Differences between groups in self-reported quit rates were significant (p=0.01) but biochemically verified quit rates were not (p=0.07).

The applicability of the two studies to a UK population is unclear.

Low income families

A quasi-RCT of motivational interviewing in Australian adolescents (**Kelly 2006 +**) noted that study participants were from lower SES families (skilled workers). There were no significant between group differences in any measures at six months.

Two studies in low-income families aimed to reduce the impact of environmental tobacco smoke on children. An RCT conducted in the USA (**Hovell 2000 ++**), and a non-randomised clinical trial conducted in Australia (**Wakefield 2002 +**) both found no evidence that behavioural interventions were effective in reducing parental smoking.

Mental health

Five small scale studies investigated interventions for mental health populations, one RCT (**Schleicher 2010 +**) in depressed college students, one quasi-RCT in "psychiatrically complex" military veterans (**Gulliver 2008 +**) and three uncontrolled studies in populations with severe mental illness (**Griffiths 2010 –**) or schizophrenia or schizoaffective disorder (**Roll 1998 –**, **Tidey 2002 –**). One further study (**Joseph 2008 +**) noted that a high prevalence of mental health disorders among participants (greater than 50% in both arms) limited study generalisability, but did not provide any data on this population.

Overall study quality in this population was limited with small populations and limited follow-up. With the exception of **Gulliver 2008 +**, study populations were between 11 and 58 participants and follow-up period varied between end of treatment and eight weeks post-intervention.

An RCT (**Schleicher 2010 +)** found no significant difference between groups in a small CBT study in a population of depressed college students.

In a quasi-RCT of a brief motivational interview for 208 "psychiatrically complex" military veterans (**Gulliver 2008 +**), no difference was found at six months post-treatment between groups on either point prevalence abstinence (p>0.30) or cigarettes per day (p>0.65).

Griffiths 2010 –, concluded that 12 weekly counselling sessions using the Tobacco Addiction Recovery Programme (TARP) with free NRT (no details on type or dosage) could help adults with severe and persistent mental illness reduce their smoking. From an analysis of 34 completers immediately following the intervention, 44% reported that they had quit smoking. Among the reducers, 78% reported that they had reduced smoking by ≥ 50%.

Two very small studies (**Tidey 2002 –**, **Roll 1998 –**) investigated the effect of contingent payment with and without NRT patches in schizophrenic or schizoaffective disordered participants. Both found a statistically significant difference during treatment but the effect declined rapidly post-treatment.

All five studies were conducted in the USA but there is no reason to assume that they are not applicable to a UK mental health population.

Evidence Statements:

7.1 There is moderate evidence from five studies (2 RCTs, 2 quasi-RCTs, 1 CBA) (**Horn 2007 +**, **McCambridge 2005 +**, **Audrain McGovern 2011 +**, **Kelly 2006 +**, **Gray 2005 –**) of no effect for motivational interviewing interventions in reducing smoking in adolescents.

7.2 There is weak evidence from one quasi-RCT (**Hanson 2008 +**) that cognitive behavioural therapy (CBT) plus NRT is not effective in reducing smoking among adolescents.

7.3 Weak evidence from one quasi-RCT in the USA (**Audrain McGovern 2011 +**) comparing a multi-session intensive MI intervention to multiple sessions of brief structured advice, suggests that white adolescents are significantly less likely than black adolescents to attempt to reduce or quit smoking.

7.4 Moderate evidence from one high quality RCT (**Chan 2011 ++**) indicates that MI plus NRT was effective in reducing smoking in adult Chinese smokers who had previously failed to quit.

7.5 There is weak evidence from one quasi-RCT (**Kelly 2006 +**) of no effect of MI on Australian adolescents from lower SES families.

7.6 Moderate evidence from 1 RCT and 1 non-randomised study (**Hovell 2000 ++**, **Wakefield 2002 +**) found no evidence of effect for behavioural interventions in reducing parental smoking in low income families.

7.7 There no evidence of sustained effect of behavioural interventions from 4 studies (1 RCT

and 3 UBAs) (**Schleicher 2010 +**, **Tidey 2002 –**, **Roll 1998 –**, **Griffiths 2010 –**) in mental health populations.

