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

Short title: Tobacco: harm reduction

Review 2: The effectiveness of tobacco harm reduction approaches with the intention of quitting (i.e. 'cutting down to quit' or 'reduction to stop smoking'), with and without assistance

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November 2021: NICE guidelines PH45 (June 2013) PH48 (November 2013) have been updated and replaced by NG209.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.

List of Contents

EXECUTIVE SUMMARY

1 INTRODUCTION

1.1 Aims of the review

To review the effectiveness of harm reduction approaches with the intention of quitting (ie 'cutting down to quit' or 'reduction to stop smoking'), with and without assistance.

1.2 Research questions

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

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 with respect to smoking 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'. Building on the review of safety, risk and pharmacokinetics of tobacco harm reduction (THR) technologies (Jones et al, 2011), this review is the first of two effectiveness reviews to support the guidance development. A second effectiveness review on long term smoking reduction without the intention of quitting and a companion review of barriers and facilitators to harm-reduction approaches will follow. 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. 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 and quality assessment were conducted independently in duplicate, with inter-rater reliability testing 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

A total of 14 papers (12 studies) have been included in the review. See Table 1 (pp. 22-23) for a brief summary of the studies. Full details are provided in the Evidence Tables (Appendix A).

The quality was generally of a moderate standard in terms of study design and clarity of reporting. Five studies are randomised controlled trials (**Etter 2009 +**, **Etter 2011 +**, **Gunther 1992–**, **Hughes 2010 ++**, **Shiffman 2009 ++**), four are quasi-randomised (**Cinciripini 1994 +**, **Cinciripini 1995 +**, **Martin 1997 +, Marks 2002 +**[2]). The remaining three papers are a partial randomised trial (**O'Leary Tevyaw 2007 –**), uncontrolled before and after studies (**Jiménez-Ruiz 2009 –, Riley 2002 –**) and a secondary analysis of Hughes 2010 (**Hughes 2011 –**). Only one UK study was identified (**Marks 2002 +**). Three were conducted in Europe (**Etter 2009 +**, **Jiménez-Ruiz 2009–** and **Gunther 1992–**), six in the USA (**Cinciripini 1994 +**, **Cinciripini 1995 +**, **Hughes 2010 ++**, **Martin 1997 +**, **Riley 2002 –, Shiffman 2009 ++**) and one was a web-based intervention that was open to users of a smoking cessation website regardless of location (**Etter 2011 +**).

Nine studies took place in community settings, two of which were in community based smokers' clinics (**Jiménez-Ruiz 2009 –**, **Marks 2002 +**). **Etter 2011 +** was a web-based intervention; **O'Leary Tevyaw 2007–** and **Riley 2002 –** were conducted in high schools.

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

[2] There are two papers reporting one study: Marks 2002 (reporting 12 month data) and Sykes 2001 (reporting six month data

4. EVIDENCE STATEMENTS

Q1. How effective are pharmacotherapies in helping people cut down smoking before quitting?

Three RCTs examined the efficacy of NRT gum (**Etter 2009 +**, **Shiffman 2009 ++**) and lozenges (**Hughes 2010 ++**). In addition there was one quasi-randomised controlled trial (**Martin 1997 +**) and one uncontrolled before and after study (**Jiménez-Ruiz 2009 –**) with a combined intervention of behavioural therapy plus gum.

Both **Shiffman 2009 ++** and **Hughes 2010 ++** were deemed to be studies at low risk of bias.

Evidence Statements:

1.1 There is moderate evidence from two randomised controlled trials (RCTs) of no significant difference in long-term abstinence rates between gradual and abrupt cessation when using NRT (gum or lozenges) (**Etter 2009 +**, **Hughes 2010 ++**) although the trend favours abrupt cessation. The CO and cotinine validated four week quit rate at 12 months was 16.5% for gradual compared to 24.0% for abrupt cessation, p=0.14 (**Etter 2009 +**), The OR for CO validated abstinence at 6 months (gradual/abrupt) was 0.6 (95% CI 0.3, 1.2) (**Hughes 2010 ++**).

1.2 There is moderate evidence from a large RCT (**Shiffman 2009 ++**) of a benefit from NRT versus placebo at 6 months; this was more marked in the 4 mg gum versus 2 mg dose rates with ORs of 6.0 (95%CI 2.9, 12.3) and 1.8 (95% CI 1.1, 2.9) respectively. Overall OR 2.86 (95% CI 1.93, 4.24).

Evidence from two much smaller studies, a quasi-RCT (**Martin 1997 +**) and an uncontrolled before and after study **(Jiménez Ruiz 2009 –**), is inconsistent. In the quasi–RCT mean quit rates for standard treatment versus behavioural counselling with NRT respectively at 6months were 21% v. 27% (NS) and at 12 months 26% v 27% (NS) (**Martin 1997 +)**. In the UCBA study (**Jiménez Ruiz 2009 –)** 39% reported abstinence at 6 months and 68% reported ≥50% reduction in cigarette consumption at the end of 8 weeks using a combination of gum and behavioural therapy. The difference in abstinence between participants who wanted to reduce to quit versus those who were refractory smokers was not significant (48% vs 32%, p=0.8).

1.3 There is inconsistent evidence from one RCT (**Etter 2009 +**) and one UBA (**Jiménez Ruiz 2009 –)** of NRT use in the longer term. **Etter 2009 +** found that, after 12 months, 9.2% participants were still using NRT daily (5 pieces per day on average). Values were similar in both abrupt and gradual cessation groups. **Jiménez Ruiz 2009 –** found that all smokers who had successfully quit at 16 weeks continued to use NRT into the abstinence phase but no subject used NRT for more than 4 months post quit date.

1.4 There is weak evidence from a single RCT that nicotine gum may be an effective aid to reducing cigarettes prior to cessation as daily cigarette consumption in the week before the quit date was 12.4 v 21.3 cigarettes /day, p<0.001 (**Etter 2009 +**).

The evidence from the RCTs (**Etter 2009 +**, **Hughes 2010 ++**, **Shiffman 2009 ++**) is partially applicable to people in the UK because, although there were no UK-based trials, the studies were community-based and are feasible within a UK setting. **Martin 1997 +** relates specifically to recovering alcoholics. **Jiménez Ruiz 2009 –** was an intensive intervention which is unlikely to be feasible within the UK.

Q2. How effective are different combinations of NRT products in helping people cut down smoking before quitting?

Evidence Statement:

2.1 No studies were found that looked at combinations of NRT products for helping people to cut down before quitting.

Q3. How effective are 'nicotine-containing products' in helping people cut down smoking before 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.

Evidence Statement:

3.1 No studies were found that looked at the effectiveness of nicotine delivery systems (electronic cigarettes) for helping people to cut down before quitting.

Q4. How effective are behavioural support, counselling, advice or self-help (with or without pharmacotherapy) in helping people cut down smoking before quitting?

Nine studies incorporated behavioural support, including three randomised controlled trials (**Etter 2011 +**, **Gunther 1992 –**, **Hughes 2010 ++**), four quasi-randomised controlled trials (**Cinciripini 1994 +**, **Cinciripini 1995 +**, **Martin 1997 +**, **Marks 2002 +**), one trial with partial randomisation (**O'Leary Tevyaw 2007 –**) and two uncontrolled before and after studies (**Jiménez-Ruiz 2009 –, Riley 2002 –**).

Studies used behavioural intervention components in a variety of ways:

- Cognitive behavioural support (**Cinciripini 1994 +, Marks 2002 +**)
- Advice giving (**Etter 2011 +**)
- Investigating the feasibility of contingency management[3] (**O'Leary Tevyaw 2007 –**)
- Investigating the feasibility of computerised scheduled reduction (**Riley 2002 –).**

In the other studies, all participants received a behavioural component (**Cinciripini 1995 +, Gunther 1992 –, Hughes 2010 ++, Jiménez-Ruiz 2009 –, Martin 1997 +**) and it is therefore not possible to infer the effectiveness of that component.

Evidence Statements:

4.1 There is moderate evidence for the effectiveness of cognitive behavioural therapy versus standard therapy from two quasi-RCTs (**Cinciripini 1994 +**, **Marks 2002 +**) both in reducing the number of cigarettes per day prior to quitting, and in quitting itself. At 12 months 41% of the CBT group and 6% of the control group were

[3] O'Leary Tevyaw describes contingency management as promoting "decreases in substance use by providing tangible reinforcers contingent on abstinence or reduction of substance use to a target level". The 'tangible reinforcers' in this study are gift certificates for use in a local shopping centre.

abstinent, p<0.01. Figures for 6 months were 53% and 6%, p<0.01 (**Cinciripini 1994 +**). At 12 months 19.8% (95% CI 13.0, 28.3) of the contactable CBT group were abstinent compared to 5.8 % (95% CI 2.1, 12.1, p<0.0001) (**Marks 2002 +**). At the same time point 11.5% (95% CI 6.4, 18.5, p<0.0001) had reduced their CPD by ≥ 25% compared to 0% in the control group.

4.2 There is moderate evidence from two RCTs (**Gunther 1992 –, Hughes 2010 ++)** of a trend towards higher abstinent rates for abrupt cessation compared to gradual reduction when counselling is offered to both groups (with nicotine as well in **Hughes 2010 ++**) but the findings are not significant. The OR for CO verified abstinence at 6 months for gradual versus abrupt cessation was 0.6 (95% CI 0.3, 1.2) **(Hughes 2010 ++).** At 12 months follow-up there was a non-significant difference in self reported abstinence between sudden and gradual withdrawal groups: 51.85% versus 38.71% (**Gunther 1992 –**).

4.3 There is weak evidence from one quasi-randomised trial (**Cinciripini 1995 +**) suggesting that cognitive behavioural therapy combined with advice to schedule and lengthen the time between cigarettes may enhance outcomes. Cotinine verified abstinence rates at 12 months were 44% (scheduled reduced), 18% (non-scheduled reduced), 32% (scheduled non-reduced) and 13% (non-scheduled non-reduced); p<0.05.

4.4 There is weak evidence from one RCT (**Etter 2011 +**) to suggest that there may be no difference in the effect of advice giving (via web and email) for gradual versus abrupt cessation but the follow up period was very short and outcomes were self reported. At four weeks 8.8% of the gradual group and 8.7% of the abrupt group reported no puff taken in the past 24 hours (p=0.97).

4.5 There is weak evidence from one RCT (**Martin 1997 +**) in a population of recovering alcoholics that there may be no difference between standard treatment with counselling, counselling plus exercise and counselling plus NRT for gradual reduction. CO-verified quit rates at 12 months for the three groups were26%, 27% and 27% respectively.

4.6 There is very weak evidence from a feasibility study (**O'Leary Tevyaw 2007 –**) suggesting that the use of contingency management (a reward for response) may be effective when used to support reduction to quit since participants had more abstinent readings in the contingency management phase than the reinforcement phase (50% vs 37%).

4.7 There is very weak evidence from two small before & after studies (**Riley 2002 –**) that computerised scheduled reduction, with or without behavioural support, is acceptable to a teenage population.

This evidence is partially applicable to people in the UK. The use of rewards for response (**O'Leary Tevyaw 2007 –**) is unlikely in this setting. However **Marks 2002 +** was based in the UK, **Etter 2011 +** was a web-based intervention and all the other studies were community- or high school-based and feasible within a UK setting.

Q5. Is there an optimal period for helping people cut down smoking with the aim of quitting

Among the included studies, the reduction period varied from 7-10 days **(Marks 2002 +)** through to 16 weeks **(Jiménez-Ruiz 2009 –)**. Five studies employed reduction periods of between two

and five weeks **(Cinciripini 1994 +, Cinciripini 1995 +, Etter 2009 +, Etter 2011 +, Hughes 2010 ++)**. **Riley 2002 –** utilised a seven-week and **Martin 1997 +** and **Shiffman 2009 ++** an eight-week schedule.

Martin 1997 + found no difference between two different reduction periods, although the interventions also differed. CO-verified quit rates at 12 months for the three groups (standard treatment with counselling over 4 weeks, counselling plus exercise and counselling plus NRT over 8 weeks) were 26%, 27% and 27% respectively.

None of the other included studies compared the effectiveness of different periods of cutting down prior to quitting. There was considerable variation in design between the studies and it is not possible to identify any relationship or trend between the length of the reduction period and the outcomes that is not subject to potential confounding by other aspects of the study designs.

However, **Hughes 2011 –** carried out a secondary analysis to examine whether delaying a quit attempt was associated with less success. This analysis was considered to be at high risk of bias.

Evidence Statement:

5.1 There is weak evidence from a secondary analysis (**Hughes 2011 –)** and a quasi-RCT (**Martin 1997 +)** to indicate that there is no relationship between time to planned or actual quit date and long term abstinence rate among those cutting down prior to quitting.

5.2 There is no evidence concerning the optimum cuttjng-down period from other studies **(Cinciripini 1994 +, Cinciripini 1995 +, Etter 2009 +, Etter 2011 +, Hughes 2010 ++, Jiménez-Ruiz 2009 –, Marks 2002 +, Riley 2002 –, Shiffman 2009 ++)**. Reduction periods varied from 7 days to 16 weeks. None of the studies explored the effect of the reduction time on outcomes and, given the huge heterogeneity between studies, no relationship between reduction time and outcomes can be inferred.

This evidence is partially applicable to people in the UK who smoke because **Hughes 2011 –** was a large community based study that may be feasible in the UK, although a secondary analysis is a methodologically weak study. **Martin 1997 +** looked specifically at recovering alcoholics.

Q6. Is it more or less effective to draw up a schedule to help someone cut down smoking with the aim of quitting?

One quasi-RCT compared scheduled versus non-scheduled reduction (**Cinciripini 1995**). One RCT (**Hughes 2010++**) and one quasi-RCT (**Martin 1997 +)** compared different types of schedule.

Evidence Statements:

6.1 There is weak evidence from one quasi-RCT for scheduled versus non-scheduled reduction. **Cinciripini 1995 +** found that cognitive behavioural therapy combined with advice to schedule and lengthen the time between cigarettes enhanced outcomes. Cotinine-verified abstinence rates at 12 months: 44% (scheduled reduced), 18% (non-scheduled reduced), 32% (scheduled non-reduced) and 22% (non-scheduled non-reduced); $p<0.05$.

6.2 There is weak evidence from one large RCT (**Hughes 2010 ++**) and one quasi-RCT (**Martin 1997 +)** that the type of smoking reduction schedule used does not make a difference. **Hughes 2010 ++**) reported that reduction and abstinence rates did not appear to differ across the initially chosen methods (formal schedule, giving up

'easiest' cigarettes first, giving up 'hardest' cigarettes first) so the results were pooled across all the methods. **Martin 1997 +** found no difference between different intervention and scheduled reduction methods. CO-verified quit rates at 12 months for the three groups (standard treatment with counselling over 4 weeks, counselling plus exercise and counselling plus NRT over 8 weeks) were 26%, 27% and 27% respectively.

This evidence is partially applicable to people in the UK since the studies are community based and feasible in UK settings. One study (**Martin 1997 +)** however was in a specific population (recovering alcoholics).

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

Only two studies, both RCTs, examined differences across groups. **Etter 2011 +** compared findings according to age and sex, whilst **Marks 2002 +** examined differences according to gender and socio-economic group. Neither study found evidence of a difference between the groups.

Evidence Statements:

7.1 There is moderate evidence from two RCTs (**Etter 2011 +**, **Marks 2002 +**) to suggest that tobacco harm reduction approaches do not appear to have a differential impact on abstinence rates (**Etter 2011 +**, **Marks 2002 +**) or CPD (**Marks 2002 +**) according to age, gender (**Etter 2011 +**, **Marks 2002 +**) or socioeconomic group (**Marks 2002 +**).

This evidence is applicable to people in the UK since **Marks 2002 +** was based in the UK and **Etter 2011 +** was web-based and is feasible in a UK setting.

Q8. Are there any unintended consequences from adopting a tobacco harm-reduction approach, for example, does it deter people from trying to stop smoking?

Three RCTs (**Cinciripini 1995 +, Etter 2009 +, Hughes 2010 ++**) and a secondary analysis (**Hughes 2011 –**) provided evidence on various unintended consequences.

Evidence Statements:

8.1 There is moderate evidence from one large well conducted RCT (**Hughes 2010 ++**) to suggest that gradual reduction may be associated with a decreased likelihood of making a quit attempt, and that delaying the quit attempt may lead to an increased risk of relapse. However it should be noted that the overall difference in 6-month quit rate from abrupt versus gradual NRT-aided cessation was not statistically significant (see statement 1.1). For every week's delay to quit date the probability of lapsing increased by 19%. In a secondary analysis of this RCT (**Hughes 2011 –**) 57% of the gradual group had either quit after their planned date or did not make a quit attempt at all, which was somewhat higher than those in the abrupt (29%) and control (33%) groups, although this relationship was not tested statistically.

8.2 There is weak evidence from one RCT (**Etter 2009 +**) suggesting there is no increased risk of long term use when NRT is first used as an aid to reduction compared to when it is used simply as an aid to abrupt cessation. After 12 months 9.2% of participants were using

nicotine gum daily and values were similar in both groups.

8.3 There is weak evidence from one RCT (**Cinciripini 1995 +**) that people cutting down to quit using a scheduled reduced approach experience fewer withdrawal symptoms in quit and post-quit weeks and less tension in the quit week compared to the other reduction approaches tested (no data provided).

This evidence partially applicable to people in the UK since the studies were community based and are feasible in UK settings.

5. DISCUSSION

This systematic review found few intervention studies that were designed to look specifically at cut down to quit interventions. Furthermore, those studies varied considerably in methodology, in the interventions used, the outcomes measured and the participant populations.

The quality of the included studies was moderate at best. Only two studies were rated as having a low risk of bias (**Hughes 2010 ++**, **Shiffman 2009 ++**) and four were rated as **being at high risk of bias** (**Gunther 1992 –**, **Jimenez-Ruiz 2009 –**, **O'Leary Tevyaw 2007 –, Riley 2002 –**); as was a secondary analysis of the **Hughes 2010 ++** data (**Hughes 2011 –)**.

There was a wide variation in the range of outcomes; both in timeframes (four weeks to twelve months) and assessment methods (self-reported, CO or cotinine verified).

Participant motivation was sometimes difficult to ascertain and few studies were conducted in participants who wanted to quit but did not want to do so abruptly. For this reason, the scope of the review was extended to include all individuals who participated in a cut down to quit study.

Only one study was conducted in the UK (**Marks 2002 +**), and it is difficult to assess how applicable the other studies are likely to be although it seems reasonable to assume web- and community-based programmes in the USA and Europe are feasible within a UK setting. Some interventions had significant resource implications (12 hours counselling for **Gunther 1992 –**, eight clinic visits for **Jiménez-Ruiz 2009–**, incentive payments for **O'Leary Tevyaw 2007 –,** and/or very specific populations (recovering alcoholics in **Martin 1997 +**, US high school students in **O'Leary Tevyaw 2007 –** and **Riley 2002 –**).

Overall, the data suggest that it is reasonable to give those who are looking to give up smoking the choice of whether they cut down gradually or quit abruptly. Also to provide choice over the method of reduction (scheduled, over a short or long time period). However, these conclusions need to be set against the findings from **Hughes 2010 ++**. This study suggests a reduction approach may allow smokers to delay their quit attempts and increase the likelihood of relapse. There are indications that NRT support may enhance the ability of smokers to quit abruptly over purely behavioural approaches.

Although some study samples were from disadvantaged groups there was very little evidence on differential impact between groups

Further research is clearly needed: more high quality studies that are adequately powered with consistent outcome measures to help answer the questions of what techniques work best and for whom (both in terms of participant motivation and particular population groups).