7.8 There is very weak evidence from two small UBAs (**Tidey 2002 –**, **Roll 1998 –**) of a 'during treatment effect' on carbon monoxide-verified reduction in mental health populations for contingency management with or without NRT.

The evidence is partially applicable to people in the UK. **McCambridge 2005 +** and **Gray 2005 –** were both based in the UK, and **Kelly 2006 +** and **Wakefield 2002 +** were based in Australia where there is a similar smoking treatment service to the UK. Of the remaining studies, **Chan 2011 ++**, **Griffiths 2010 –** and **Hovell 2000 ++** were based in the community and interventions may be feasible for the UK.

Q8. Are there any unintended consequences from adopting a tobacco harm-reduction approach; for example, does it deter people from trying to cut down or abstain from smoking, temporarily or indefinitely?

Motivation/readiness to quit

Two studies (**Carpenter 2004 +**, **Wennike 2003 +**) suggest that NRT does not reduce subjects' motivations to quit smoking. In a quasi-RCT looking at NRT aided reduction (R-NRT) versus motivational treatment (MI) or no treatment (NT). **Carpenter 2004 +** found that readiness to quit increased across all groups. By week 24, R-NRT and MI subjects had similar intentions to quit and these were significantly greater than NT participants ($p<0.05$; data in graph form only). In another quasi-RCT comparing nicotine gum (2 or 4 mg) to placebo gum, **Wennike 2003 +** found similar motivations to quit in both groups at 24 months: intervention: 4.7 (SD 2.8); placebo: 5.2 (3.2).

It is likely that further evidence regarding smokers' motivations in relation to smoking reduction will be provided within the barriers and facilitators review (Review 4).

Differences in psychological characteristics

Etter 2002 (linked to Etter 2007 +) found no difference in psychological characteristics between nicotine and placebo groups. Following the intervention, at 5 years (**Etter 2007 +**) the same proportion of participants was using NRT in all groups (nicotine = 12%, placebo = 9%; no treatment – 11%).

Adverse events from long term NRT use

Evidence from nine studies looking at NRT use for periods between 6 months and five years suggests that NRT is generally well tolerated with few serious adverse events. These findings are in keeping with those from Review 1 which concluded that "evidence from nine randomised controlled trials strongly suggests that adverse events are common when NRT is used for smoking harm reduction, but these tend to be mild or moderate and are rarely severe."

Over a 13 month study period **Batra 2005 +** found no serious adverse effects related to NRT (4mg gum) and no discontinuations reportedly resulting from side effects. During 24 months therapy with a 10mg nicotine/1mg menthol inhaler **Bollinger 2000 ++** found throat irritation (14 vs 4; 95%

CI 1.13, 15.6) and coughing (13 vs 4; 95% CI 1.1, 10.6) were significantly more frequently reported in the active vs placebo groups. **Carpenter 2004 +** found that 21% of participants who used NRT (4 mg gum or 7, 14, 21 mg patch) for reduction up to 24 weeks reported an adverse event compared to 9% of those who used NRT only for a quit attempt (week 6-24) ($p<0.01$). In an RCT of NRT aided reduction (15 mg patch, 4 mg gum, 10 mg inhaler or combination).

Etter 2007 + followed up a population using NRT for smoking reduction at six months, two years and five years. Data on adverse events associated with NRT use were only reported at six months. Two deaths were reported in the NRT group which the authors state the deaths were unlikely to be due to treatment. No significant difference was identified between groups ($p=0.25$).

Jiménez-Ruiz 2002 – noted that 5 patients (29%) continued to use 10-12 pieces of 4 mg nicotine gum per day up to 18 months though no adverse event data are reported. **Joseph 2008 +** in a study of patients with heart disease noted that serious events were approximately equally distributed in smoking reduction (4mg NRT gum) other than need for urgent cardiac care at 6 months which was higher in the usual care group (n=0 SR vs n=5 UC, $p=0.02$). Over a 12 month period **Kralikova 2009 +** reported no unexpected events over 12 months use of nicotine gum (4 mg) or inhaler (10 mg). **Rennard 2006 +** reported similar rates of adverse events and serious adverse events in both nicotine inhaler (10 mg) and placebo inhaler groups within a 12 month intervention. Adverse events reported by 159 subjects (I) and 147 subjects (C). Serious adverse events: 15 events reported by 9 subjects (I) and 13 events reported by 11 subjects (C). **Wennike 2003 +** found similar adverse events over a 12 month intervention in both nicotine gum (2 or 4 mg) and placebo gum groups (166 versus 147).

Adverse events from e-cigarette use

From a single UBA study of e-cigarette use over a 24 week period (**Polosa 2011 –**) the most frequent adverse events reported were mouth irritation (20.6%), throat irritation (32.4%) and dry cough (32.4%). 67.5% of participants completed the study. Findings from review 1 suggested that "there is no evidence on the long term safety of e-cigarettes, whether used alone or with concurrent cigarette smoking. There isn't a large volume of reliable evidence on the short term safety of e-cigarettes."

Evidence Statements:

8.1 There is strong evidence from eight studies reporting usage of NRT for periods between six months and five years (**Batra 2005 +**, **Bollinger 2000 ++**, **Etter 2007 +**, **Jiménez-Ruiz 2002 –**, **Joseph 2008 +**, **Kralikova 2009 +**, **Rennard 2006 +**, **Wennike 2003 +**) to suggest that NRT is generally well tolerated long term with severe side effects being relatively rare.

8.2 There is moderate evidence from two quasi-RCTS (**Carpenter 2004 +**, **Wennike 2003 +**) that harm reduction interventions do not deter smokers from wishing to quit.

8.3 There is weak evidence from a single UBA (**Polosa 2011 –**) that frequent adverse events are reported by e-cigarette users. This finding supports the conclusions from Review One (Toxicity) that more evidence is required concerning the safety of e-cigarettes.

Adverse event studies are likely to be applicable to the UK.

Comparison with two previous systematic reviews

A Cochrane systematic review found within the literature search looked specifically at interventions to reduce harm from continued tobacco use (**Stead 2010**). A Health Technology Assessment (**Wang 2008** also published as **Moore 2009**) initially identified for Review 2 looked at long term smoking reduction and abstinence in populations not willing or able to quit. Both reviews were unpicked for relevant primary studies as well as being briefly summarised here.

Stead 2010 conducted a systematic review to assess the effect of interventions intended to reduce the harm from smoking on: biomarkers of damage caused by tobacco, biomarkers of tobacco exposure, number of cigarettes smoked, quitting, and long-term health status. Several interventions that are outside the scope of this review (bupropion, and tobacco containing products) were included; however, types of intervention were reported separately throughout.

The review included 12 studies with NRT interventions, ten of which had been identified for inclusion in this review (**Batra 2005 +**, **Bolliger 2000 ++**, **Carpenter 2004 +** [also including a pilot **Carpenter 2003**], **Etter 2007 +** [**included as Etter 2004**], **Hanson 2008 +**, **Joseph 2008 +**, **Kralikova 2009 +**, **Rennard 2006 +**, **Wennike 2003**). The two remaining studies were unpublished data from the manufacturer (Australia NNCG-017) and Haustein 2003, a conference abstract. Three behavioural intervention studies all identified for inclusion in this review (**Glasgow 2009 +**, **Pisinger 2005 −**, **Riley 2002 +**) were also included.

The authors found that in a pooled analysis of nine studies NRT significantly increased the odds of reducing CPD by 50% or more compared to placebo at end of follow-up, RR 1.72; (95% CI 1.41, 2.10). Also in a pooled analysis of nine studies, NRT was found to increase the odds of quitting, RR 1.73 (95% CIU 1.36, 2.19) at end of follow-up. However there was no clear evidence of effect from behavioural interventions.

A second systematic review of seven studies (published both as **Wang 2008** and **Moore 2009**) looked at the impact of NRT on abstinence in populations not looking to quit. As with **Stead 2010**, all studies other than the two which were unpublished data (Australia NNCG-017/Wood Baker and Haustein) were included.

Pooling results using a random effects model the review found statistically significant results for NRT versus placebo in both reduction and abstinence measures: sustained reduction to end of follow up RR, 3.84 (95% CI 2.32 to 6.35); point prevalence reduction at end of follow up, RR 1.32 (95% CI 1.14 to 1.54); sustained abstinence of at least six months, RR 1.99, (95% CI 1.01, 3.91). Additionally, the 12-month sustained abstinence rate was found to be approximately 5.3% for NRT versus 2.6% for the placebo group.