ABBREVIATIONS

ALA	American Lung Association
BEX	Behavioural counselling plus exercise
BNIC	Behavioural counselling plus nicotine replacement therapy
C	Control group
CM	Contingency management
CO	Carbon monoxide
CPD	Cigarettes per day
DH	Department of Health
DSM	Diagnostic and Statistical Manual of Mental Disorders
GEE	Generalised estimating equation
GP	General Practitioner
HR-E	Hierarchical reduction – easiest first
HR –H	Hierarchical reduction – hardest first
I	Intervention group
ITT	Intention to treat
MANOVA	Multiple analysis of variance
MI	Motivational interviewing
NA	Nicotine Anonymous
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NM	New Mexico
NRT	Nicotine replacement therapy
NS	Not significant
NTIS	National Technical Information Service
OR	Odds ratio
QFL	Quit for Life
RA	Reinforcement for attendance
RT	Randomised trial (all intervention arms, no control)
RCT	Randomised controlled trial
SA	Secondary analysis
SC	South Carolina
SES	Socio-economic status
SSME	Stop Smoking Made Easier
SR	Scheduled reduction
ST	Standard treatment
UBA	Uncontrolled before and after study
WHO	World Health Organisation

1 INTRODUCTION

1.1 Aims of the review

To review the effectiveness of harm reduction approaches with the intention of quitting (ie 'cutting down to quit' or 'reduction to stop smoking'), with and without assistance.

1.2 Research questions

- How effective are pharmacotherapies in helping people cut down smoking before quitting?
- How effective are different combinations of NRT products in helping people cut down smoking before quitting?
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- Is there an optimal period for helping people cut down smoking with the aim of quitting?
- Is it more or less effective to draw up a schedule to help someone cut down smoking with the aim of quitting?
- Do some tobacco harm-reduction approaches have a differential impact on different groups (for example, people of different ages, gender, socioeconomic status or ethnicity)?
- Are there any unintended consequences from adopting a tobacco harm-reduction approach, for example, does it deter people from trying to stop smoking?

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 with respect to smoking 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; 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.

The following study designs were excluded:

- Surveys and other observational studies that were not designed to measure the efficacy of an intervention. Data from these types of study, where relevant to barriers and facilitators to tobacco harm reduction approaches, will be considered in Review 4.

2.1.1 Electronic sources (databases and websites)

The following sources were searched in August 2011 to identify relevant intervention studies in the English language published between 1990 and 2011.

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) 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 - *Drug & Alcohol Dependence* (3 papers) and *Nicotine & Tobacco Research* (2 papers)] - 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 (Appendix A) 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 and exclusion criteria:

	Inclusion	Exclusion
Population	People of all ages who want to quit smoking but feel unable to do so abruptly; or those who participate in cut down to quit interventions; with a particular focus on those who have been identified as: • to smoke, • at increased health risk from smoking, • from more disadvantaged groups and, thus, vulnerable to health inequalities.	Pregnant women [but the post partum population was included]
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[4]) • 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.

[4] 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)

		• 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)	

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.

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 independently in duplicate using the GATE checklist for quantitative studies [NICE 2009]. 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 insufficient, the study is described as quasi-randomised. Inter-rater reliability scores were explored and resulted in an overall kappa score of 0.71.

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 and cessation 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 are used (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.

Where feasible, meta-analyses of the data were conducted (see Appendix I).

Dichotomous outcomes data are presented as relative risk ratios (RR) and, where possible, all outcomes data are provided with associated 95% confidence intervals (CI) and p-values.

Clinical heterogeneity was assessed by examining the characteristics of the studies, the similarity between the types of participants, interventions, and comparisons. The degree of heterogeneity between the studies was assessed using the I^2 statistic. (Higgins 2011).

Following discussion between the review team and the Expert Advisory Group it was agreed that the included studies were highly clinically heterogeneous and the value of meta-analysis was very doubtful. Thus the results are not included in the Key Findings section 4.

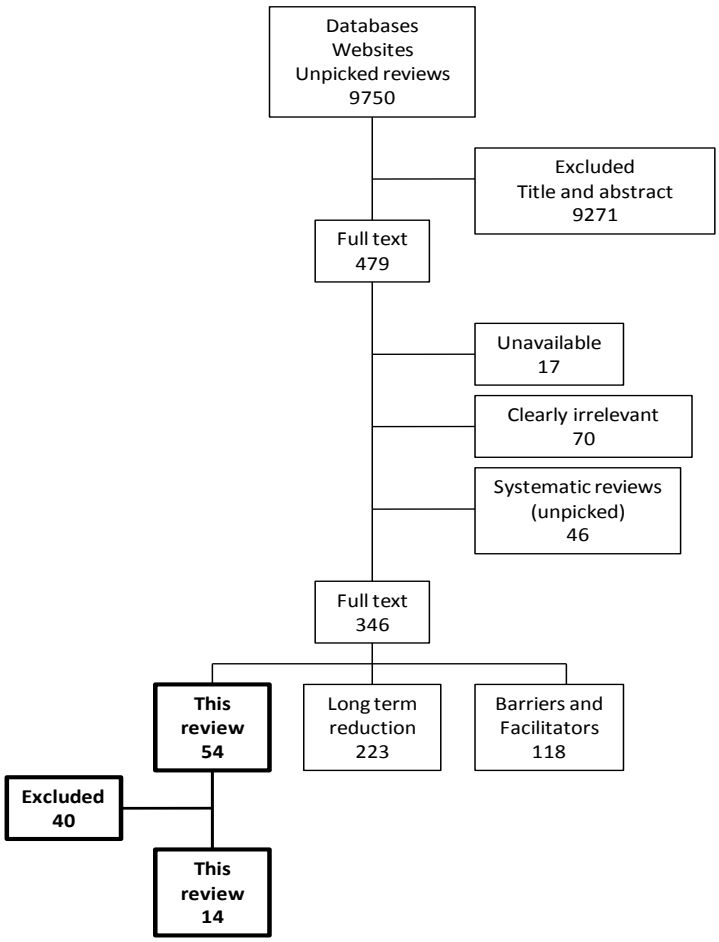
The strength of evidence assessment in the evidence statements is based on the most recent GRADE guidance (Guyatt 2010). The definitions used are broadly defined as follows with potential for moving up or down a grade as summarised in the guidance (Guyatt 2010):

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, 17 were unavailable, 70 were found to be clearly irrelevant and 46 were systematic reviews. This left 346 papers which were considered for inclusion in one or more of the three reviews. 54 papers were considered for this review, of which 14 papers from 12 studies were included. A full list of excluded papers for this review with reasons for exclusion is provided in Appendix



Note:
1) Some papers may be relevant to more than one review
2) New studies are likely to be identified whilst the reviews are being conducted

Note:
1) Some papers may be relevant to more than one review
2) New studies may be identified within update searches for the long term reduction and barriers & facilitators reviews

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

Of the 14 papers, five are randomised controlled trials (**Etter 2009 +**, **Etter 2011 +**, **Gunther 1992 –**, **Hughes 2010 ++**, **Shiffman 2009 ++**), four are quasi-randomised (**Cinciripini 1994 +**, **Cinciripini 1995 +**, **Martin 1997 +**, **Marks 2002 +)**; receiving that designation because the allocation method was either unclear or inappropriate. The remaining five papers are a partial randomised trial (**O'Leary Tevyaw 2007 –**), uncontrolled before and after studies (**Jiménez-Ruiz 2009 –, Riley 2002 –**), six month data for Marks 2002 (**Sykes 2001 +)** and secondary analysis of Hughes 2010 (**Hughes 2011 –**).

3.2 Quality and applicability of studies

Only two of the RCTs were assessed as being of high quality and received a rating of **++** (**Hughes 2010**, **Shiffman 2009**). Four studies were deemed to be at serious risk of bias and received a rating of **–** (**Gunther 1992**, **Jiménez-Ruiz 2009**, **O'Leary Tevyaw 2007**, **Riley 2002 –**) as did the secondary analysis (**Hughes 2011**). The remaining studies all received a rating of **+** (**Cinciripini 1994**, **Cinciripini 1995**, **Etter 2009**, **Etter 2011**, **Martin 1997**, **Marks 2002**) reflecting concerns about potential sources of bias.

Only one of the studies included a power calculation (**Etter 2011 +**) and three were conducted in very small populations (**Cinciripini 1994 +**, **O'Leary Tevyaw 2007 –**, **Riley 2002 –**). Four of the studies which described themselves as randomised, provided no information on study allocation and are consequently described throughout as quasi-randomised (**Cinciripini 1994 +**, **Cinciripini 1995 +**, **Martin 1997 +**, **Marks 2002 +**). Several studies had limited population data (**Cinciripini 1994 +**, **Cinciripini 1995 +**, **Gunther 1992 –**). Two had no intention to treat analysis (**Gunther 1992–, Marks 2002 +**).

Both the studies that received a quality rating of ++ had lead authors with strong ties to manufacturers of smoking cessation products and **Shiffman 2009 ++** was funded and co-authored by a pharmaceutical company.

Study applicability is limited. Only one study was conducted in the UK (**Marks 2002 +**). Three were conducted in Europe (**Etter 2009 +**, **Jiménez-Ruiz 2009 –**, **Gunther 1992 –**), six in the USA (**Cinciripini 1994 +**, **Cinciripini 1995 +**, **Hughes 2010 ++**, **Martin 1997 +**, **O'Leary Tevyaw –**, **Riley 2002 –, Shiffman 2009 ++**) and one was a web-based intervention that was open to users of a smoking cessation website regardless of location (**Etter 2011 +**).

Nine studies took place in community settings; two of which were in smokers' clinics (**Jiménez-Ruiz 2009 –**, **Marks 2002 +**). Of those not-community based, **Etter 2011 +** was a web based intervention and **O'Leary Tevyaw 2007 –** and **Riley 2002 –** were conducted in high schools.

3.3 Outcomes

Data were extracted for all smoking-related outcomes. Abstinence data (both sustained and point prevalence) were extracted for six and twelve months follow-ups, or the longest available period if these data were not available. Both self-report and verified abstinence (CO or cotinine) were extracted. In addition, information on reduction in smoking, number of cigarettes smoked per day (CPD) was identified.

Whilst data concerning the impact of reducing smoking on mood was sought, particularly in relation to withdrawal symptoms, only one study (**Cinciripini 1995 +**) contained any relevant data.

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[5]	Population	Study outline	Internal validity[6]
Cinciripini 1994 Quasi RCT	USA + (community-based)	34 adults Attrition: 6%	Behavioural support for scheduled smoking reduction (over a three-week period) with a minimal self-help treatment. Control provided with an "I Quit Kit" advocating reduction to quit over a 7 day period. C0-verified abstinence, CPD to 12 months. Participants' motivations unknown.	+ Small sample), limited baseline data, no information on allocation, no power calc.
Cinciripini 1995 Quasi-RCT	USA + (community-based)	128 adults Attrition: not stated	Behavioural support (CBT) for scheduled and non-scheduled reduction with scheduled and non scheduled abrupt cessation with meetings held up to 9 weeks. Cotinine verfied abstinence, CPD to 12 months. Tension to 6 months. Participants' motivations unknown.	+ No information on allocation, little population detail, no power calc.
Etter 2009 RCT	Switzerland ++ (community-based)	314 adults Attrition: 11.8%	NRT (nicotine polacrilex gum) 4 weeks before and 8 weeks after target quit date. Control had NRT for 8 weeks post quit date. Cotinine and CO verified abstinence, CPD to 12 months. Participants committed to a quit date.	+ Pre-quit delay (2 weeks) may have introduced bias, no power calc.
Etter 2011 RCT	Website + (multiple countries)	974 adult internet users Attrition: 'high'	Behavioural support via email. Instruction via web/email to quit abruptly or gradually (via 2 week reduction period).Abstinence to 4 weeks Participants without preference for gradual/abrupt quitting	+ 'High' drop-out rate reported by authors (no data provided), no biochemical verification of outcomes, short term follow up (4 weeks).
Gunther 1992 RCT	Austria + (community smokers' centre)	110 adults Attrition: 53%	Behavioural support by 12 hours counselling for sudden versus gradual withdrawal. Abstinence and CPD to 12 months. Participants' motivations unknown.	– No baseline data, significant loss to follow up, no biochemical verification of outcomes, no ITT, no power calc.
Hughes 2010 RCT	USA + (community-based)	746 adults Attrition: 21-24% but ITT	Behavioural support by counselling and NRT for gradual reduction (cessation 3-5 weeks after initiation) or abrupt cessation (1-3 weeks after initiation) CO verified abstinence and CO verified reduction, self efficacy, motivation, confidence, preference for quitting method to 6 months. Participants wanted to quit gradually.	++ Team, though not this study, funded by pharma companies. No power calc and authors indicate study may be underpowered, but generally well conducted.

[5] 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 –.

[6] 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 –.

Hughes 2011 Secondary analysis	As above	As above	To explore the effect of delaying the quit attempt on outcomes.	– Secondary analysis (and thus open to significant bias)
Jiménez-Ruiz 2009 Uncontrolled B&A	Spain – (Smokers' Clinic)	116 adults Attrition: 49% by week 16	Cognitive behavioural support over 16 weeks with NRT for progressive reduction leading to abstinence. No control group. CO verified abstinence up to 6 months. Reduction in CPD ≥50% at week 8. Adverse events. Participants wanted to quit gradually.	– Uncontrolled study and potential bias in self-selected study sample. No power calc.
Martin 1997 Quasi-RCT	USA + (community-based)	205 recovering alcoholics Attrition: not stated	Standard treatment plus behavioural support for quitting (by week 4) versus 8 weeks behavioural counselling and exercise for reduction to quit vs behavioural counselling plus NRT for reduction to quit. CO verified abstinence up to 12 months. Participants' motivations unknown.	+ Unclear whether appropriate allocation, no usual care control group, no power calc.
Marks 2002 Sykes 2001 Quasi RCT	UK ++ (Smoking clinic in deprived London community)	260 adults Attrition: 15%	Cognitive behavioural support (an 'eclectic' mix) for a 7-10 day reduction period versus leaflet with staged preparation for abrupt cessation. CO verified abstinence and CPD reduction ≥ 25% up to 6 and 12 months. Participants' motivations unknown but all contacted a cessation clinic.	+ Unclear allocation concealment. no ITT, no power calc. Authors are suppliers of the QFL (cognitive behavioural) intervention.
O'Leary Tevyaw 2007 Partial RCT	USA – (High school)	23 adolescents Attrition: 7%	Contingency management (by voucher payments) for reinforcement for reduction leading to abstinence versus reinforcement of abstinence only over a 3 week intervention. CO verified abstinence 2 weeks post intervention. Participants did not need to be motivated to quit.	– Very small sample (23) and short time-frame for outcome measures (2 weeks post intervention). No power calc.
Riley 2002 Uncontrolled B&A	USA – (High school)	17 (Study 1) and 18 (Study 2) adolescents Attrition: 71% - 12 month CO validated	Two studies using computerised scheduled reduction combined with 7 weekly support meetings (study 1) or brief mid-point contact only (study 2). Self report CPD and 7-day abstinence, CO validated, at post-treatment (study 1 & 2), and 12 months (study 2 only). Participants had a desire to quit smoking.	– Very small samples (17/13), groups very different so can't compare, high attrition for 12 month CO measure. No power calc. Authors work for company with commercial interests in computerised smoking cessation products.
Shiffman 2009 RCT	USA + (community-based)	3297 adults Attrition: not stated	NRT (2 mg or 4mg depending on participant choice) versus placebo for reduction to quit, over 8 weeks. CO verified abstinence up to 6 months, CPD, adverse events during reduction period (0-8 weeks). Participants were interested in quitting gradually.	++ No data on attrition, pharma company funded and were involved in write up, no power calc. (though large study, n=3297) and generally well conducted.

4. FINDINGS

Q1. How effective are pharmacotherapies in helping people cut down smoking before quitting?

No studies provided cost-effectiveness data.

Nicotine replacement therapy (NRT) products are the only pharmacotherapies with a UK marketing authorisation for cutting down, temporary abstinence or harm reduction.[7] NRT is available in the following formulations: chewing gum, transdermal patches, inhalers, microtabs, mouth/nasal sprays and lozenges.

RCTs comparing gradual versus abrupt cessation:

Etter 2009 + gave intervention participants 4mg nicotine gum for four weeks before and eight weeks after the target quit date and told participants to decrease their cigarette consumption by 50% before quitting. Control group participants were recommended to quit abruptly and were given nicotine gum for eight weeks after the quit date only. Participants were instructed to use ≥ 10 pieces of gum per day and received a booklet and a url for a cessation web site. At the 12 month follow-up survey there was no statistically significant difference between the two groups in terms of biochemically validated four week quit rate (16.5% of the gradual group compared to 24% of the abrupt group p=0.14). After 12 months, 9.2% participants were still using NRT daily (5 pieces per day on average). Values were similar in both abrupt and gradual cessation groups.

Hughes 2010 ++ carried out a three arm trial comparing nicotine lozenges combined with gradual cessation counselling, abrupt cessation counselling, and brief advice. Participants in the gradual group were asked to set a quit date between three and five weeks after the study initiation and received nicotine lozenges for use; those in the abrupt and brief advice groups were asked to set a quit date between one and three weeks from the study onset. All participants were sent a booklet and nicotine lozenges to use starting on their quit date and for up to 12 weeks post quit date. The three conditions did not differ statistically in CO validated abstinence at six month follow-up, although there was a non-significant trend for lower 6-month CO validated abstinence in the gradual group compared to the abrupt groups (OR=0.6, 95% CI 0.3, 1.2). Smokers in the gradual condition were less likely to make a quit attempt than those in the abrupt and minimal treatment conditions.

RCTs comparing nicotine gum versus placebo to facilitate gradual reduction prior to cessation:

Shiffman 2009 ++ tested the efficacy of nicotine gum in facilitating cessation through gradual reduction. Participants were randomised to receive either gum, at 2mg or 4 mg, or a placebo, and were instructed to extend the time to their first cigarette (using the gum) by one hour each day. At six month follow-up, overall those using nicotine gum were almost three times more likely than those using placebo to be CO verified abstinent (OR=2.86, 95% CI 1.93, 4.24). These differences were more noticeable when comparing those using 4mg gum to those using placebo (OR=6.0, 95% CI=2.9, 12.3), although the difference between those using 2mg gum and those using placebo also just reached significance (OR=1.8, 95% CI 1.1, 2.9).

RCT comparing NRT with other types of intervention:

Martin 1997 + compared behavioural counselling plus exercise, behavioural counselling plus nicotine replacement therapy (2mg gum), and standard treatment (which also had behavioural components – counselling and attendance at Nicotine Anonymous meeting) in a population of recovering alcoholics. There was no statistically significant difference in CO verified quit rates at 12 months between the three groups; 27%, 27% and 26% respectively.

[7] 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)

Uncontrolled study examining the efficacy of NRT as an aid to gradual cessation:

Jiménez-Ruiz 2009 – examined the outcome of a programme of progressive reduction, using nicotine gum, as a prelude to complete cessation among current smokers who sought treatment in a smokers' clinic but who did not want to quit abruptly. Smokers were instructed to use 2mg nicotine gum at recommended levels according to their baseline cigarette consumption, with a target of a reduction in the number of cigarettes per day of 50% or more by week 8, and abstinence by week 16. Participants also received intensive cognitive behavioural therapy during the reduction phase (eight fortnightly one to one sessions). Two groups of smokers were compared: those who went to the clinic wanting to quit but not abruptly, and refractory smokers, who had failed to quit several times and who were advised to follow a progressive reduction programme. CO verified continuous abstinence rates were 39% at the 6 month follow-up. Differences between the two groups in abstinence rates were not significant. All smokers who had successfully quit at 16 weeks continued to use NRT into the abstinence phase but no subject used NRT for more than 4 months post quit date.

Evidence Statements:

1.1 There is moderate evidence from two randomised controlled trials (RCTs) of no significant difference in long-term abstinence rates between gradual and abrupt cessation when using NRT (gum or lozenges) (**Etter 2009 +**, **Hughes 2010 ++**) although the trend favours abrupt cessation. The CO and cotinine validated four week quit rate at 12 months was 16.5% for gradual compared to 24.0% for abrupt cessation, p=0.14 (**Etter 2009 +**), The OR for CO validated abstinence at 6 months (gradual/abrupt) was 0.6 (95% CI 0.3, 1.2) (**Hughes 2010 ++**).

1.2 There is moderate evidence from a large RCT (**Shiffman 2009 ++**) of a benefit from NRT versus placebo at 6 months; this was more marked in the 4 mg gum versus 2 mg dose rates with ORs of 6.0 (95%CI 2.9, 12.3) and 1.8 (95% CI 1.1, 2.9) respectively. Overall OR 2.86 (95% CI 1.93, 4.24).

Evidence from two much smaller studies, a quasi-RCT (**Martin 1997 +**) and an uncontrolled before and after study **(Jiménez Ruiz 2009 –**) is inconsistent. In the quasi–RCT mean quit rates for standard treatment versus behavioural counselling with NRT respectively at 6months were 21% v. 27% (NS) and at 12 months 26% v 27% (NS) (**Martin 1997 +)**. In the UCBA study (**Jiménez Ruiz 2009 –)** 39% reported abstinence at 6 months and 68% reported ≥50% reduction in cigarette consumption at the end of 8 weeks using a combination of gum and behavioural therapy. The difference in abstinence between participants who wanted to reduce to quit versus those who were refractory smokers was not significant (48% vs 32%, p=0.8).

1.3 There is inconsistent evidence from one RCT (**Etter 2009 +**) and one UBA (**Jiménez Ruiz 2009 –)** of NRT use in the longer term. **Etter 2009 +** found that, after 12 months, 9.2% participants were still using NRT daily (5 pieces per day on average). Values were similar in both abrupt and gradual cessation groups. **Jiménez Ruiz 2009 –** found that all smokers who had successfully quit at 16 weeks continued to use NRT into the abstinence phase but no subject used NRT for more than 4 months post quit date.

1.4 There is weak evidence from a single RCT that nicotine gum may be an effective aid to reducing cigarettes prior to cessation as daily cigarette consumption in the week before the quit date was 12.4 v 21.3 cigarettes /day, p<0.001 (**Etter 2009 +**).

The evidence from the RCTs (**Etter 2009 +**, **Hughes 2010 ++**, **Shiffman 2009 ++**) is partially

applicable to people in the UK because, although there were no UK-based trials, the studies were community-based and are feasible within a UK setting. **Martin 1997 +** relates specifically to recovering alcoholics. **Jiménez Ruiz 2009 –** was an intensive intervention which is unlikely to be feasible within the UK.

Q2. How effective are different combinations of NRT products in helping people cut down smoking before quitting?

Evidence Statement:

2.1 No studies were found that looked at combinations of NRT products for helping people to cut down before quitting.

Q3. How effective are 'nicotine-containing products' in helping people cut down smoking before 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.

Evidence Statement:

3.1 No studies were found that looked at the effectiveness of nicotine delivery systems (electronic cigarettes) for helping people to cut down before quitting.

Q4. How effective are behavioural support, counselling, advice or self-help (with or without pharmacotherapy) in helping people cut down smoking before quitting?

Nine studies incorporated behavioural support, including three randomised controlled trials (**Etter 2011 +**, **Gunther 1992 –**, **Hughes 2010 ++**), four quasi-randomised controlled trials (**Cinciripini 1994 +**, **Cinciripini 1995 +**, **Martin 1997 +**, **Marks 2002 +**), one trial with partial randomisation (**O'Leary Tevyaw 2007 –**) and one uncontrolled before and after study (**Jiménez-Ruiz 2009 –**).

One study was based in the UK (**Marks 2002 +**), three in Europe (**Etter 2009 +**, **Gunther 1992 –**, **Jimenez Ruiz 2009 –**), five in the USA (**Cinciripini 1994 +**, **Cinciripini 1995 +**, **Hughes 2010 ++**, **Martin 1997 +**, **O'Leary Tevyaw 2007 –**) and one was a multi-country web-based intervention (**Etter 2011 +)**. The community-based trials may be applicable to the UK.

Both **Martin 1997 +** and **O'Leary Tevyaw 2007 –** had very specific populations; recovering alchoholics in the former and a US high school in the latter.

Quasi-RCTs comprising a behavioural support element:

Participants in the experimental condition in **Cinciripini's 1994 +** quasi-randomised controlled trial were provided with an eight week programme. Participants were instructed to gradually reduce the amount of cigarettes smoked, prior to quitting in week 5. During weeks two to five cognitive behaviour modification was provided, and during weeks five to nine relapse

prevention training was given. Participants in the control condition received an "I Quit Kit" and participated in a one hour discussion on its use. The control arm also involved a pre quit reduction period, of seven days. The mean number of cigarettes per day gradually declined across the pre-quit period in the intervention group; this was not the case in the control group. Intervention group subjects smoked an average of 21.39 (9.33), 12.21 (6.72), 8.02 (3.43) and 5.45 (2.61) CPD in weeks 1 to 4 of the programme. The equivalent figures for the control group were 27 (6.76), 28.79 (15.26), 26.71 (11.37) and 20 (14.99). At the 12 month follow-up, CO validated abstinence rates were significantly higher in the intervention group than they were in the control group. 53% and 41% of the gradual reduction group was abstinent at the 6- and 12-month follow up periods respectively, compared to 6% of the control group at each time point.

A further quasi-randomised controlled trial (**Marks 2002 +**) offered intervention participants a combination of '30 cognitive behavioural and other relevant methods in a self-help package consisting of a handbook (also provided as a cassette tape with relaxing music on the other side), reduction cards, a progress chart and other necessary materials' to guide them towards a daily reduction of 50% over the course of 7-10 days. The programme also provided relapse prevention support post quit date, to three months. Those in the control group received a pocket sized leaflet recommending a staged preparation with an abrupt cessation date, and recommendations to phone the national 'quitline', GP or health centre for further support. Results showed that at the twelve month follow-up, significantly more participants in the intervention group were CO-verified abstinent than in the control group. It is worthwhile noting that the two programmes were quite different and that this was not a study primarily comparing abrupt versus gradual cessation.

RCT comprising an advice giving element:

Etter 2011 + emailed intervention participants with the instruction to gradually reduce their consumption by half over the next two weeks and then quit. Participants received an individually tailored calendar via email with their target cigarette consumption for each day for the following two weeks. The control group were emailed the instruction to quit abruptly and immediately. There were no significant differences between groups at any follow-up points. Note, however, that follow-ups only took place at two and four weeks after the quit date.

Study comprising RCT element investigating the feasibility of contingency management:

O'Leary Tevyaw 2007 – investigated the efficacy and feasibility of a contingency management protocol for adolescent smokers that included use of a reduction phase. This involved providing participants with gift certificates for use in a local shopping centre in return for carbon monoxide samples, with the amount of the voucher paid increasing based on the amount of carbon monoxide reduction. Participants completed three phases: 1) reinforcement for attendance and provision of breath samples (RA phase); 2) a washout phase; and 3) a contingency management (CM) phase, with the order of the RA and CM phases being counterbalanced between participants. In addition, participants were randomised to one of two conditions during the CM phase: 1) abstinence condition, where participants earned reinforcement only for carbon monoxide levels indicating abstinence; and 2) reduction condition, where participants earned reinforcement for reduction from baseline CO levels for the first half of the CM phase, followed by an abstinence contingency for the remainder of the phase. Compared with the abstinence group, those in the reduction group demonstrated trends for more abstinence readings and had a significantly higher percentage of readings meeting criteria for reinforcement during the CM phase. Note that this study had a very small sample size as it was primarily designed as a feasibility study. Findings are therefore limited in their applicability.

Uncontrolled study involving behavioural support:

As an adjunct to using nicotine gum to aid reduction, participants in **Jiménez-Ruiz's 2009 –** study also received cognitive behavioural therapy during the reduction phase. At the 6 month post-quit follow-up, CO verified continuous abstinence rates were 39%. **Riley 2002 –** carried out two small before and after studies with a US high-school population. Both employed computerised scheduled reduction combined with 7 weekly support meetings (study 1) or brief mid-point contact only (study 2). The authors noted that this was just a feasibility study showing that this type of intervention is acceptable to an adolescent population; groups were not comparable and the results were not generalisable.

Studies involving a behavioural component across both intervention and control groups where it is therefore not possible to infer the effectiveness of the behavioural component:

In **Cinciripini's 1995 +** quasi-randomised trial comparing scheduled and non-scheduled gradual approaches to cessation, participants received cognitive behavioural training in week two to five. Cotinine verified abstinence rates at 12 months were 44% (scheduled reduced), 18% (non-scheduled reduced), 32% (scheduled non-reduced) and 22% (non- scheduled non-reduced); $p<0.05$.

In **Gunther's 1992 –** RCT comparing sudden withdrawal with gradual withdrawal, all participants received 12 hours of individual counselling delivered by a behaviour therapist. At 12 months follow-up there was a non significant difference in abstinence between sudden and gradual withdrawal groups: 51.85% versus 38.71%.

Hughes 2010 ++ offered gradual or abrupt cessation counselling plus nicotine lonzenge (2 or 4 mg) according to intervention arm and also found a non significant difference between arms with a trend to favouring abrupt cessation. The OR for CO verified abstinence at 6 months for gradual versus abrupt cessation was 0.6 (95% CI 0.3, 1.2).

Martin 1997 + (in a population of recovering alcoholics) offered behavioural counselling in all three arms: modified standard treatment including maintenance counselling and group meetings; counselling plus exercise; counselling plus nicotine replacement therapy. There was no statistically significant difference in CO verified quit rates at 12 months between the three groups; 26%, 27% and 27% respectively.

Evidence Statements:

4.1 There is moderate evidence for the effectiveness of cognitive behavioural therapy versus standard therapy from two quasi-RCTs (**Cinciripini 1994 +**, **Marks 2002 +**) both in reducing the number of cigarettes per day prior to quitting, and in quitting itself. At 12 months 41% of the CBT group and 6% of the control group were abstinent, $p<0.01$. Figures for 6 months were 53% and 6%, $p< .01$ (**Cinciripini 1994 +**). At 12 months 19.8% (95% CI 13.0, 28.3) of the contactable CBT group were abstinent compared to 5.8 % (95% CI 2.1, 12.1) $p<0.0001$ (**Marks 2002 +**). At the same time point 11.5% (95% CI 6.4, 18.5, $p<0.0001$) had reduced their CPD by ≥ 25% compared to 0% in the control group.

4.2 There is moderate evidence from two RCTs (**Gunther 1992 –, Hughes 2010 ++)** of a trend towards higher abstinent rates for abrupt cessation compared to gradual reduction when counselling is offered to both groups (with nicotine as well in **Hughes 2010 ++**) but the findings are not significant. The OR for CO verified abstinence at 6 months for gradual versus abrupt cessation was 0.6 (95% CI 0.3, 1.2) **(Hughes 2010 ++).** At 12 months follow-up there was a non-significant difference in self reported abstinence between sudden and gradual withdrawal groups: 51.85% versus 38.71% (**Gunther 1992 –**).

4.3 There is weak evidence from one quasi-randomised trial (**Cinciripini 1995 +**) suggesting that cognitive behavioural therapy combined with advice to schedule and lengthen the time between cigarettes may enhance outcomes. Cotinine verified abstinence rates at 12

months were 44% (scheduled reduced), 18% (non-scheduled reduced), 32% (scheduled non-reduced) and 13% (non-scheduled non-reduced); p<0.05.

4.4 There is weak evidence from one RCT (**Etter 2011 +**) to suggest that there may be no difference in the effect of advice giving (via web and email) for gradual versus abrupt cessation but the follow up period was very short and outcomes were self reported. At four weeks 8.8% of the gradual group and 8.7% of the abrupt group reported no puff taken in the past 24 hours (p=0.97).

4.5 There is weak evidence from one RCT (**Martin 1997 +**) in a population of recovering alcoholics that there may be no difference between standard treatment with counselling, counselling plus exercise and counselling plus NRT for gradual reduction. CO-verified quit rates at 12 months for the three groups were26%, 27% and 27% respectively.

4.6 There is very weak evidence from a feasibility study (**O'Leary Tevyaw 2007 –**) suggesting that the use of contingency management (a reward for response) may be effective when used to support reduction to quit since participants had more abstinent readings in the contingency management phase than the reinforcement phase (50% vs 37%).

4.7 There is very weak evidence from two small before & after studies (**Riley 2002 –**) that computerised scheduled reduction, with or without behavioural support, is acceptable to a teenage population.

This evidence is partially applicable to people in the UK. The use of rewards for response (**O'Leary Tevyaw 2007 –**) is unlikely in this setting. However **Marks 2002 +** was based in the UK, **Etter 2011 +** was a web-based intervention, and all the other studies were community- or high school-based and feasible within a UK setting. One study (**Martin 1997 +)** was in a specific population (recovering alcoholics).

Q5. Is there an optimal period for helping people cut down smoking with the aim of quitting?

The reduction period across the included studies varied from 7-10 days **(Marks 2002 +)** through to 16 weeks **(Jiménez-Ruiz 2009 –)**. Five studies employed reduction periods of between two and five weeks **(Cinciripini 1994 +, Cinciripini 1995 +, Etter 2009 +, Etter 2011 +, Hughes 2010 ++)**. **Riley 2002 –** utilised a seven-week and **Martin 1997 +** and **Shiffman 2009 ++** an eight-week schedule. The studies vary considerably in design and it is not possible to identify any relationship or trend between the length of the reduction period and outcomes that is not be subject to potential confounding by other aspects of the study designs.

Martin 1997 + found no difference between two different reduction periods, although the interventions also differed. CO-verified quit rates at 12 months for the three groups (standard treatment with counselling over 4 weeks, counselling plus exercise and counselling plus NRT over 8 weeks) were 26%, 27% and 27% respectively.

None of the other studies compared the effectiveness of different periods of cutting down prior to quitting. There was considerable variation in design between the studies and it is not possible to identify any relationship or trend between the length of the reduction period and the outcomes that is not subject to potential confounding by other aspects of the study designs.

However, **Hughes 2011 –** carried out a secondary analysis to examine whether delaying a quit attempt was associated with less success. For those assigned to the gradual cessation condition, no relationship was found between time to planned quit date, time to actual quit date, or quitting after versus on the quit date and six month abstinence. There was also no relationship between time to the planned quit date and the likelihood of never making a quit attempt.

Evidence Statement:

5.1 There is weak evidence from a secondary analysis (**Hughes 2011 –)** and a quasi-RCT (**Martin 1997 +)** to indicate that there is no relationship between time to planned or actual quit date and long term abstinence rate among those cutting down prior to quitting.

5.2 There is no evidence concerning the optimum cuttjng-down period from other studies **(Cinciripini 1994 +, Cinciripini 1995 +, Etter 2009 +, Etter 2011 +, Hughes 2010 ++, Jiménez-Ruiz 2009 –, Marks 2002 +, Riley 2002 –, Shiffman 2009 ++)**. Reduction periods varied from 7 days to 16 weeks. None of the studies explored the effect of the reduction time on outcomes and, given the huge heterogeneity between studies, no relationship between reduction time and outcomes can be inferred.

This evidence is partially applicable to people in the UK who smoke because **Hughes 2011 –** was a large community based study that may be feasible in the UK, although a secondary analysis is a methodologically weak study. **Martin 1997 +** looked specifically at recovering alcoholics.

Q6. Is it more or less effective to draw up a schedule to help someone cut down smoking with the aim of quitting?

RCTs/Quasi-RCTs comparing scheduled versus non-scheduled reduction:

Cinciripini 1995 + compared scheduled and non-scheduled gradual and abrupt approaches to cessation. Participants were randomised to one of four arms: scheduled reduced (Group A), non-scheduled reduced (Group B), scheduled non-reduced (Group C), or non-scheduled non-reduced (Group D). Participants attended weekly meetings – cognitive behavioural training was given in week two to five, and in week five to nine the focus was on maintenance for abstainers and cessation for those who had not yet quit. At 12 month follow-up salivary cotinine verified abstinence rates were higher in the scheduled groups than in the non-scheduled groups, with the highest rate being observed in the scheduled reduced group. Cotinine verified abstinence rates at 12 months were 44% (Group A), 18% (Group B), 32% (Group C) and 22% (Group D); $p<0.05$. Participants in the scheduled reduced groups exhibited significantly reduced tension from week 8 to 6 months follow up (no data provided).

Martin 1997 + a study in recovering alcoholics, instructed those in the standard treatment group to carry out three large-scale smoking rate reductions by one third each week prior to the target quit date in week four. This compared with those in the two intervention groups who made more gradual and unscheduled reductions over an eight week period. CO verified quit rates at 12 months were not statistically different between the three groups.

Study comparing different types of schedule:

In an RCT comparing gradual versus abrupt cessation approaches, **Hughes 2010 ++** recommended that participants in the gradual reduction group reduced by 25% in the first week, 50% in the second week, and 75% in the third week, although each smoker chose his or her own goal and rate of progress. Three different reduction methods were described to participants: a) scheduled reduction (SR) in which smokers gradually increase the time between cigarettes; b) hierarchical reduction-easiest first (HR-E) in which smokers eliminate cigarettes from easiest to hardest to give up; and c) hierarchical reduction hardest first (HR-H) in which they eliminated the hardest to give up cigarettes first. Sixty percent of participants chose SR, 25% chose HR-E, 11% chose HR-H, and in 4% it was unclear which method they chose. Reduction and abstinence rates did not appear to differ across the initially chosen methods and the authors' clinical observation was that the large majority of smokers did not exclusively use their

chosen method of reduction, but instead used several methods or reduced without using any of the described methods. Therefore the results were pooled across all the methods.

Evidence Statements:

6.1 There is weak evidence from one quasi-RCT for scheduled versus non-scheduled reduction. (**Cinciripini 1995 +**) found that cognitive behavioural therapy combined with advice to schedule and lengthen the time between cigarettes enhanced outcomes. Cotinine-verified abstinence rates at 12 months: 44% (scheduled reduced), 18% (non-scheduled reduced), 32% (scheduled non-reduced) and 22% (non-scheduled non-reduced); $p<0.05$.

6.2 There is weak evidence from one large RCT (**Hughes 2010 ++**) and one quasi-RCT (**Martin 1997 +)** that the type of smoking reduction schedule used does not make a difference. **Hughes 2010 ++**reported that reduction and abstinence rates did not appear to differ across the initially chosen methods (formal schedule, giving up 'easiest' cigarettes first, giving up 'hardest' cigarettes first) so the results were pooled across all the methods. **Martin 1997 +** found no difference between different intervention and scheduled reduction methods. CO-verified quit rates at 12 months for the three groups (standard treatment with counselling over 4 weeks, counselling plus exercise and counselling plus NRT over 8 weeks) were26%, 27% and 27% respectively.

This evidence is partially applicable to people in the UK since the studies are community based and feasible in UK settings. One study (**Martin 1997 +)** was in a specific population (recovering alcoholics).

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

Only two studies, both RCTs, examined differences across groups. **Etter 2011 +** compared findings according to age and sex, whilst **Marks 2002 +** examined differences according to gender and socio-economic group. Neither study found evidence of a difference between the groups.