Moore 2009 makes the point that most of the effectiveness evidence came from studies with considerable participant-investigator contact and suggests that to obtain similar rates of abstinence would require an enhanced level of service delivery in a real-world setting.

However, it should be noted that any behavioural support, advice or contact was the same in both NRT and placebo groups and evidence from this review suggests a lack of effect for behavioural interventions.

Overall the results of this review concur with those of **Stead 2010** and **Wang 2008**/**Moore 2009** in suggesting that, in populations not able or willing to quit, NRT may be effective for long term smoking reduction and abstinence. In contrast, there is little evidence to support the use of behavioural interventions alone.

5. DISCUSSION

This review contains a large body of evidence of relevance to long term harm reduction without the prior aim of quitting.

Five studies were conducted in the UK, and six in countries with similar smoking treatment programmes. In general, applicability to the UK was good with many other studies based in the community.

The quality of the included studies was variable with a wide variation in time periods and outcomes. There was a good body of consistent evidence for some topics and outcomes for NRT studies (measures of CPD, ≥50% reduction and continuous or point-prevalent abstinence) were generally consistent. By contrast, reduction outcomes for behavioural studies varied considerably and it was not possible to conduct meta-analyses other than for abstinence. Reduction outcomes were generally self-reported so there is little information on reduction in exposure. However, where studies identify abstinence at follow-up and report this outcome, it is generally biochemically verified.

Participant motivations were difficult to ascertain in some studies. Thus, the scope of the review included studies that were designed as long term harm reduction studies, as well as those where the included participants did not wish to quit smoking.

All six randomised/quasi-randomised studies investigating the use NRT in the general population were either industry sponsored (**Bolliger 2000 ++**, **Batra 2005 +**, **Kralikova 2009 +**, **Rennard 2006 +**, **Wennike 2003 +**), or the authors had financial ties to industry (**Etter 2007 +**). As noted in Review 2, authors declared sources of funding and any potential conflicts of interest. However, a 2003 meta-analysis of RCTs included in a Cochrane review of smoking cessation interventions concluded that "Compared with independent trials, industry-supported trials were more likely to produce statistically significant results and larger odds ratios. These differences persisted after adjustment for basic trial characteristics." (Etter 2003) The authors suggested that this difference may be the result of publication bias.

By contrast, potential conflicts of interest were only identified in one behavioural study (**Riley 2002 +**) in which the computerised scheduled reduction intervention had been developed and was being marketed by a company employing the authors.

Nine of the behavioural studies (three RCTs, five quasi-RCTs and one CBA) included a 'motivational interview' component as part of the intervention (**Chan 2011++**, **Horn 2007 +**, **McCambridge 2005 +**, **Audrain-McGovern 2011 +**, **Carpenter 2004 +**, **Davis 2011 +**, **Gulliver 2008 +**, **Kelly 2006 +**, **Gray 2005 –**); two studies combining that component with NRT (**Chan 2011 ++**, **Carpenter 2004 +**). The component ranged from a single brief interview to multiple intensive sessions. There appeared to be little difference in outcome between brief and intensive interventions. Fidelity to the principles and practice of motivational interviewing (Miller 2002) was also considered. Six of the seven studies looking at motivational interviewing alone identified key elements of principles and practice. Fidelity was unclear in both studies combining a motivational component with NRT.

Overall, the evidence within the review suggests that:

- Across all studies of NRT versus placebo where reduction is an intended outcome, meta-analyses indicate significant benefits from NRT.
- NRT may also be effective for abstinence in the longer term in populations not looking to quit.
- NRT supplementation may help reduce *ad libitum* smoking (where there is no instruction to reduce) but the evidence base is weak.
- No evidence comparing combinations of NRT was found but it appears that there are no clear differences in effectiveness between different types of medication and some modest evidence that offering smokers a choice of medication may enhance efficacy.
- Nicotine patch is effective in reducing post-operative smoking consumption in the short term but this is not maintained long term.
- Evidence for the value of e-cigarettes to date is available only from a single UBA study and, although suggestive of benefit, no conclusions can be drawn as yet. We note that the MHRA is currently considering whether to regulate e-cigarettes and other nicotine-containing products.
- Two studies suggest NRT combined with a brief motivational component may be effective for abstinence in populations not looking to quit. However, the impact of the motivational component is unclear.
- There is consistent evidence that motivational interviewing alone, either in single or multiple sessions, is not effective as a long-term harm reduction strategy.
- MI does not appear to be effective for abstinence in populations unable or unwilling to quit. This is at variance with the evidence from a Cochrane systematic review looking at the effect on abrupt cessation (Lai 2010); which found some evidence that MI may assist abstinence. The reason for this variance is not clear, although it may reflect the impact of the two statistically significant studies - Hollis 2007 and Soria 2006. In the first, which contributed considerable weight to pooled analyses, study participants had to be motivated to quit. In the second study bupropion was provided to a small proportion of the MI group, which may have skewed the results.
- The evidence available for other types of behavioural intervention is weaker but it is also suggestive of no benefit.
- Both brief and intensive pre-operative smoking interventions, combining counselling with NRT, increase smoking cessation at the time of surgery. However only intensive interventions were effective long term.
- There is no evidence of effect on parental smoking levels from interventions to reduce environmental tobacco smoke. Results do not appear to vary between parents of asthmatics and those with generally healthy children.
- No evidence was found to suggest an optimal reduction period.
- Limited weak evidence suggests that scheduled smoking reduction may be more effective than non-scheduled smoking reduction; although there do not appear to be differences in effect between types of scheduled reduction.
- There is very little evidence to distinguish the effectiveness of interventions across socio-economic groups.

- The small amount of evidence available suggests that harm reduction interventions do not deter smokers from wishing to quit. More evidence of smokers' views is likely to be provided within the barriers and facilitators review (Review 4).
- Longer-term NRT use appears to be well tolerated over periods between six months and five years with severe side effects being relatively rare.

Further research is needed in a number of areas: the differential effects for socio-economic and ethnic groups, the impact of different NRT combinations and the efficacy of e-cigarettes, the effect of intensity of the intervention.

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7. ACKNOWLEDGEMENTS

The authors acknowledge the very helpful advice provided, at both protocol and draft review stages, by the Expert Advisory Group (Appendix C).

We also acknowledge with thanks the following experts in the field who reviewed and commented on the list of included studies:

Professor Paul Aveyard, Primary Care Clinical Sciences, University of Birmingham

Dr Alex Bobak, Wandsworth Medical Centre, London

Gillian Bruce, Smoking Cessation Nurse Specialist, Forth Valley Royal Hospital

Dr Karl Fagerström, Smokers Information Centre, Helsberg, Sweden[8]

Dr Andy McEwan, Senior Research Associate and Assistant Director of Tobacco Studies, University College London

Dr Mike Ward, Consultant Physician, Sherwood Forest Hospitals

Professor Robert West, Department of Epidemiology and Public Health, University College London

In addition, thanks are owed to the following study authors who responded to our emails and where appropriate, suggested additional studies for consideration:

Professor Chris Bolliger, Division of Pulmonology, Stellenbosch University, South Africa

Professor Ron Borland, Nigel Gray Distinguished Fellow in Cancer Prevention, Cancer Council Victoria, Australia.

Professor M J Carpenter, Department of Psychiatry, Hollings Cancer Center, Medical University of South Carolina

Dr John A Cunningham, Centre for Addiction and Mental Health, Toronto

Dr J-F Etter, Institute of Social and Preventive Medicine, Faculty of Medicine, University of Geneva

Dr Bjorn Fossum, Sophiahemmet University College, Stockholm

Dr Dorothy Hatsukami, Associate Director of Cancer Prevention and Control, Masonic Cancer Center, University of Minnesota

Dr Richard Hurt, Director, Mayo Clinic Nicotine Dependence Center, Minnesota

Dr Carlos Jimenez-Ruiz, Public Health Institute, Madrid

Dr Adrian Kelly, Centre for Youth Substance Abuse Research, University of Queensland, Brisbane

Dr Charlotta Pisinger, Research Centre for Prevention and Health, Capital Region of Denmark

Professor Riccardo Polosa, Centre for Tobacco Research, University of Catania, Italy

Dr Thordis Thomsen, Department of Anaesthesiology, Herlev University Hospital

Professor Melanie Wakefield, Director of the Centre for Behavioural Research in Cancer, Cancer Council Victoria, Australia

[8] Dr Fagerström was also the lead author on one of the papers included in this review.