Evidence Statements:

7.1 There is moderate evidence from two RCTs (**Etter 2011 +**, **Marks 2002 +**) to suggest that tobacco harm reduction approaches do not appear to have a differential impact on abstinence rates (**Etter 2011 +**, **Marks 2002 +**) or CPD (**Marks 2002 +**) according to age, gender (**Etter 2011 +**, **Marks 2002 +**) or socioeconomic group (**Marks 2002 +**).

This evidence is applicable to people in the UK since **Marks 2002 +** was based in the UK and **Etter 2011 +** was web-based and is feasible in a UK setting.

Q8. Are there any unintended consequences from adopting a tobacco harm-reduction approach, for example, does it deter people from trying to stop smoking?

In their RCT comparing gradual cessation, abrupt cessation, and minimal treatment, **Hughes 2010 ++** reported that smokers in the gradual condition were less likely to make a quit attempt than those in the abrupt and minimal treatment conditions. In the gradual condition, for every

week delay to quit date the probability of lapsing increased by 19%. In a secondary analysis of this study, **Hughes 2011** – found that 57% of the gradual group had either quit after their planned date or did not make a quit attempt at all, which was somewhat higher than those in the abrupt (29%) and control (33%) group.

Etter's 2009 + RCT tested whether starting nicotine gum four weeks before the quit date alongside reducing the number of cigarettes per day improved abstinence rates compared to starting gum on the quit date. The authors reported that after 12 months, 9.2% of participants were still using nicotine gum daily. These values were similar in both groups.

Cinciripini 1995 + reported on withdrawal symptoms and tension during the quit week. From quit week through the follow-ups (except Week 7), scheduled reduced participants experienced significantly fewer withdrawal symptoms than the other groups, who did not significantly differ from each other (no data provided). During the quit week (Week 5), scheduled reduced participants reported the least amount of tension and non-scheduled non-reduced participants reported the most. Thereafter, tension scores fell for all groups, but those for scheduled reduced participants remained significantly below the others from Week 8 through the 6 month follow-up. The remaining groups did not differ (no data provided).

Evidence Statements:

8.1 There is moderate evidence from one large well conducted RCT (**Hughes 2010 ++**) to suggest that gradual reduction may be associated with a decreased likelihood of making a quit attempt, and that delaying the quit attempt may lead to an increased risk of relapse. However it should be noted that the overall difference in 6-month quit rate from abrupt versus gradual NRT-aided cessation was not statistically significant (see statement 1.1). For every week delay to quit date the probability of lapsing increased by 19%. In a secondary analysis of this RCT (**Hughes 2011–**) 57% of the gradual group had either quit after their planned date or did not make a quit attempt at all, which was somewhat higher than those in the abrupt (29%) and control (33%) groups, although this relationship was not tested statistically.

8.2 There is weak evidence from one RCT in relation to NRT (**Etter 2009 +**) suggesting that there is no increased risk of long term use when NRT is first used as an aid to reduction compared to when it is used simply as an aid to abrupt cessation. After 12 months 9.2% of participants were using nicotine gum daily and values were similar in both groups.

8.3 There is weak evidence from one RCT (**Cinciripini 1995 +**) that people cutting down to quit using a scheduled reduced approach experience fewer withdrawal symptoms in quit and post-quit weeks and less tension in the quit week compared to the other reduction approaches tested (no data provided).

This evidence partially applicable to people in the UK since the studies were community based and are feasible in UK settings.

Comparison with two previous systematic reviews

Authors of two systematic reviews found within the literature search aimed specifically to look at cutting down to quit interventions (**Lindson 2010**, **Wang 2008**). Both studies were unpicked for relevant primary studies as well as being briefly summarised here.

The systematic review by **Wang 2008** considered seven studies. The authors noted that no RCTs specifically addressing cutting down to quit were identified (search to July 2006) but inclusion criteria were broad enough to include some reduction studies. Two of the included RCTs remain unpublished and five appear to meet the inclusion criteria for the long-term harm reduction review, review 3, and are being considered within that review (Batra 2005, Bolliger 2000, Etter 2004, Rennard 2006, Wennike 2003).

Lindson 2010 carried out a systematic review of ten studies (3,760 participants) of reduction prior to quitting versus abrupt quitting. The literature search was completed in November 2009. Pharmacotherapy, self help and behavioural support were all considered. None of the studies reviewed by Wang 2008 were included in the review.

Of the studies considered by Lindson 2010, two remain unpublished (Jerome 1999, Riley 2005), one was published in Spanish (Roales-Nieto 1992) and three were published before 1990 (Flaxman 1978, Curry 1988, Cummings 1988) and are thus excluded from this review. The four remaining studies are all considered in the results section of this review (**Cinciripini 1995**, **Etter 1999**, **Hughes 2009** [now published **2010/11**] and **Gunther 1992**.

Lindson 2010 found that neither reduction nor abrupt quitting was found to have superior abstinence rates at six months or more when all the studies were combined in a meta-analysis (RR=0.94, 95% CI 0.79, 1.13). This was the case regardless of whether pharmacotherapy was used (RR=0.87, 95% CI 0.65, 1.22), studies included behavioural support (RR=0.87, 95% CI 0.64, 1.17) or self-help therapy (RR=0.98, 95% CI 0.78, 1.23). Authors were unable to draw conclusions about the difference in adverse events between interventions from the intervention studies examined.

They concluded that reducing cigarettes smoked before quit day and quitting abruptly, with no prior reduction, produced comparable quit rates; therefore patients can be given the choice to quit in either of these ways. Reduction interventions can be carried out using self-help materials or aided by behavioural support, and can be carried out with the aid of pre-quit NRT. They also proposed further research to investigate which method of reduction before quitting is the most effective, and which categories of smokers benefit the most from each method.

Supplementary evidence from four smoking cessation studies with data on pre-quit reduction

Following discussion with NICE, four studies that did not meet inclusion criteria for the review have been retained for information since they contained data that might be of contextual interest on pre-quit reduction (**Brown 2003, Cropsey 2011, Hughes 1999, Hughes 2004**).

The interventions were designed for smoking cessation (rather than as cut down to quit). However they provide some outcome data on pre-quit reduction. As the studies are outside the systematic review they are not discussed in the results section or detailed in the Evidence Tables (Appendix A); but data are provided in Appendix H.

One was a non randomised study (**Brown 2003**) and three were secondary analyses of RCTs (**Cropsey 2011, Hughes 1999, Hughes 2004**) and thus have considerable potential for bias.

Brown 2003 looked at the effect of motivational interviewing (MI) to support smoking cessation in adolescent smokers hospitalised for psychiatric and substance use disorders in the US. The authors concluded that MI might be more effective for adolescents with little or no intention to change their smoking habits, but less so for those with pre-existing intentions to cut down or quit.

Cropsey 2011 carried out an NRT and behavioural smoking cessation intervention for female prisoners in the US. This secondary analysis measured the differences in smoking success based on any pre-quit reduction by participants in the 6-month wait-listed group. Smokers who showed no pre-quit reduction had significantly lower quit rates early in cessation treatment but there were no differences at long term follow up (12 months).

Hughes 1999 carried out a secondary analysis of a huge smoking cessation trial (COMMIT) by analysing 1410 subjects who smoked at both baseline and 2-year follow up. The odds ratio for successful cessation at 4 years for those who had reduced smoking by ≥ 50% at 2-years, compared to those who had increased their smoking by ≥ 5% was not significant.

Finally **Hughes 2004** conducted a secondary analysis of 1722 participants in the Lung Health Study. All had early lung disease and were still smoking at 1-year follow up. Overall they found that reduction predicted neither an increased nor a decreased probability of future cessation. Of subjects who did not reduce smoking at 1 year, 3% had quit by year 5. Of those who had reduced by 75-99% at year 1, 4% had quit by year 5. Relapse was common. In all cases (no reduction and various % reduction groups) quit rates at 2 years were higher than those at 5 years (see Appendix H for details).

5. DISCUSSION

This systematic review found few intervention studies that were designed to look specifically at cut down to quit interventions. Furthermore, those studies varied considerably in methodology, in the interventions used, the outcomes measured and the participant populations.

The quality of the included studies was moderate at best. Only two studies were rated as having a low risk of bias (**Hughes 2010 ++**, **Shiffman 2009 ++**) and four were rated as being significantly biased (**Gunther 1992 –**, **Jimenez-Ruiz 2009 –**, **O'Leary Tevyaw 2007 –, Riley 2002 –**); as was a secondary analysis of the Hughes 2010 data (**Hughes 2011 –)**.

The two RCTs of highest quality involved the use of NRT (**Hughes 2010** ++ and **Shiffman 2009 ++**). Lead authors of both studies had strong ties to manufacturers of smoking cessation products and **Shiffman 2009 ++** was funded and co- authored by a pharmaceutical company. Authors clearly 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.

Even in the relatively small number of included studies, there was a wide variation in the range of outcomes; both in timeframes (four weeks to twelve months) and assessment methods (self-reported, CO or cotinine verified). Furthermore, there did not appear to be consistency even within methods. CO measures to assess abstinence varied from ≤5ppm to ≤10ppm across the different studies. If the debate on this topic is to move forward, outcome measures need to be agreed and standardised.

Participant motivation was sometimes difficult to ascertain and few studies were in participants who wanted to quit but did not want to do so abruptly. For this reason, the scope of the review was extended to include all individuals who participated in a cut down to quit study.

Only one study was conducted in the UK (**Marks 2002 +**), and it is difficult to assess how applicable the other studies are likely to be although it seems reasonable to assume community-based programmes in the USA and Europe are feasible within a UK setting. Some interventions had significant resource implications (12 hours counselling for **Gunther 1992 –**, eight clinic visits for **Jimenez-Ruiz 2009 –**, incentive payments for **O'Leary Tevyaw 2007 –**, and/or very specific populations (alcoholics in **Martin 1997 +**, US high school students in **O'Leary Tevyaw 2007 –** and **Riley 2002 –**).

In light of the huge design variation between the studies included in this review, meta-analyses were not considered appropriate. Consequently, the results of the analyses carried out for this review are provided in Appendix I for information, although they are not discussed in the main body of the text. In a recent Cochrane review **Lindson 2010** did undertake meta-analyses for their collection of studies and their results are summarised in Section 4.9.

Despite the differing approaches to analysis by statisticians and the differences in included studies, the narrative findings of this review and that by **Lindson 2010**, which looked specifically at gradual versus abrupt quitting, both indicate there is no evidence of difference between gradual reduction and abrupt cessation methods.

Overall, the data suggest it is reasonable to give those who are looking to give up smoking the choice of whether they cut down gradually or quit abruptly. Also to provide choice over the method of reduction (scheduled, over a short or long time period). However, these conclusions need to be set against the findings from **Hughes 2010 ++**. This study suggests a reduction approach may allow smokers to delay their quit attempts and increase the likelihood of relapse. There are indications that NRT support may enhance the ability of smokers to quit abruptly over purely behavioural approaches.

Although some study samples were from disadvantaged groups there was very little evidence on differential impact between groups.

Although there is useful contextual information from the studies which is likely to be enhanced in due course by the findings from the long term reduction review (Review 3) and barriers and facilitators review (Review 4), further research is clearly needed: more high quality studies that are adequately powered with consistent outcome measures to help answer the questions of what techniques work best and for whom (both in terms of participant motivation and particular population groups).

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No further studies were identified that had not already been evaluated for this review.

APPENDIX A – INCLUDED STUDIES - EVIDENCE TABLES

First author and year: Cinciripini 1994 **Aim of study:** To compare the efficacy of scheduled smoking reduction with a minimal self-help treatment control **Study Design :** Individual quasi-randomised controlled trial **Quality score:** + **External validity score:** +	**Setting:** Texas, USA (developed) **Participants:** 34 smokers (19 males, 15 females) recruited through newspaper and radio advertisements. Subjects had no history of a psychiatric disorder or major medical illness. All participants smoked more than one packet of cigarettes a day. Mean age was 43.5 years in group 1 (intervention) and 38.2 years in group 2 (control) **Inclusion:** Not specified. **Exclusion:** Not specified Participants' motivations unknown	**Method of allocation:** Block randomisation – successive sequences of five subjects were alternately assigned to the two groups **Intervention(s):** Eight weekly sessions consisting of baseline, cessation, and relapse prevention phases. Baseline: participants self-monitored smoking and the total hours spent awake. Cessation (3 weeks): participants progressively increased inter-cigarette intervals, thereby gradually reducing total daily intake of nicotine. Participants were expected to quit on a target date at the end of this period. Relapse prevention: behavioural rehearsal of non-smoking skills in a relapse prone environment. **Control:** Participants given American Cancer Society "I Quit Kit" and participated in a one-hour discussion on use of the kit, which advocated a 7-day reduction to quit schedule. **Sample sizes:** 34 (17 in each group): I = 8 males and 9 females C = 11 males and 6 females **Baseline comparisons:** Age, CPD, nicotine yield from cigarettes, and cotinine levels reported for each group at baseline but no comparisons to examine differences. **Study power:** No power calculation reported. **Intervention delivery:** Authors are university researchers	**Primary outcomes:** Self reported two week point prevalent CO-verified abstinence (< 8 ppm) at 6 and 12 months follow up. Other measures: Mean CPD weeks 1-4 and self reported 24-hour point prevalent CO-verified abstinence (< 7 ppm) at weeks 5 & 9. **Follow-up periods:** 6 and 12 months **Method of analysis:** χ^2 comparisons between the groups on percentage of subjects reporting abstinence at each assessment point.	**Primary:** At 12 months 7 out of 17 (41%) of the intervention group and 1 out of 17 (6%) of the control group were abstinent (χ^2=5.65, p<0.01). At 6 months 9 out of 17 (53%) of the intervention group and 1/17 (6%) of the control group were abstinent (χ2=6.90, p<0.01). Cigarettes per week in weeks 1-4 as mean (standard deviation): I: 21.39(9.33), 12.21(6.72), 8.02(3.43), 5.45(2.61) C: 27(6.76), 28.79(15.26), 26.71(11.37), 20(14.99). **Attrition:** At the 12 month follow-up period one person in each group was unable to provide CO verification of their abstinence status. The authors report that since both of these people were CO verified abstinent from the target quit date through to the 6 month follow-up, they were counted as abstainers at 12 months.	**Limitations (author):** An initial test of treatment efficacy and a larger scale replication would be necessary to allow for further confidence in the results. **Limitations (review team):** Inappropriate analysis – see attrition section. Very small sample size. Limited baseline data. Methods of analysis poorly defined, with no adjustment for multiple testing. Verification method unclear: text refers to CO_2 data (<8ppm); table refers to CO data (<7ppm) **Evidence gaps:** Would this kind of approach be effective in a larger and more representative sample? **Funding sources:** Texas Affiliate of the American Heart Association and the National Institute of Drug Abuse. **Applicable to UK?** A small study although this type of programme could be delivered in a UK setting.

First author and year: Cinciripini 1995 **Aim of study:** To compare the efficacy of scheduled and non-scheduled gradual and abrupt approaches to nicotine withdrawal (i.e. cessation) **Study Design :** Individual quasi-randomised trial **Quality score:** + **External validity score:** +	**Setting:** Galveston-Houston, USA (developed) **Participants:** 128 community dwelling daily smokers. Gender: 42% male, 58% female **Inclusion:** A 3-year smoking history; consumption of ≥ 15 cigarettes per day. No current cessation treatment, no current psychiatric disorder or uncontrolled systemic illness. **Exclusion:** Those with SCL-90-R (Symptom Check List-90—Revised) t scores > 65. Participants' motivations unknown.	**Method of allocation:** Not stated **Intervention(s):** Scheduled reduced (Group A) participants instructed to smoke only at specific times of the day, and inter-cigarette interval progressively lengthened. Non-scheduled reduced (Group B) participants gradually reduced number of cigarettes smoked per day but inter-cigarette interval was self-selected. Scheduled non-reduced (Group C) participants told to smoke at specific times of the day but no adjustment made to inter-cigarette interval or consumption frequency. **Control:** Non-scheduled non-reduced (Group D) participants received no manipulation of either smoking frequency or inter-cigarette interval. Cognitive behavioural training and relapse prevention advice given to all four groups. Cognitive behavioural training given in weeks 2-5. Meetings in weeks 5-9 emphasised maintenance for abstainers and cessation for others. **Sample sizes:** 128 participants, 32 in Group A, 33 in Group B, 31 in Group C, 32 in Group D. **Baseline comparisons:** No significant differences. **Study power:** No power calculation provided. **Intervention delivery:** Authors are university researchers	**Primary outcomes:** Primary and secondary outcomes were not specified. The main outcomes were smoking abstinence and tobacco consumption: these were measured using the Smoking Status Questionnaire (SSQ, developed for this study), abstinence verified with salivary cotinine (<14ng/ml) and expired CO (<6ppm). Withdrawal symptoms [Hughes (Minnesota) Withdrawal Symptoms Checklist], mood states [The Tension and Fatigue subscales from the Profile of Mood States] and self efficacy were also measured. **Follow-up periods:** 1, 6 and 12 months post treatment. **Method of analysis:** MANOVAs for tobacco consumption, with significant outcomes being followed by planned contrasts. Abstinence was evaluated using logistic regression analyses and $\chi 2$ comparisons. A series of planned contrasts were also conducted to compare both scheduled groups (Groups A and C) against both non-scheduled ones (Groups B and D).	**Primary:** Salivary cotinine verified abstinence rates at 12 months were 44% in group A, 18% in group B, 32% in group C, and 22% in group D ($p<0.05$). Cigarettes consumed and cotinine concentrations were significantly lower for all groups at 12 months than at baseline. Cotinine values (standard deviations) at 12 months were 132.8 (50.6) ng/ml for group A, 310.2 (201.4) for group B, 245.3 (190.6) for group C, and 289.6 (206.0) group D (significance values not reported). At six months cotinine verified abstinence rates were 41% (group A), 12% (group B), 29% (group C), and 13% (group D), ($p<0.001$). Cigarette consumption and cotinine fell significantly for all groups from baseline through to the quit week. Groups A and B (reduced groups) decreased consumption significantly more than groups C and D (non-reduced groups). Consumption in the quit week averaged 4.5 (group A), 7.4 (group B), 11.9 (group C), and 15.2 cigarettes per day (significance not reported). From quit week through the follow-ups (except Week 7), scheduled reduced participants experienced significantly fewer withdrawal symptoms than the other groups, who did not significantly differ from each other (no data provided). During the quit week (Week 5), scheduled reduced participants	**Limitations (author):** The authors did not identify any limitation **Limitations (review team):** Gaps in reporting of study design, eg unclear randomisation method and allocation, very little description of eligible and recruited populations. **Evidence gaps:** Study doesn't consider participants' preferences for gradual versus abrupt cessation or fixed versus non-fixed schedules. **Funding sources:** National Institute of Drug Abuse. **Applicable to UK?** Yes, potentially feasible.

				reported the least amount of tension and non-scheduled non-reduced participants reported the most. Thereafter, tension scores fell for all groups, but those for scheduled reduced participants remained significantly below the others from Week 8 through the 6 month follow-up. The remaining groups did not differ (no data provided). **Attrition:** Not reported	
First author and year: Etter 2009 **Aim of study:** To test whether starting Nicotine polacrilex gum 4 weeks before quit date improved abstinence rates compared to starting treatment on quit date. **Study Design :** Individual randomised controlled trial **Quality score** + **External validity score** ++	**Setting:** Geneva and Vaud Cantons of Switzerland (developed). **Participants:** 314 community dwelling daily smokers (≥ 15 cigs/day) aged ≥18. Gender: 64.9% men (I), 52.% (C) Age: 42.0 (I), 44.1 (C) Years of schooling: 14.5 (I), 14.7 (C) **Inclusion:** Participants had to be committed to quit at a pre-set future date and agree to chewing ≥ 10 pieces of nicotine gum per day. **Exclusion:** Exclusion criteria included lactation, current or planned pregnancy, unstable angina pectoris, and myocardial infarction or stroke in the past 3	**Method of allocation:** Computer-generated random numbers **Intervention(s):** Pre-cessation treatment group was given nicotine polacrilex gum (4mg unflavoured) for 4 weeks before and 8 weeks after target quit date and was recommended to decrease their cigarette consumption by 50% before quitting, although no schedule was specified **Control:** Nicotine polacrilex gum (4mg unflavoured) for 8 weeks after target quit date and was recommended to quit abruptly. Both groups were instructed to use ≥ 10 pieces of nicotine gum per day, sent a booklet and provided with the url for a smoking cessation website. **Sample sizes:** Eligible:349 Intervention: 154 Control: 160 **Baseline comparisons:** Balanced other than more men in	**Primary outcomes:** Abstinence (self report) and CPD at 3 days, 8 weeks. Abstinence (self report, salivary cotinine ≤10ng/ml, CO ≤10ppm) at 12 months **Follow-up periods:** 3 days, 8 weeks, 12 months post target quit date. **Method of analysis:** χ^2 tests and odds ratios to compare proportions.	**Primary:** At the 12 months survey there was no statistically significant difference: (24.0% [37 of 154] for biochemically validated 4-week quit rate for abrupt and 16.5% [18 of 109] for gradual, P=0.14). [8 week data also available.] Daily cigarette consumption during the week before the quit date, as reported on the 3-day survey, was lower in the pre-cessation treatment group than in the usual care group (12.4 vs 21.3 CPD; P<0.001). After 12 months, 9.2% of participants were still using NRT daily. Gum users chewed on average 5 pieces per day. These values were similar in both groups. **Attrition:** 11.8% attrition at 12 month survey; 16.1% for salivary cotinine measures; 44.5% CO for those with +ve cotinine. Results at 12 months not significant. No process info on optimal period, schedule or SES. No 'serious' adverse events reported during treatment.	**Limitations (author):** • Target quit date was delayed by two months. • One third of participants in the pre-cessation treatment group quit abruptly and a few in the other group quit gradually. **Limitations (review team):** No power calculation or blinding. **Evidence gaps:** Comparison between gum and patch in this setting. **Funding sources:** Grant 3200-067835 from the Swiss National Science Foundation. Nicotine gum provided at no charge by Pfizer. The Institute of Social and Preventive Medicine (Etter) received funding from Novartis and Pfizer to develop internet-based smoking cessation

	months. Patients with substance use disorder or a psychiatric condition and those with a dental or mouth problem were excluded if indicated by a physician.	control **Study power:** No power calculation provided. **Intervention delivery:** Authors are university researchers			programs. Etter and Cornuz have acted as advisers to Pfizer. **Applicable to UK?** Yes
First author and year: Etter 2011 **Aim of study:** To compare abrupt and gradual smoking cessation. **Study Design :** Individual randomised controlled trial **Quality score:** + **External validity score:** +	**Setting:** French language internet website: stop-tabac.ch **Participants:** 974 daily smokers aged ≥18 who were interested in quitting and responded to a website survey. **Inclusion:** No preference for abrupt or gradual cessation. Commit to quit as requested. Respond to follow up surveys. **Exclusion:** Declined data storage. Former/non/daily/never smoker. Did not provide email address.	**Method of allocation:** Computer-generated randomised numbers. **Intervention(s):** Group 1: Sent the instruction (on the web page and by e-mail) to quit abruptly and immediately. Group 2: Sent the instruction to gradually reduce their cigarette consumption by half over the next 2 weeks and then quit. They received by e-mail an individually tailored calendar sent by email with target cigarette consumption for each day of the next 2 weeks. For each participant, the computer calculated a linear reduction in cig./day, ending with a 50% reduction on the day before the target quit date. **Sample sizes:** Eligible: 19,025 Of these 974 participants did not have a preference for gradual or abrupt quitting and so were randomised as follows: Immediate quit: 472 Reduce and quit: 502 (Those who did have a preference were allocated to their preferred group; separate analyses were done for these participants). **Baseline comparisons:**	**Primary outcomes:** Quit rate at follow-up **Follow-up periods:** Two and four weeks after target quit date. **Method of analysis:** χ^2 tests to compare proportions and Kruskal–Wallis χ^2 tests to compare medians. Data were analyzed "intention to treat" (including all participants and counting dropouts as smokers).	**Primary:** Abstinence rates were similar between abrupt and gradual groups for all follow-up durations (This outcome was unchanged when data were analyzed separately in subgroups defined by dependence level, craving, motivation, confidence, depression, method used for last quit attempt, age or sex). At 4 weeks: abrupt 8.7% of abrupt and 8.8% of gradual smokers reported no puff in past 24 hours (χ^2 0.0, p=0.97). 3.0% and 4.4% respectively reported no puff in past 4 weeks (χ^2 1.4, p=0.24). [Two week results are also reported] **Attrition:** Not stated, although the authors note it was high. An ITT analysis was conducted.	**Limitations (author):** Study conducted in visitors to a smoking cessation website who were highly motivated to quit. Sample contained more women and heavier smokers. Drop-out rates were high. No biochemical verification of abstinence. Short term results only. **Limitations (review team):** Authors do not report whether respondents were using any method(s) of support to quit. **Evidence gaps:** Lack of long term evidence **Funding sources:** The study received no external funding. Etter consulted for Pfizer, a manufacturer of smoking cessation medications, in 2006–2007 (on the Swiss varenicline advisory board), and received medications for a clinical trial from Pfizer in 2006. **Applicable to UK?** Yes

		No comparison between groups. **Study power:** Calculated that 950 participants would provide sufficient power at 80% with a significance level of 0.05, based on an expected quit rate of 20% in the abrupt group and on the assumption that abrupt would be more effective than gradual with a risk ratio of 1.4. **Intervention delivery:** Not stated. Author is an academic.			
First author and year: Gunther 1992 **Aim of study:** To determine if the sudden cessation method is more successful than the gradual method in addictive smokers with regard to a relapse during the follow-up period of 1 year. **Study Design :** Individual randomised controlled trial **Quality score:** – **External validity score:** +	**Setting:** Community-based smokers' counselling centre, Austria. **Participants:** 110 smokers who consulted the counselling centre between Feb-Dec 1988. **Inclusion:** Psychiatrist-determined nicotine dependence as per DSM- III-R. Value of ≥6 on the Fagerstrom Questionnaire **Exclusion:** Patients with psychiatric disorders and medical illness (especially cardiac diseases or cancer) Participants' motivations unknown.	**Method of allocation:** Computer generated randomisation list. **Intervention(s):** Group 1: Sudden withdrawal Group 2: Gradual withdrawal All patients were treated in individual sessions by a behaviour therapist. They received 12 hours of counselling of which the first hour was used for history-taking. Group 1: Patients were made familiar with self-control techniques in the first five sessions after history-taking and a date was agreed for sudden cessation. After the date had been fixed, the remaining five sessions were used for follow-up treatment. [*Note: this appears to add to a maximum of 11 sessions*] Group 2: the number of cigarettes was reduced in the gradual withdrawal therapy. Depending on the initial consumption, the number of cigarettes per week was reduced by 5- 10 cigarettes. Parallel to this, the patients were taught techniques of behaviour therapy and cognitive self-control.	**Primary outcomes:** Self-reported abstinence at 12 months and time of relapse **Secondary outcomes:** Self-reported cigarette consumption **Follow-up periods:** End of therapy and 12 months post therapy. **Method of analysis:** Wilcoxon test comparing groups for cigarette consumption at end of therapy and 12 month follow-up. Abstinence and time of relapse were compared by χ^2test. Kruskal-Wallis test to compare smoking behaviour of groups prior to the start of the therapy, and CPD at start of therapy and 12 month follow-up.	**Primary:** At 12 months follow-up, 51.85% of group 1 (sudden withdrawal) and 38.71% of group 2 (gradual withdrawal) reported abstinence. The difference is not significant. Those who relapsed started using nicotine again 2.31±1.96 months after the end of therapy in group 1, and 4.29±2.84 months after the end of therapy in group 2 (χ^2=0.36, p value not reported) **Secondary:** Data for cigarette consumption at 1-year follow-up showed that patients in group 1 smoked significantly more per day than patients in group 2. (25.39± 8.53 and 18.47 ±8.17 CPD respectively, p≤.05)). Comparison of cigarette consumption at baseline and at 12 month follow-up in each group showed that for group 1 there was no significant difference between the two time points (27.08±7.21 and 25.39±8.53, W=0.34, n.s.), whereas for group 2 the number of cigarettes smoked at follow-up was significantly	**Limitations (author):** No biochemically validated measures of abstinence **Limitations (review team):** No baseline data for participants. No power calculation. No ITT – analysis based on 58/110 who completed therapy and responded to questionnaire. **Evidence gaps:** None reported. **Funding sources:** Not reported. **Applicable to UK?** Yes but length of therapy period is not current practice.

		Successful clients of both groups subsequently had three additional booster sessions at monthly intervals. CO levels were measured regularly. Urinary cotinine levels were determined in the last therapeutic session and at the follow-up appointments. **Sample sizes:** 110 eligible patients of the 148 treated in the counselling centre in the timeframe. 55 allocated to each group. **Baseline comparisons:** No comparisons reported. **Study power:** No power calculation reported. **Intervention delivery:** Smoking counselling centre behaviour therapists.		less than at baseline (27.47±12.33 and 18.47±8.17, W=0.0001, p≤.01). **Attrition:** 20 did not become totally abstinent within the 12 weeks of therapy; 4 discontinued therapy prematurely; 3 did not attend the booster sessions; 1 refused the therapy recommended. Analysis relates to 82 persons remaining: 42 clients in group I and 40 in group II. 58 responded to questionnaire: Group 1: 27; Group 2: 31	
First author and year: Hughes 2010 Hughes 2011 (secondary analysis) **Aim of study:** To compare gradual cessation vs. abrupt cessation vs. minimal treatment among smokers who wanted to quit and preferred to quit gradually. **Study Design :** Individual randomised controlled trial. **Quality score:**	**Setting:** USA (Columbia and Florence, SC and Albuquerque, NM) **Participants:** 746 community dwelling adults 46% male; 46 (+/- 13) years old; 82% white, 10% black/African American, 8% other, 13% classed as Hispanic; 47% married, 38% divorced, widowed, separated, 16% never married; 9% below high school, 60% high school, 31%	**Method of allocation:** Concealed **Intervention(s):** Smokers who wished to quit were randomised to one of two intervention arms or a control arm. The intervention arms were (a) gradual cessation counselling and nicotine lozenges to reduce prior to quitting (n=297), (b) abrupt cessation counselling (n=299). **Control:** Brief advice (n=150) Participants in the gradual group were asked to set a quit date between 3 and 5 weeks after the study initiation; those in the abrupt and control groups were asked to set a quit date between	**Hughes 2010 primary outcomes:** Prolonged and point prevalence abstinence (past 7 days) by self report at each follow up time. Reported abstinence at 6 months, verified by CO sample (<10 ppm). CO verified reduction in smoking levels; self-report for: nicotine dependence, disrupted pattern of smoking, self-efficacy for resisting smoking, motivation to quit, confidence in ability to qui, perceived difficulty in quitting, preference for quitting method. **Method of analysis:**	**Primary:** No statistical difference at 6 month CO verified prolonged abstinence. Odds ratio for gradual vs abrupt = 0.6 (95% CI: 0.3, 1.2) Smokers in the gradual condition were less likely to make a quit attempt, defined as ≥ 1 day of not smoking, than those in the abrupt and minimal treatment conditions (48% vs 64% vs 60%, $\chi 2=15.9$, $p < .001$). In the gradual condition, for every week delay to quit date increased the probability of lapsing by 19% ($p<0.001$) NB The authors noted that the type of schedule used (formal schedule, giving up 'easiest' cigarettes first, giving up 'hardest' cigarettes first)	**Limitations (author)** **Hughes 2010:** Lack of power in study; Abrupt group may have had more traditional behavioural support. Gradual condition received more pre- and fewer post-cessation calls than the abrupt condition but overall number was the same. Counselling time in the gradual condition was spent on teaching rather than coping mechanisms. Longer reduction time. Patch instead of lozenge. Authors question validity of

++ (Hughes 2010) **External validity score:** +	college graduate. **Inclusion:** ≥18-year-old smokers of ≥ 15 CPD; want to quit smoking in the next 30 days and prefer to quit gradually rather than abruptly; no change in cigarettes/day by ± 20% or more in the last month; willing to use nicotine lozenge; no FDA caution for use of lozenge requiring physician contact. **Exclusion:** None provided Participants wanted to quit gradually.	1 and 3 weeks from the study onset. All participants were sent a booklet and nicotine lozenges to use starting on their pre quit (for the gradual group) or quit date (for the abrupt or brief advice group) and for up to 12 weeks post quit date. **Sample sizes:** N=746 (297 gradual cessation, 299 abrupt cessation, 150 minimal treatment) **Baseline comparisons:** Differences in marital status and confidence in quitting – adjusted in analysis and did not affect results. **Hughes 2011:** 1.Time to planned quit date among 720 participants (97%) who set a quit date. 2.Time to actual quit date (first day of abstinence) among the 508 participants (68%) who made a quit attempt. 3.Among those who made a quit attempt (508), whether participants quit on or after the planned quit date. **Study power:** Hughes 2010: not provided only stated that lower than expected. Hughes 2011 did not appear to conduct a power calculation. **Intervention delivery:** University researchers	Baseline characteristics compared using χ^2 tests for categorical variables and analysis of variance or the Kruskal-Wallis test for continuous variables. Abstinence outcomes and quit attempts were analyzed bi-variately using χ^2 tests, with assessment of possible confounding variables and interactions performed via logistic regression. **Hughes 2011 primary outcomes:** 1.Never making a quit attempt. 2.Not quitting (≥1 day of abstinence) by or on the planned quit date. 3.Probability of early lapse (any smoking) within the first 12 weeks. 4.Not achieving 7-day point-prevalent abstinence at 6 months. **Method of analysis:** Secondary analysis of data subsets. Logistic regression was used to obtain odds ratios for dichotomous outcomes. Proportional hazards regression provided hazard ratios for the analysis of probability of an early lapse, with time to lapse as the survival variable. All analyses for the combined sample adjusted for experimental condition by including design variables for the conditions as covariates in	did not make a difference and the results were pooled. **Attrition:** Response rate 76-79% at six months but ITT analysis used and non respondents assumed to be smokers. **Hughes 2011** 1. The relationship between time to the planned quit date and never making a quit attempt was significant for the **abrupt condition** (χ^2 = 8.9, p = .003) but not for the **gradual condition** (χ^2 = 3.8, p = .05) 2. 57% of the **gradual** group either quit after their planned date or did not make a quit attempt at all, which was somewhat higher than those in abrupt (29%) and control (33%) groups. No formal comparison between groups was made. 3. The relationship between time to planned quit date and the probability of lapsing early was significant within both the **gradual** (χ^2 = 4.8, p = .03) and **abrupt** (χ^2 = 5.2, p = .02) conditions. Those who quit after their planned quit date were more likely **t**o lapse early on than those who quit on their quit date both within the **abrupt** (χ^2 = 5.7, p = .02) and **brief advice** (χ^2 = 8.0, p = .005) groups. This finding was not significant for the **gradua**l group. 4. No relationship was found between time to planned quit date, time to actual quit date, or quitting after versus on quit date and 6 month abstinence for any of	self-reports as approx 50% of those reporting abstinence did not agree to CO test or their test result was high. **Limitations (review team):** Lack of power calculation. **Evidence gaps:** Need for more RCTs of gradual v abrupt. **Hughes 2011** **Limitations (author):** Identified differences may be due to baseline differences in motivation in those choosing shorter vs longer delays till quitting. Participants self-selected delayed versus immediate cessation, rather than being randomised. Secondary analysis using subsets of data from the original study. **Limitations (review team):** As above. **Evidence gaps:** Further replications of study findings (delaying a quit attempt in smokers trying to quit is associated with worse outcomes) are needed. **Funding sources both papers:** Grant DA-017825 (JH), Senior Scientist Award DA-00490 (JH) and Institutional Training Grant DA-07242

			the models. Odds ratios and hazard ratios quantified the increased probability of the worse outcome for each 1-week delay. **Follow-up periods:** 2 weeks, 4 weeks, 6 weeks, 3 months, and 6 months after the quit date set by the participant at study onset.	the intervention groups or for the combined sample.	(EP) from the US National Institute on Drug Abuse. Hughes: Research grants from Pfizer; honoraria or consulting fees from companies that develop, sell or promote smoking cessation products or services including Abbot Pharmaceuticals; Acrux; Aradigm; EPI-Q, Evotec; Exchange Limited; Free and Clear; Glaxo-Smith Kline; Golin Harris; Healthwise; McNeil Pharmaceuticals; Novartis Pharmaceuticals; Oglivy Health PR, Pfizer Pharmaceuticals; Pinney Associates; Propagate Pharmaceuticals. Xenova. All other authors have nothing to declare. **Applicable to UK?** Yes noting country differences
First author and year: Jiménez-Ruiz 2009 **Aim of study:** To examine the outcome of a programme of progressive reduction, using nicotine gum, as a prelude to complete cessation among current smokers who sought treatment in	**Setting:** Smokers' Clinic Madrid, Spain **Participants:** 116 smokers, 70 (60%) men and 46 (40%) women; Age 45.7 (+/- 12.65) years **Inclusion:** Current smokers aged ≥18 who wanted to quit but not abruptly. **Exclusion:** None stated	**Method of allocation:** Uncontrolled study therefore no allocation **Intervention(s):** The programme comprised two phases: 16 weeks of progressive reduction preceding complete cessation, followed by an abstinence phase of 6 months. The reduction phase involved eight clinic visits which included cognitive behavioural therapy. Smokers were instructed to use nicotine gum at recommended levels based on according to their	**Primary outcomes:** Continuous abstinence, defined as not even a puff, verified by an expired CO level of ≥10ppm. **Secondary outcomes:** Numbers reducing consumption by 50% at week 8. Numbers having successfully quit by week 16. Also reported adverse events. **Follow-up periods:** Weeks 8 and 16 after baseline. 3 and 6 months after the quit date.	**Primary:** Continuous abstinence rates were 39% at the 6 month follow-up and 44% at 3 months. At six months differences in abstinence rates within subgroups were not significant (48% in the group wanting to use reduction to quit compared to 32% in the refractory group, p=0.8). **Secondary:** At the end of week 8 68% achieved reduction in consumption of ≥50%. By the target quite date 57% achieved complete cessation.	**Limitations (author):** No comparison group. Selection bias - outcomes in smokers who chose to follow a progressive reduction programme. All smokers received psychological and pharmacological treatments free of charge. **Limitations (review team):** As above. **Evidence gaps:** None reported.

smokers' clinic but who did not want to quit abruptly. **Study Design :** Uncontrolled before and after study **Quality score:** - **External validity score:** -	Participants wanted to quit gradually.	baseline cigarette consumption in week 1, with a target of progressively reducing CPD. By the end of week 8 the target was a reduction of ≥50%, with abstinence by week 16 Smokers who had not quit by Week 16 were discharged from the programme. Two groups of smokers were compared: those who went to the clinic wanted to quit but not abruptly, and refractory smokers, who had failed to quit several times and who were advised to follow a progressive reduction programme. **Control:** No control group **Sample sizes:** 116 participants in total, 50 (43%) asking for progressive reduction treatment, and 66 (57%) refractory smokers **Baseline comparisons:** No statistically significant differences between the two groups. **Study power:** No power calculation provided. **Intervention delivery:** Authors based in smokers' clinic at the Institute of Public Health in Madrid.	**Method of analysis:** Not stated.	Point prevalence abstinence rate at week 16 was higher among smokers who had successfully reduced by half at week 8 compared with those who had failed to reduce by half at week 8 (75% v. 19%, OR = 3.2, 95% CI = 2.12, 4.82; p<0.001). All smokers who had successfully quit at 16 weeks continued to use NRT into the abstinence phase but no subject used NRT for more than 4 months post quit date. **Attrition:** 80 (69%) completed the reduction phase and 59 (51%) completed the abstinence phase. Smokers who missed a visit or withdrew from the study were counted as smokers for the analysis, so follow-up data are presented for all 116 participants.	**Funding sources:** Department of Health of the Government of Madrid, Spain. CAJ-R consults for manufacturers of smoking cessation medications. **Applicable to UK?** A highly intensive programme and Expert Advisory Group indicate this is not likely to be feasible in the UK.
First author and year: Marks 2002 Sykes 2001 **Aim of study:** To test the effect of a self-help cognitive behavioural therapy programme for	**Setting:** Community-based smoking cessation clinic in deprived area of North London. **Participants:** 260 adults (no age data) who were recruited via posters and pamphlets in	**Method of allocation:** Interventions were randomly allocated to dates. When smoker phoned to volunteer the receptionist (blinded to intervention status) booked them into the first available date. **Intervention(s):** The QFL programme is an 'eclectic combination' of 30 cognitive	**Primary outcomes:** Participants' self-reported point prevalence abstinence at six months (post intervention) validated by CO. **Secondary outcomes:** 7-day point prevalence abstinence (confirmed by CO for 74% of reports);	**Primary:** *Note: 12 month results (Marks 2002) relate to 116/131 in the intervention group and 104/129 in the control group.* *6 month results (Sykes 2001) relate to 122/131 in the intervention group and 107/129 in the control group.* At 12 months 19.8% [23] (95% CI	**Limitations (author):** High pre-enrolment drop out (88%) suggests that participants were highly motivated. Only 25% of those who volunteered by phone booked in, and only 50% of those attended the first session.

smokers 'Quit for Life' (QFL) in comparison with control treatment 'Stopping Smoking Made Easier' (SSME). **Study Design :** Individual quasi-randomised controlled trial **Quality score:** + **External validity score:** ++	GP waiting rooms, pharmacies and a library notice board; also local newspaper story about successful quitters. 28% from manual occupations; 14% unemployed; 64% female **Inclusion:** Participants who phoned the clinic to volunteer and appeared at the first session. **Exclusion:** No exclusion criteria. Participants' motivations unknown but had all contacted the smoking cessation clinic	behavioural and other relevant methods in a self-help package consisting of a handbook (also provided as a cassette tape with relaxing music on the other side), reduction cards, a progress chart and other necessary materials. The aims are gradual reduction over 7-10 days, by offering a choice of psychological support methods which guide the smoker towards a daily reduction of 50%. The programme also provides relapse prevention support post quit date, to three months. **Control:** SSME is a pocket sized leaflet recommending a staged preparation with an abrupt cessation date and recommendations to phone the national 'quitline', GP or health centre for further support. **Sample sizes:** Eligible: 2080 Intervention: 131 Control: 129 **Baseline comparisons:** Balanced **Study power:** No power calculation reported **Intervention delivery:** University researchers	Cigarettes per day ≥25% less than baseline for at least 4 weeks **Follow-up periods:** 6 months after the intervention (not clear if start date or quit date) **Method of analysis:** X2 and % difference with 95% CI.	13.0, 28.3) participants in the in the QFL group were abstinent compared to 5.8 % [6] (95% CI 2.1, 12.1) in the SSME group. P<0.0001 At 6 months, 17.2 % (95% CI 11.0, 25.1) participants in the QFL group were abstinent compared to 5.6 % (2.1, 11.8) in the SSME group. P<0.0001 **Secondary:** 11.5% (95% CI 6.4, 18.5) had reduced CPD+ by ≥25% compared to 0% 71.3 % (62.4, 79.1) had made no change compared to 94.4% (88.2, 97.9). Abstinence and reduction rates were analysed separately for: • Male vs female • Participants in SES groups I-IIIN and IIIM-V and SES groups I vs V. There were no statistically significant differences (figures not provided). **Attrition:** 15% at 12 months.	**Limitations (review team):** No power calculation; CO confirmation for 74% of reports only. No maximum level of CO ppm was specified) and it appears that those who had ≥10ppm CO levels were considered abstinent. No ITT analysis. Authors are suppliers of the QFL (cognitive behavioural) intervention. **Evidence gaps:** Further investigation of free cognitive behavioural therapy combined with free NRT in a community setting. **Funding sources:** Not reported **Applicable to UK?** Yes
First author and year: Martin 1997 **Aim of study:** Martin: To evaluate the effect of three specially adapted	**Setting:** San Diego, California **Participants:** 205 community dwelling recovering alcoholics ≥18 M: 113; F 92 Mean age 41.8	**Method of allocation:** Not stated **Intervention(s):** 1. Standard treatment [ST] – modified American Lung Assn (ALA 1986) 20-day quit program, followed by four weeks of maintenance counselling	**Primary outcomes:** Quit status using point-prevalence rates at 6- and 12-month follow-ups, and continuous abstinence at the 1-week post-treatment quit point. Participants were coded	**Primary:** Verified mean quit rate at 6 months ST = 21% BEX = 29% BNIC = 27% Verified mean quit rate at 12 months ST = 26%	**Limitations (author):** No control group and standard treatment has been adapted extensively to incorporate a behavioural support component similar to

smoking treatment and maintenance programs in recovering alcoholic smokers. **Study Design :** Quasi-randomised trial of three interventions (no control group) **Quality score:** + **External validity score:** +	Ethnicity: 92.7% Caucasian Mean years of education 14.6 Married with partner 30% Employed 95% **Inclusion:** Report significant histories of alcohol abuse and dependence with ≥ 3 months of alcohol and drug abstinence. Consume average of ≥10 CPD Provide physician permission to use nicotine gum or undertake moderate physical activity **Exclusion:** Use of psychotropic medications or any physical disabilities that would hinder engaging in a program of moderate physical activity. Participants' motivations unknown.	and of attendance at three Nicotine Anonymous (NA) meetings per week. Quit program comprised four weekly 60-75 minute group sessions covering self-monitoring, relaxation, urge control instruction, relapse prevention training and quit contracts, and three large-scale smoking rate reductions by one third each week prior to target quit date (week 4), in addition to facilitated group discussions. Participants were instructed to quit smoking at week 4 and requested to attend Nicotine Anonymous meetings 3x per week. 2. Behavioural counselling plus exercise [BEX]. Eight weekly, 60-75 min sessions, using a more gradual reduction schedule and treatment delivery adapted for recovering alcoholic smokers. Former smoker group "mentors" were employed to adapt the language and techniques of the behavioural interventions and group discussions to 12-step recovery processes. From week 8, moderate aerobic exercise prescriptions including on-site moderate-to-brisk walking, around an outdoor track, and use of exercise equipment, progressing from 15 to 45 min, and thrice weekly home exercise of a similar nature. 3. Behavioural counselling plus NRT [BNIC] Counselling similar to the BEX Group was combined with free post-quit nicotine gum (2mg) throughout maintenance. Participants were instructed to chew between one and six pieces of nicotine gum through the day, as prophylaxis or on strong	as non-smokers if they reported not smoking within the previous 24 hr (7 days for 1-week post-treatment measure) and had CO levels < 10 ppm. If CO data were not available, an informant verified that the participant was not smoking. Participants gave details of two informants – one each from their home and work environments. Results report only verified smoking status. **Follow-up periods:** Post treatment, 6 and 12 months. **Method of analysis:** Chi-square analysis was performed at each time point on the verified quit status.	BEX = 27% BNIC = 27% No differences were statistically significant at 6 or 12 months I week rates also reported. **Attrition:** **N**ot reported	treatments for groups 2 and 3. **Limitations (review team):** Three interventions with multiple components – no control/standard treatment. Authors only report percentage quit rates. They go up between 6 and 12 months in ST group. This is not discussed. **Evidence gaps:** None reported. **Funding sources:** Grant No. 2RT0053 from the California Tobacco-Related Disease Research Program. **Applicable to UK?** Limitations particularly around Nicotine Anonymous which has very little UK presence.

		urges. All participants continuing nicotine gum use beyond 3 months post-quit were systematically faded from its use by 6 months post-quit. In addition a treatment deposit of $50 was collected initially from all participants. Deposits were returned contingent on session attendance and completion of homework assignments. All three groups received instructions to reduce the number of cigarettes smoked prior to target quit date. The target quit date was week 4 for the TS group, and week 8 for the two other groups. **Control:** No control group **Sample sizes:** ST = 70, BEX = 72, BNIC = 63 **Baseline comparisons:** Significant differences between BNIC group and the other two groups in two measures: number of years abstinent from alcohol and drugs, and employment status. The authors do not report whether these factors were adjusted for in the analyses. **Study power:** No power calculation reported **Intervention delivery:** **ST**: Trained, PhD-level, and master's level smoking health educators **BEX**: Doctoral- and master's-level group co-leaders with ≥1 year of experience co-facilitating at least two former treatment groups using the techniques under supervision. **BNIC** Behavioural counselling similar to			

		the BEX Group			
First author and year: O'Leary Tevyaw 2007 **Aim of study:** To investigate the efficacy and feasibility of a contingency management* (CM) protocol for adolescent smokers that included use of a reduction phase. ***Rewards for response **Study Design :** Individual partial randomised controlled trial **Quality score:** – **External validity score:** –	**Setting:** US high schools in Providence RI. **Participants:** 23 students. 19 analysed - 52.6% female, 74% white, 21% other, 5% native American, age 16.4 ± 1.2 **Inclusion:** Aged 14-18 with CO ≥10ppm at baseline. Did not need to be motivated to quit. **Exclusion:** None stated. Participants did not need to be motivated to quit.	**Method of allocation:** Randomisation using sealed envelopes **Intervention(s):** One week reinforcement for attendance to encourage provision of CO samples (RA); one week washout and one week contingency management (CM). Order of weeks was counterbalanced (RA/washout/CM and CM/washout/RA). Vouchers (for use at local shopping mall) for CO samples based on amount of CO reduction (contingency management). Participants were also randomised during the CM phase to reductions followed by abstinence (CM-reduction). **Control:** Participants were randomised in the CM phase to reinforcement for abstinence only (CM-abstinence). **Sample sizes:** N=23 but 2 deemed ineligible after enrolling and 2 missed 3+consecutive readings and excluded, leaving 19. Non random distribution to phase: RA/washout/CM: 7 CM/Washout/RA: 12 Random distribution to condition: CM-reduction: 10 CM-abstinence: 9 **Baseline comparisons:** No statistically significant differences - very wide confidence intervals **Study power:** No power calculation reported **Intervention delivery:**	**Primary outcomes:** C O readings (≤5ppm denoting abstinence). **Secondary outcomes:** **Follow-up periods:** Three week intervention (randomisation at CM stage in third week), with two weeks post-intervention follow up. **Method of analysis:** % abstinent readings	**Primary:** Participants randomised to the CM-abstinence condition had a similar percentage of abstinent readings in the CM and RA phases (59% vs 48%). Participants in the CM-reduction condition tended to have more abstinent readings in the CM phase than in the RA phase (50% vs 37%). **Attrition:** 93% attendance at scheduled visits.	**Limitations (author):** None reported. **Limitations (review team):** Very small study with complex permutations. Analysis on only 19/23 students. Results could have been by chance. **Evidence gaps:** Further exploration of the effect of introducing reinforcement for attendance prior to administration of contingency management. **Funding sources:** Not stated **Applicable to UK?** Unlikely. US high school setting. Large incentive payments (subjects could earn up to $185)

		University researchers			
First author and year: Riley 2002 **Aim of study:** To modify a smoking cessation programme that uses computerized scheduled gradual reduction (The LifeSign programme) for use with adolescent smokers and to test the feasibility of this cessation approach in group support and minimal contact modalities. **Study Design :** Two uncontrolled before and after studies **Quality score:** - **External validity score:** -	**Setting:** USA Local area high schools in Fairfax County, Virginia (different schools for each study). **Participants:** High school students Study 1: 17 students, 47% female, 82% Caucasian, mean age 16.7 (SD 0.72) Study 2: 18 students, 72% female, 83% Caucasian, mean age 16.1 (SD 0.86) **Inclusion:** Self report ≥7 CPD, desire to quit smoking, no current use of smokeless tobacco or NRT **Exclusion:** None stated	**Method of allocation:** Study 1: Volunteers recruited by the school Vice-Principal following 30 min lunchtime information meeting. Study 2: Response to posters and announcements in school. **Intervention(s):** Study 1: 7 weekly 30 min support meetings by health educator. After week 1 computer prompted cigarette use on a scheduled gradual reduction lasting 10-28 days, depending on initial use and on adjustments for difficulties following the schedule. Study 2: Computer scheduled reduction as per Study 1 but modified as per marketing class feedback from previous study. No weekly meetings; one mid-point contact after 3 weeks. **Control:** No control. **Sample sizes:** Study 1: 17; Study 2: 18 **Baseline comparisons:** Not applicable (uncontrolled) **Study power:** Not provided **Intervention delivery:** Authors are developers computerised interventions or university researchers.	**Primary outcomes:** Both studies: Self report and CO-corroborated (≤10 ppm) 7-day abstinence. Self reported CPD. **Follow-up periods:** Study 1: Post-treatment at 7 weeks. Study 2: Post-treatment at 7 weeks and 1 year follow-up phone interviews with CO-validation for those reporting abstinence. **Method of analysis:** % and CPD (standard deviation).	**Primary:** Study 1: Post-treatment 5 (29%) were 7-day abstinent and 10 (59%) had reduced CPD by ≥50%. Among non-quitters an overall self reported reduction of CPD from 12.5 (SD 4.6) to 7.0 (SD 6.4). Study 2: Post-treatment 3 (17%) were 7-day abstinent. Among non-quitters there was a 43% self reported reduction in CPD from 11.4 (SD 7.8) to 6.5 (SD 5.8). At 1-year follow up, 7 claimed ongoing abstinence but only two provided samples for CO-verification, reducing the validated quit rate to 11%. Mean CPD for ongoing smokers was 9 (SD 4.4); a 2.5 mean CPD increase from the post-treatment rate. **Attrition:** Study 1: 15/17 (88%) completed post-treatment evaluation. 5 reporting 7-day abstinence were corroborated by CO. Study 2: 17/18 (94%) completed post-treatment evaluation. 3 reporting 7-day abstinence were corroborated by CO. At one year 7 reported 7-day abstinence but CO validation only for 2 subjects (29%).	**Limitations (author):** Small sample sizes severely limit generalisability. Groups were quite different and no direct comparisons can be made between the two delivery modalities. No control group. **Limitations (review team):** Feasibility studies only and methodologically very weak. Authors work for company that has commercial interests in developing computerised smoking cessation products. **Evidence gaps:** Need for a large scale controlled trial with long-term follow-up. **Funding sources:** Partial funding from the National Cancer Institute of the National Institutes of Health. Several authors work for a company that develops computerised smoking cessation products. **Applicable to UK?** No. Not generalisable beyond the very small populations studied.
First author and year:	**Setting:** 27 study sites across the	**Method of allocation:** Self selected for dose of NRT, then randomised via computer generated	**Primary outcomes:** 28 day self-reported continuous abstinence, verified	**Primary:** 28 days continuous abstinence for NRT vs placebo(95% CI):	**Limitations (author):** • Lack of information on

Shiffman 2009 **Aim of study:** To test the efficacy of nicotine gum in facilitating cessation through gradual reduction. **Study Design :** Individual randomised controlled trial **Quality score** ++ **External validity score** +	USA. **Participants:** 3297 US smokers interested in quitting gradually, community-recruited via print and radio advertisements. ≥18 years. 57% women. Circa 97% white, circa 76% had some college education, income data provided (but dates of intervention unclear- although funding commenced pre-2001) Participants interested in quitting gradually.	randomisation scheme **Intervention(s):** NRT gum at 2 mg or 4 mg (as selected by patient) plus instruction to extend time to first cigarette (using gum) by one hour each day. **Control:** As above, with placebo gum **Sample sizes:** 6923 eligible participants screened; of whom 3297 enrolled. 1636 selected 2 mg gum 1661 selected 4mg gum. Allocation: 2mg active 819 2mg placebo 817 4mg active 830 4 mg placebo 831 **Baseline comparisons:** Balanced **Study power:** No power calculation reported but a large study **Intervention delivery:** Authors are university researchers and pharmaceutical company	by CO ≤10 ppm. **Secondary outcomes**: Reduction in smoking, achievement of initial abstinence (24 hrs) and abstinence at 6 months verified by two CO readings, with an average of ≤10 ppm. **Follow-up periods:** 24 hour, 28 day and 6 months following first day of abstinence during cut-down period (up to 8 weeks) Cigarettes per day, serum thiocyanate, gum use, adverse events measured during cut down periods. During weeks 1-8 42.4% of participants reported an adverse event with those on active gum more likely to report than those on placebo (48.2% vs 36.6%; p<0.001). Most common events were nausea, hiccups and heartburn. For gastrointestinal symptoms figures for active vs placebo gum were26% vs 14.5% (p<0.001) and 12% vs 8.6% (p=0.002) for respiratory symptoms. **Method of analysis:** Cochran-Mantel-Haenszel tests controlled for study site and dose. Odds ratios and 95% CI	Overall OR = 2.83 (1.10, 3.1) 2mg OR = 2.0 (1.4, 2.9) 4mg OR = 4.7 (2.8, 7.7) **Secondary:** 6 months continuous abstinence for NRT vs placebo: Overall OR = 2.86 (1.93, 4.24) 2mg OR = 1.8 (1.1, 2.9) 4mg OR = 6.0 (2.9, 12.3) [Also OR data for 24 hours abstinence and smoking reduction at 2 weeks] **Attrition:** Not possible to calculate	subjects screened out of participation (to help assess generalisability?) • Some groups excluded (eg those with cardiovascular disease) **Limitations (review team)** • Not possible to assess attrition • Concerns about drug company involvement in write up. **Evidence gaps:** None reported **Funding sources:** Funded by SmithKline Beecham (now GlaxoSmithKline) Consumer Healthcare. One author employed by GSK; two are consultants to the company and one has a financial interest in the development of new NRT medications. **Applicable to UK?** Seems feasible

APPENDIX B: SUMMARY OF QUALITY APPRAISAL – INCLUDED STUDIES

Key to headings (brief summary from Appendix F, NICE 2009): 1.1 Source population described; 1.2 Eligible population representative of source ; 1.3 Selected population representative of eligible; 2.1 Population described; 2.2 Intervention/comparison described; 2.3 Allocation concealed; 2.4 Blinded; 2.5 Exposure adequate; 2.6 Contamination low; 2.7 Other interventions similar in groups; 2.8 All participants accounted for; 2.9 Setting reflects UK practice; 2.10 Intervention reflects UK practice; 3.1 Reliable outcomes; 3.2 Complete outcomes; 3.3 Important outcomes assessed; 3.4 Relevant outcomes; 3.5 Similar follow up times; 3.6 Meaningful follow up; 4.1 Groups similar at baseline; 4.2 ITT used; 4.3 Sufficient power; 4.4 Estimates of effect size given; 4.5 Appropriate analysis; 4.6 Precision; 5.1 Internally valid; 5.2 Externally valid; ++ Minimal bias; +Bias unclear; - Risk of bias; nr Not reported; na Not applicable

Author Year	Study design	Population			Method of allocation to intervention (or comparison)										Outcomes						Analyses						Summary	
		1.1	1.2	1.3	2.1	2.2	2.3	2.4	2.5	2.6	2.7	2.8	2.9	2.10	3.1	3.2	3.3	3.4	3.5	3.6	4.1	4.2	4.3	4.4	4.5	4.6	5.1	5.2
Cinciripini 1994	Quasi RCT	–	+	nr	+	++	–	–	+	++	nr	++	+	+	++	++	++	++	++	++	nr	–	–	++	+	–	+	+
Cinciripini 1995	Quasi RCT	–	nr	nr	nr	++	nr	–	++	++	++	nr	++	++	++	+	++	++	++	++	+	++	nr	++	++	+	+	+
Etter 2009	RCT	++	+	++	++	++	++	–	+	+	+	+	++	++	++	+	++	++	++	++	+	++	nr	++	++	++	+	++
Etter 2011	RCT	++	+	+	++	++	++	++	++	++	++	–	++	++	–	+	+	++	++	–	–	++	++	++	++	++	+	+
Gunther 1992	RCT	nr	nr	nr	++	+	++	nr	++	++	+	–	+	+	–	–	+	++	++	++	nr	–	nr	++	++	+	–	+
Hughes 2010	RCT	++	++	+	++	++	++	+	++	++	++	+	++	++	++	+	++	++	++	++	++	++	–	++	++	++	++	+
Hughes 2011	SA	++	+	++	–	na	–	–	na	na	na	na	++	++	+	na	++	++	++	++	na	–	–	+	++	+	–	+
Jiménez-Ruiz 2009	UBA	+	+	+	–	++	–	–	na	na	na	–	–	+	++	++	++	++	na	++	na	++	nr	++	nr	++	–	–
Marks 2002	Quasi RCT	++	++	+	+	++	na	+	++	++	++	++	++	++	++	–	++	++	++	++	++	–	nr	++	+	++	+	++
Martin 1997	Quasi RT	++	++	+	+	++	nr	nr	++	++	++	–	+	+	+	nr	++	++	++	++	+	++	nr	++	++	+	+	+
O'Leary Tevyaw 2007	Partial RCT	–	+	–	++	+	++	+	+	nr	++	++	+	–	++	+	++	++	++	–	+	++	–	–	–	–	–	–
Riley 2002	UBA	+	+	na	na	+	na	na	+	na	na	+	–	+	+	+	++	++	na	–	na	–	nr	++	+	–	–	–
Shiffman 2009	RCT	++	+	+	++	++	++	++	++	++	++	++	++	++	++	+	++	++	++	++	++	++	++	++	++	++	++	+

RCT = individual randomised controlled trial SA = Secondary analysis; UBA = UBA = uncontrolled before and after study; RT = randomised trial, no control group (interventions only)

APPENDIX C: EXPERT ADVISORY GROUP

Dr Julie Bishop	Consultant in Public Health and currently Acting Director of Health Improvement for Public Health Wales.
Ms Elen de Lacy	Newly appointed Chief Executive of ASH Wales, following a role as Research and Policy Manger.
Dr Keir Lewis	Senior Lecturer at Swansea University and Honorary Respiratory Consultant to the Hywel Dda Health Board, Wales, UK.
Professor Laurence Moore	Professor of Public Health Improvement at Cardiff University, and Director of DECIPHer, a UKCRC Centre Public Health Research Excellence
Ms Helen Poole	Secondary care smoking cessation counsellor at the University Hospital of Wales.
Dr Marianne van den Bree	Reader at Cardiff University in the Department of Psychological Medicine and Neurology.

APPENDIX D: REVIEW TEAM

Staff/Resource Description	Role
Ms Ellie Byrne, CISHE, Cardiff University	Study selection
Dr Ben Carter, North Wales Clinical School, Cardiff University	Statistical analysis including meta-analysis and advice
Mr Andrew Cleves, CEDAR	Technical advice
Ms Fiona Morgan, SURE, Cardiff University	Project management, searching, study selection, quality assessment, data extraction, narrative synthesis and report writing.
Dr Helen Morgan, SURE, Cardiff University	Searching study selection, quality assessment, data extraction
Ms Ruth Turley, SURE, Cardiff University	Study selection, quality assessment, data extraction
Dr Alison Weightman, SURE, Cardiff University	Project Director. Searching, study selection, quality assessment, data extraction and report writing.
Dr Sarah Whitehead, CISHE, Cardiff University	Study selection, quality assessment, data extraction and report writing.

APPENDIX E: SEARCH STRATEGY

The search strategy below was used for effectiveness and barrier/facilitator reviews. It was designed for the Ovid MEDLINE(R) database 1966 to August Week 1 2011 and was adapted for use in the other databases listed in section 2.1.1.

1. Smoking Cessation/ or exp Smoking/ 112950
2. ((Nicotine adj4 (therapy or gum* or inhal* or replace* or lozenge* or tablet* or microtab* or nasal spray* or patch* or delivery device* or delivery system* or gel*)) or ((smok* or tobacco or nicotine or cigarette*) adj10 NRT)).ti,ab. 3472
3. 1 and 2 2800
4. (exp smoking/ or smoking cessation/) and harm reduction/ 156
5. nicotine/th 2
6. (Cigarette* adj2 substitut*).ti,ab. 40
7. ("electronic cigarette*" or e-cigarette* or ecigarette* or ecig* or e-cig* or Intellcig).ti,ab.27
8. (vaping or (personal adj4 vapori?er)).ti,ab. 3
9. (Nicotine adj4 (therapy or gum* or inhal* or replace* or lozenge* or tablet* or microtab* or nasal spray* or patch* or delivery device* or delivery system* or gel*)).ti,ab. 3465
10. (Pastille* and (smok* or tobacco or nicotine or cigarette*)).ti,ab. 0
11. (Nicorette or Nicotinell or Niconil or NiQuitin or Polacrilex or Habitrol or Nicabate or NicoDerm or Nicotex or Nicotrol or ProStep or Quickmist).ti,ab. 195
12. ((Stoppers or Commit or pharmacotherap*) adj3 (smok* or tobacco or nicotine or cigarette*)).ti,ab. 372
13. (Stubit or super-25).ti,ab. 0
14. (pharmacotherapy/ or drug therapy/) and (smok* or tobacco or nicotine or cigarette*).ti,ab. 198
15. (((pre-quit or prequit or "Stop/start" or abstain* or abstinence or reduc* or declin* or quit* or stop* or cess* or cease* or cut down or giv* up) adj4 (smok* or tobacco or cigarette*)) and nicotine).ti,ab. 5085
16. or/3-15 6746
17. *counseling/ or *directive counseling/ or behavior therapy/ or cognitive therapy/ or Self help groups/ 50185
18. (advis* or advic* or counsel* or help line* or helpline* or self help or selfhelp or ((behavio?r* or group or cognitive) adj (support or therap*))).ti,ab. 128768
19. (((mobile or cell*) adj (phone*1 or telephone*1)) or (SMS or short message service or text messag* or instant messag* or videomessag* or video messag* or multimedia messag* or web or internet or computer* or e-mail* or email* or electronic mail* or mailing list*)).ti,ab. 239196
20. *internet/ or *cellular phone/ or *User-computer interface/ or Therapy, Computer-assisted/mt 33263
21. or/17-20 408269
22. smoking cessation/ or ((pre-quit or prequit or "Stop/start" or abstain* or abstinence or reduc* or declin* or quit* or stop* or cess* or cease* or cut down or giv* up) adj4 (smok* or tobacco or cigarette*)).ti,ab. 29968
23. 21 and 22 5821
24. 16 or 23 10954
25. randomized controlled trial.pt. 313813
26. controlled clinical trial.pt. 83155
27. clinical trial.pt. 466468
28. trial.ti,ab. 272946
29. randomi?ed.ti,ab. 279552

30. Random allocation/ or ((randomly adj1 (allocat$ or assign$)) or placebo-controlled or placebo group).ti,ab. 185061
31. "controlled before and after".ti,ab. 331
32. (time adj series).ti,ab. 10470
33. quasi-experiment*.ti,ab. 3683
34. Control groups/ or Evaluation studies as topic/ or ((evaluation or intervention) adj3 (control group or controlled or study or program* or comparison or "before and after" or comparative)).ti,ab. 164284
35. (pre test or pretest or pre-intervention or post-intervention or posttest or post test).ti,ab. 14740
36. ((systematic* adj1 review) or meta analys*).ti,ab. or meta-analysis/ 60586
37. "mixed methods".ti,ab. 999
38. or/25-37 1034277
39. 24 and 38 3685
40. (interviews or interview or interviewed or qualitative or ethnograph* or thematic analysis or grounded theory).ti,ab. 233563
41. ((perception* or perceive* or attitude* or view*1 or viewpoint* or standpoint* or encounter* or experience* or story or stories or narrative*1 or description* or theme* or opinion* or need*1) adj3 (survey* or questionnaire*)).ti,ab. 12123
42. ((field or case) adj (stud* or research)).ti,ab. 46844
43. Focus groups/ or Qualitative research/ or Interviews as topic/ or Questionnaires/ or Interview, Psychological/ or ((focus or discussion) adj group*1).ti,ab. 293785
44. process evaluation/ or process evaluation.ti,ab. 871
45. or/40-44 509964
46. 24 and 45 2094
47. 39 or 46 5125
48. animal/ not (animal/ and human/) 3568174
49. 47 not 48 5112
50. (letter or editorial or historical article).pt. 1269683
51. 49 not 50 5082
52. limit 51 to (english language and yr="1990 - Current") 4468

APPENDIX F: LIST OF INCLUDED STUDIES

Cinciripini, P.M., Lapitsky, L.G., Wallfisch, A., Mace, R., Nezami, E, Van Vunakis, H. 1994. An evaluation of a multicomponent treatment program involving scheduled smoking and relapse prevention procedures: initial findings. *Addictive Behaviors*, 19, (1) 13-22

Cinciripini, P.M., Lapitsky, L., Seay, S., Wallfisch, A., Kitchens, K., Van Vunakis, H. 1995. The effects of smoking schedules on cessation outcome: can we improve on common methods of gradual and abrupt nicotine withdrawal? *Journal of Consulting & Clinical Psychology*, 63, (3) 388-399

Etter, J.-F. 2011. Comparing abrupt and gradual smoking cessation: A randomized trial. *Drug and Alcohol Dependence*, 118, (2-3) 360-365

Etter, J.F., Huguelet, P., Perneger, T.V., Cornuz, J. 2009. Nicotine gum treatment before smoking cessation: a randomized trial. *Archives of Internal Medicine*, 169, (11) 1028-1034

Gunther, V., Gritsch, S., Meise, U. 1992. Smoking cessation--gradual or sudden stopping? *Drug & Alcohol Dependence*, 29, (3) 231-236

Hughes, J.R., Solomon, L.J., Livingston, A.E., Callas, P.W., Peters, E.N. 2010. A randomized, controlled trial of NRT-aided gradual vs. abrupt cessation in smokers actively trying to quit. *Drug & Alcohol Dependence*, 111, (1-2) 105-113

Hughes, J.R. & Callas, P.W. 2011. Is delaying a quit attempt associated with less success? *Nicotine & Tobacco Research*, e-text ahead of print

Jiménez-Ruiz, C.A., Ulibarri, M.M., Besada, N.A., Guerrero, A.C., Garcia, A.G., Cuadrado, A.R. 2009. Progressive reduction using nicotine gum as a prelude to quitting. *Nicotine & Tobacco Research*, 11, (7) 847-850

Marks, D.F., Sykes, C.M. 2002. Randomized controlled trial of cognitive behavioural therapy for smokers living in a deprived are of London: Outcome at one-year follow-up. Psychology, Health and Medicine, 7, (1) 17-24

Riley, W., Jerome, A., Behar, A., Zack, S. 2002. Faesibility of computerized scheduled gradual reduction for adolescent smoking cessation. *Substance Use & Misuse*, 37, (2) 255-263

Martin, J.E., Calfas, K.J., Patten, C.A., Polarek, M., Hofstetter, C.R., Noto, J., Beach, D. 1997. Prospective evaluation of three smoking interventions in 205 recovering alcoholics: one-year results of Project SCRAP-Tobacco. *Journal of Consulting & Clinical Psychology*, 65, (1) 190-194

Shiffman, S., Ferguson, S.G., Strahs, K.R. 2009. Quitting by gradual smoking reduction using nicotine gum: a randomized controlled trial. *American Journal of Preventive Medicine*, 36, (2) 96-104

Sykes, C.M., Marks, D.F. 2001. Effectiveness of a cognitive behaviour therapy self-help programme for smokers in London, UK. *Health Promotion International*, 16, (3) 255-260

O'Leary Tevyaw, T.O., Gwaltney, C., Tidey, J.W., Colby, S.M., Kahler, C.W., Miranda, R., Barnett, N.P., Rohsenow, D.J., Monti, P.M. 2007. Contingency management for adolescent smokers: An exploratory study. *Journal of Child & Adolescent Substance Abuse*, 16, (4) 23-44

SYSTEMATIC REVIEWS

Lindson N, Aveyard P, Hughes JR. Reduction versus abrupt cessation in smokers who want to quit. Cochrane Database of Systematic Reviews 2010 Issue 3. 2010.

Wang D, Connock M, Barton P, Fry-Smith A, Aveyard P, Moore D. 'Cut down to quit' with nicotine replacement therapies in smoking cessation: A systematic review of effectiveness and economic analysis. Health Technology Assessment 12[2]. 2008.

APPENDIX G: EXCLUDED STUDIES WITH REASONS FOR EXCLUSION

Reference	Reason for exclusion
Adelman, W.P., Duggan, A.K., Hauptman, P., & Joffe, A. 2001. Effectiveness of a high school smoking cessation program. *Pediatrics*, 107, (4)	Smoking cessation study with no gradual reduction element.
Ames, S.C., Patten, C.A., Offord, K.P., Pennebaker, J.W., Croghan, I.T., Tri, D.M., Stevens, S.R., & Hurt, R.D. 2005. Expressive writing intervention for young adult cigarette smokers. *Journal of Clinical Psychology*, 61, (12) 1555-1570	Smoking cessation study with no gradual reduction element.
Aryanpour, M., Tarahomi, M., Heydari, G.R., Hesami, Z., Ramezankhani, A. 2009. The relation between exhaled carbon monoxide level and smoking cessation outcome. *Tanaffos*, 8, (3) 10-16	Smoking cessation study with no gradual reduction element.
Ashton, M., Miller, C.L., Bowden, J.A., Bertossa, S. 2010. People with mental illness can tackle tobacco. *Australian and New Zealand Journal of Psychiatry*, 44, (11) 1021-1028	Study includes some who wanted to cut down to quit, but data on reduction only. **To Review 3**
Audrain-McGovern, J., Stevens, S., Murray, P.J., Kinsman, S., Zuckoff, A., Pletcher, J., Moss, D., Baumritter, A., Kalkhuis-Beam, S., Carlson, E., Rodriguez, D., Wileyto, E.P. 2011. The efficacy of motivational interviewing versus brief advice for adolescent smoking behavior change. *Pediatrics*, 128, (1) e101-e111	Smoking cessation and reduction but no cut down to quit. **To Review 3**
Baker, A., Richmond, R., Haile, M., Lewin, T.J., Carr, V.J., Taylor, R.L., Jansons, S., Wilhelm, K., 2006. A randomized controlled trial of a smoking cessation intervention among people with a psychotic disorder. *American Journal of Psychiatry*, 163, (11) 1934-1942	Smoking cessation and reduction but no cut down to quit. **To Review 3**
Baker, A., Richmond, R., Lewin, T.J., Kay-Lambkin, F., Baker, A., Richmond, R., Lewin, T.J., Kay-Lambkin, F. 2010. Cigarette smoking and psychosis: naturalistic follow up 4 years after an intervention trial. *Australian & New Zealand Journal of Psychiatry*, 44, (4) 342-350	Smoking cessation and reduction but no cut down to quit. **To Review 3**
Beard E et al. (2011) Association between use of nicotine replacement therapy for harm reduction and smoking cessation: a prospective study of English smokers. Tobacco Control (2011). e-pub ahead of print 1 Dec 2011. doi:10.1136/tobaccocontrol-2011-050007	Study design: observational study. **To Review 4**
Brown, R.A., Ramsey, S.E., Strong, D.R., Myers, M.G., Kahler, C.W., Lejuez, C.W., Niaura, R., Pallonen, U.E., Kazura, A.N., Goldstein, M.G., Abrams, D.B. 2003. Effects of motivational interviewing on smoking cessation in adolescents with psychiatric disorders. *Tobacco Control*, 12 Suppl 4, IV3-10	Smoking cessation study with no gradual reduction element. **Study data captured in Appendix H** at the request of NICE since information provided on a vulnerable group

	(those with mental illness) though the study does not meet the inclusion criteria for this review.
Bullen, C., Whittaker, R., Walker, N., Wallace-Bell, M. 2006. Pre-quitting nicotine replacement therapy: findings from a pilot study. *Tobacco Induced Diseases*, 3, (2) 35-40	Smoking cessation study with no gradual reduction element.
Chalmers, K., Bramadat, I.J., Cantin, B., Murnaghan, D., Shuttleworth, E., Scott-Findlay, S., Tataryn, D. 2001. A smoking reduction and cessation program with registered nurses: findings and implications for community health nursing. *Journal of Community Health Nursing*, 18, (2) 115-134	Only potentially relevant data are available in a figure and could not be extracted. Attempts to contact the authors were unsuccessful.
Chou, K.R., Chen, R., Lee, J.F., Ku, C.H., Lu, R.B., Chou, K.R., Chen, R., Lee, J.F., Ku, C.H., & Lu, R.B. 2004. The effectiveness of nicotine-patch therapy for smoking cessation in patients with schizophrenia. *International Journal of Nursing Studies*, 41, (3) 321-330	Smoking cessation study with no gradual reduction element.
Cropsey, K.L., Jackson, D.O., Hale, G.J., Carpenter, M.J., Stitzer, M.L., Cropsey, K.L., Jackson, D.O., Hale, G.J., Carpenter, M.J., & Stitzer, M.L. 2011. Impact of self-initiated pre-quit smoking reduction on cessation rates: results of a clinical trial of smoking cessation among female prisoners. *Addictive Behaviors*, 36, (1-2) 73-78	Secondary analysis of subset of a smoking cessation study; the control group (intervention delayed for 6 months). Considers self selected reduction vs not reducing or increasing during the six months before receiving the intervention, on subsequent abstinence. **Study data captured in Appendix H** at the request of NICE since information provided on a vulnerable group (female prisoners) though the study does not meet the inclusion criteria for this review.
Eliasson, B., Hjalmarson, A., Kruse, E., Landfeldt, B., Westin, A. 2001. Effects of smoking reduction and cessation on cardiovascular risk factors. *Nicotine & Tobacco Research* (3) 249-255	Does not measure the effects of gradual reduction on cessation rates. Those that were not abstinent at the end of the intervention were removed from the analysis.
Etter, J.F., Laszlo E. 2007. Postintervention effect of nicotine replacement therapy for smoking reduction: a randomized trial with a 5-year follow-up. *Journal of Clinical Psychopharmacology* 27 (2) 151-5.	Long term reduction, not cut down to quit. **To Review 3.**

Fornai, E., Desideri, M., Pistelli, F., Carrozzi, L., Puntoni, R., Avino, S., Gustavsson, G., Sawe, U., Viegi, G., Giuntini, C. 2001. Smoking reduction in smokers compliant to a smoking cessation trial with nicotine patch. *Monaldi Archives for Chest Disease*, 56, (1) 5-10	Smoking cessation study with no gradual reduction element.
Glasgow, R.E., Gaglio, B., Estabrooks, P.A., Marcus, A.C., Ritzwoller, D.P., Smith, T.L., Levinson, A.H., Sukhanova, A., O'Donnell, C., Ferro, E.F., France, E.K. 2009. Long-term results of a smoking reduction program. *Medical Care*, 47, (1) 115-120	Smoking reduction study. Eligible participants were not interested in quitting. **To Review 3.**
Gulliver, S.B., Kamholz, B.W., Helstrom, A.W., Morissette, S.B., Kahler, C.W. 2008. A Preliminary Evaluation of Adjuncts to Motivational Interviewing for Psychiatrically Complex Smokers. *Journal of Dual Diagnosis*, 4, (4) 394-413	Smoking reduction not cut down to quit study. **To Review 3.**
Hovell, M.F., Zakarian, J.M., Matt, G.E., Liles, S., Jones, J.A., Hofstetter, C.R., Larson, S.N., Benowitz, N.L. 2009. Counseling to reduce children's secondhand smoke exposure and help parents quit smoking: a controlled trial. *Nicotine & Tobacco Research*, 11, (12) 1383-1394	Smoking cessation study with no gradual reduction element.
Hughes, J., Lindgren, P., Connett, J., Nides, M., Lung, H.S. 2004. Smoking reduction in the Lung Health Study. *Nicotine & Tobacco Research*, 6, (2) 275-280	Secondary analysis of a smoking cessation study. **Study data captured in Appendix H** at the request of NICE since information provided on a large population (Lung Health Study) though the primary study does not meet the inclusion criteria for this review.
Hughes, J.R., Cummings, K.M., Hyland, A. 1999. Ability of smokers to reduce their smoking and its association with future smoking cessation. *Addiction*, 94, (1) 109-114	Secondary analysis of a smoking cessation study. **Study data captured in Appendix H** at the request of NICE since information provided on a large population (COMMIT study) though the primary study does not meet the inclusion criteria for this review.
Hurt, R.D., Croghan, G.A., Beede, S.D., Wolter, T.D., Croghan, I.T., Patten, C.A. 2000. Nicotine patch therapy in 101 adolescent smokers: efficacy, withdrawal symptom relief, and carbon monoxide and plasma cotinine levels. *Archives of Pediatrics & Adolescent Medicine*, 154, (1) 31-37	Smoking cessation study with no gradual reduction element.
Ingersoll, K.S., Cropsey, K.L., Heckman, C.J. 2009. A test of motivational plus nicotine replacement interventions for HIV	Reduction but not cut down to

positive smokers. *AIDS & Behavior*, 13, (3) 545-554	quit. **To Review 3.**
Jolicoeur, D.G., Richter, K.P., Ahluwalia, J.S., Mosier, M.C., Resnicow, K. 2003. Smoking cessation, smoking reduction, and delayed quitting among smokers given nicotine patches and a self-help pamphlet. *Substance Abuse*, 24, (2) 101-106	Reduction and cessation but not cut down to quit. **To Review 3.**
Kilburn, K.H., Warshaw, R.H. 1990. Effects of individually motivating smoking cessation in male blue collar workers. *American Journal of Public Health*, 80, (Nov 90) 1334-1337	Smoking cessation study with no gradual reduction element.
Kralikova, E., Kozak, J.T., Rasmussen, T., Gustavsson, G., Le Houezec, J. 2009. Smoking cessation or reduction with nicotine replacement therapy: a placebo-controlled double blind trial with nicotine gum and inhaler. *BMC Public Health*, 9, 433	Reduction and cessation but not cut down to quit. **To Review 3.**
Ma, G.X., Fang, C., Shive, S.E., Su, X., Toubbeh, J.I., Miller, S., & Tan, Y. 2005. A culturally enhanced smoking cessation study among Chinese and Korean smokers. *International Electronic Journal of Health Education*, 8, 1-10	Smoking cessation study with no gradual reduction element.
May, R., Tofler, G.H., Bartrop, R., Heinrich, P., Baird, J., Jozefiak, E., & de Burgh, S. 2010. Smoking cessation through a novel behavior modification technique. *American Journal of Cardiology*, 106, (1) 44-46	Smoking cessation study with no gradual reduction element.
Nollen, N., Ahluwalia, J.S., Mayo, M.S., Richter, K., Choi, W.S., Okuyemi, K.S., Resnicow, K. 2007. A randomized trial of targeted educational materials for smoking cessation in African Americans using transdermal nicotine. *Health Education & Behavior*, 34, (6) 911-927	Smoking cessation study with no gradual reduction element.
Okuyemi, K.S., Thomas, J.L., Warren, J., Guo, H., Ahluwalia, J.S. 2010. Relationship between smoking reduction and cessation among light smokers. *Nicotine & Tobacco Research*, 12, (10) 1005-1010	Secondary analysis of retrospectively gathered data on reduction in year prior to study enrolment. Information is not related to the groups into which each participant was subsequently randomised.
Owen, L. 2000. Impact of a telephone helpline for smokers who called during a mass media campaign. *Tobacco Control*, 9, (2) 148-154	Smoking cessation study with no gradual reduction element.
Patten, C.A., Martin, J.E., Calfas, K.J., Brown, S.A., Schroeder, D.R. Effect of three smoking cessation treatments on nicotine withdrawal in 141 abstinent alcoholic smokers. *Addictive Behaviors*, 25, (2) 301-306	Sub-group analysis from later cohorts of Martin 1997 (an included study). No useable supplementary data since data are only available for approx 60% of group.
Poole, H. Pre-quit in practice: a No Smoking Day initiative. Presentation to National Smoking Cessation Conference.	Explorative observational

Glasgow June 2010. Available at http://www.uknscc.org/2010_UKNSCC/speakers/helen_poole.html [Accessed 24 October 2011]	rather than intervention study.
Rose, J.E., Behm, F.M., Drgon, T., Johnson, C., Uhl, G.R. 2010. Personalized smoking cessation: interactions between nicotine dose, dependence and quit-success genotype score. *Molecular Medicine*, 16, (7-8) 247-253	Smoking cessation study with no gradual reduction element.
Royce, J.M., Ashford, A., Resnicow, K., Freeman, H.P., Caesar, A.A., Orlandi, M.A. 1995. Physician- and nurse-assisted smoking cessation in Harlem. *Journal of the National Medical Association*, 87, (4) 291-300	Smoking cessation study with no gradual reduction element.
Schuurmans, M.M., Diacon, A.H., van, B., X, Bolliger, C.T. 2004. Effect of pre-treatment with nicotine patch on withdrawal symptoms and abstinence rates in smokers subsequently quitting with the nicotine patch: a randomized controlled trial. *Addiction*, 99, (5) 634-640	Smoking cessation study with no gradual reduction element.
Shoptaw, S., Rotheram-Fuller, E., Yang, X., Frosch, D., Nahom, D., Jarvik, M.E., Rawson, R.A., Ling, W. 2002. Smoking cessation in methadone maintenance. *Addiction*, 97, (10) 1317-1328	Smoking cessation study with no gradual reduction element.
Stewart, M.J., Kushner, K.E., Greaves, L., Letourneau, N., Spitzer, D., Boscoe, M., Stewart, M.J., Kushner, K.E., Greaves, L., Letourneau, N., Spitzer, D., & Boscoe, M. 2010. Impacts of a support intervention for low-income women who smoke. *Social Science & Medicine*, 71, (11) 1901-1909	Smoking cessation study with no gradual reduction element.
Sun, H.Q., Guo, S., Chen, D.F., Jiang, Z.N., Liu, Y., Di, X.L., Yang, F.D., Zhang, X.Y., Kosten, T.R., Lu, L. 2009. Family support and employment as predictors of smoking cessation success: a randomized, double-blind, placebo-controlled trial of nicotine sublingual tablets in chinese smokers. *American Journal of Drug & Alcohol Abuse* , 35, (3) 183-188	Smoking cessation study with no gradual reduction element.
Wennike, P., Danielsson, T., Landfeldt, B., Westin, A., Tonnesen, P. 2003. Smoking reduction promotes smoking cessation: results from a double blind, randomized, placebo-controlled trial of nicotine gum with 2-year follow-up. *Addiction*, 98, (10) 1395-1402	Smoking reduction study which did not require participants to quit. **To Review 3.**
Wojtyna, E.J. & Dosiak, M.M. 2009. Cognitive-behaviour therapy to enhancing self-esteem concerns improves smoking cessation outcome in patients with mental disorders: The pilot study. *European Psychiatry*, 24(Suppl 1) S709	Conference abstract only – no subsequent publication. Appears to be a cessation study with reduction outcomes but no data provided.

APPENDIX H: ADDITIONAL STUDIES

The following studies were identified during study selection. They have data that are potentially of interest and are included at the request of NICE. However, they were developed as smoking cessation studies not as cut down to quit studies, and therefore do not meet the review's inclusion criteria. As these studies are not part of the review, they have not been quality assessed. However, as three of the four studies are secondary analyses, they have significant potential for bias and would have been given a quality rating of - (minus).

First author and year: Brown 2003 **Aim of study:** To test the hypothesis that among adolescent smokers hospitalised for psychiatric and substance use disorders, motivational interviewing (MI) would lead to longer and more quit attempts, reduced smoking, and more abstinence from smoking over a 12 month follow up. **Study Design :** Non-randomised controlled study.	**Setting:** Private, university-affiliated psychiatric hospital in Rhode Island, USA **Participants:** Consecutive sample of 191 adolescents admitted for psychiatric hospitalisation. **Inclusion:** Age 13-17 years, smoking ≥1 cigarettes per week for past 4 weeks; access to a telephone. **Exclusion:** Meeting DSM-IV criteria for current psychotic disorder. Also recent violent behaviour, current participation in another study, uncertain guardianship status, having a sibling in the study, language incompatibility, living too far away, cognitive or hearing impairment.	**Method of allocation:** In cohorts to avoid potential contamination - planned randomisation of cohorts but recruitment ended before completion **Intervention(s):** MI in two 45-minute therapist delivered individual sessions, if possible during hospital stay, plus 6 brief monthly telephone sessions post discharge for participants and 4 for their parents. **Control:** Brief advice (BA): 5-10 minutes of advice and information on how to quit smoking; The "I Quit!" self help pamphlet. Smoking was banned in hospital and 26% participants elected to use NRT as in-patients. Participants in both conditions with quit intentions were offered 8-weeks transdermal nicotine patch upon hospital discharge. All were paid in gift certificates for their participation.	**Primary outcomes:** 7-day point prevalent abstinence, quit attempts, changes in smoking rate (monthly average) and longest quit attempt. Reported abstinence verified by salivary cotinine (≤15 ng/ml) and CO (<10 ppm) at 1, 6 and 12 month visits. **Secondary outcomes:** Proximal outcomes were intent to change smoking behaviour on discharge and self efficacy for smoking cessation. **Follow-up periods:** 1, 3, 6, 9, 12 months **Method of analysis:** x^2 for abstinence comparison. To examine frequency and length of longest quit attempt - Hierarchical linear modelling and generalised estimating equation (GEE). Baseline measures as covariates.	**Primary:** At 12 months follow up 7-day point prevalent abstinence was: MI 14.0% BA 9.9% At 6 months % were: MI 13.3% BA 8.5% All p>0.30. Across the whole follow up period the odds of abstinence was not significantly associated with receiving motivational interviewing compared to brief advice: OR=1.16 (p=0.68). **Secondary:** MI increased self efficacy compared to BA and appeared more effective for adolescents with little/no intention to change smoking but less so for those with pre-existing intention to cut down or quit. All effects were modest. **Attrition:** Not reported although authors state that rates of missing data were not significantly different between groups. Of 369 patients meeting inclusion criteria 147 refused to participate.	**Limitations (author):** High participant refusal rate (147/369 = 39.8%). Could not generalise outside adolescent participants with psychiatric/substance use disorders. **Limitations (review team):** Study designed as a cessation intervention and not cut down to quit. Large number of exclusions which may limit generalisability. No baseline data. No attrition or power calculation reported. **Evidence gaps:** Further exploration of participant self efficacy and intentions in relation to the potential effectiveness of MI. **Funding sources:** Not reported **Applicable to UK?** Marginal, though MI and BA interventions both feasible. Private hospital setting and participants were paid.

		Sample sizes: Screened: 1099 Eligible: 369 Intervention - 116 Control - 75 **Baseline comparisons:** No data provided though authors reported no significant differences. **Study power:** No power calculation reported **Intervention delivery:** Authors were university researchers, some with hospital affiliations.			
First author and year: Cropsey 2011 **Aim of study:** To measure differences in cessation success based on smokers' self-initiated pre-quit reductions in cigarettes per day. **Study design :** Secondary analysis of data from a randomised controlled trial. **Primary study report:** Cropsey K, Eldridge G, Weaver M, Villalobos G, Stitzer M, Best A. 2009. Smoking cessation intervention for female prisoners: addressing an urgent	**Setting:** Medium-maximum security prison in the South Eastern USA **Participants (Original study)** 539 female prisoners (250 intervention; 289 control) **For this analysis:** 179 women from the original study control group which had been waitlisted for 6 months, prior to receiving an NRT (nicotine patches) and behavioural therapy smoking cessation intervention. Reduction group: 43% white, 46% black; 34% less than high school, 41% high schools, 26% some college education, mean age 33.1. No reduction group: 48% white, 50% black; 28% less than high school, 41% high school,	**Method of allocation:** Secondary analysis of participants who self-selected to reduce smoking or retain/ increase smoking rates pre-cessation intervention. **Intervention(s):** Following 6 month wait-list, 10 week NRT and behavioural intervention, Mood Management Training to Prevent Smoking Relapse, modified for correctional setting. **Control:** N/A **Sample sizes:** Reduction: 77 No reduction: 102 **Baseline comparisons:** No significant differences other than reduction group	**Primary outcomes:** Self reported CPD and seven day point prevalence abstinence confirmed by CO (≤2 ppm). Follow-up periods: 10 weekly visits during intervention plus 3, 6 and 12 months post intervention. **Method of analysis:** Between-group comparisons were carried out using X^2 and ANOVA analyses. Generalised Estimating Equation (GEE) to estimate long term impact of pre-quit cigarette reduction.	**Primary:** Smokers who showed no pre-quit reduction had significantly lower quit rates early in cessation treatment compared to those who had reduced prior to quitting, although the differences between the groups were not maintained either at the end of treatment or during the follow up points. X2 (GEE) for reduction group across time = 28.29 (p=0.003). 12 months: 13% reduction group; 11% no reduction group. 6 months: 13% reduction group; 14% no reduction group. [*Results provided by author*] **Attrition:** Not applicable. Post hoc analysis of completers. Though 20% of the screened group did not sign consent and 30% of the randomized group did not start the intervention.	**Limitations (author):** Lack of a scheduled reduction condition so not applicable to interventions where subjects are instructed to reduce; Self initiated smoking reduction may serve as a motivational marker although no baseline state of change measure difference. **Limitations (review team):** Secondary (post hoc) analysis of a cessation study; Cutting down to quit was not intervention aim. **Evidence gaps:** Study specifically designed to explore pre-quit reduction. **Funding sources:** National Institutes of

public health need. *American Journal of Public Health* 98(10) pp 1894-901.	31% some college education, mean age 33.2. **Inclusion:** Aged 18+, smoking ≥5 CPD, in general prison population (not isolation) and with a desire to quit. **Exclusion:** Allergy to nicotine, less than one year left of sentence, non-English speaking, serious mental illness, mental retardation or cognitive impairment that would limit ability to consent.	had higher CPD (18.5 vs 14.9, p 0.01) **Study power:** Not provided **Intervention delivery:** Authors are university researchers			Health/National Institute on Drug Abuse. **Applicable to UK?** Likely - with similar prison populations.
First author and year: Hughes 1999 **Aim of study:** To examine whether cigarette smokers in the United States can significantly reduce their smoking and retain this reduction and, if so, whether this predicts an increase or decrease in the probability of smoking cessation in the future. **Study Design :** A secondary analysis of the COMMIT trial, a cluster randomised trial. **Primary study:** Commit Research Group. Community Intervention Trial for	**Setting:** 22 US cities (11 matched pairs) of the Community Intervention Trial for Smoking Cessation (COMMIT). **Participants:** 1410 subjects from the COMMIT trial who smoked at both baseline and 2-year follow up. Average age 42, 53% female, 20% non-white, 58% with college education. Average consumption of 25 cigarettes per day at baseline.	**Method of allocation:** Not relevant – secondary analysis of a post-cessation study cohort. **Intervention(s):** **Control:** **Sample sizes:** 1410 ongoing smokers **Baseline comparisons:** **Study power:** **Intervention delivery:** Authors were university researchers	**Primary outcomes:** Self-reported cigarettes per day and abstinence measured via random digit telephone survey of ca 5400 households in each of the 11 COMMIT communities. **Secondary outcomes:** **Follow-up periods:** 2 and 4 years. **Method of analysis:** Odds ratios (95% Confidence Intervals); Linear regression analysis for exploration of reduction/quitting behaviours over time.	**Primary:** Smoking reduction neither promotes nor undermines cessation. The odds ratio for successful cessation at 4 years for those who had reduced smoking by ≥50% at two years compared to those who had increased their smoking by ≥ 5% at two years was not significant at 1.72 (0.85, 3.46). Among the 40% of participants who had reduced their smoking by ≥5% at 2 years, 52% reported the same or greater reduction at 4 year follow up. **Secondary:** **Attrition:** 34% loss to follow up by 4 years.	**Limitations (author):** Lack of biochemical verification of cessation. **Limitations (review team):** Self reported results only. Secondary analysis of a smoking cessation trial that did not promote smoking reduction as a goal. **Evidence gaps:** **Funding sources:** **Applicable to UK?** COMMIT was a huge US community-based study. May be generalisable to the UK.

Smoking Cessation (COMMIT): Summary of design and intervention. *Journal of the National Cancer Institute* 1991; 83(22):1620-8.					
First author and year: Hughes 2004 **Aim of study:** To examine the ability of smokers who failed to quit smoking in the Lung Health Study to reduce the number of cigarettes per day and maintain this reduction and whether reduction predicted increased or decreased future cessation. **Study Design :** Secondary analysis of a smoking cessation RCT (counselling and nicotine gum)	**Setting:** Multiple recruitment methods from centres in the USA. **Participants:** 1,722 (of 3,923) participants with early lung disease who enrolled in the Lung Health Study and were still smoking at first year follow up. **Inclusion:** Aged 35-60 years; Smoked at least 10 CPD on at least 1 of 30 days prior to screening; had mild obstructive lung disease **Exclusion:** Serious health condition that would affect the lungs or interfere with participation.	**Method of allocation:** Not relevant – secondary analysis **Intervention(s):** Smoking cessation (10 weeks cognitive behavioural counselling and nicotine gum) plus active bronchodilator; Smoking cessation plus placebo. Beyond intervention, clinic visits each four months for counselling. **Control:** Usual care (no intervention) **Sample sizes:** **Baseline comparisons:** **Study power:** **Intervention delivery:**	**Primary outcomes:** CPD and point prevalent (no time period - check?) abstinence. Abstinence verified by salivary cotinine and CO at annual visits. **Follow-up periods:** Annually from 1-5 years. **Method of analysis:** x^2 for categorical variables (incl. abstinence), t statistics for quantitative variables. Logistic regression to explore the effect of reduction and other co-variates on quit attempts and long term abstinence. NB Bronchodilator had no effect and the two intervention groups were combined.	**Primary:** Reduction can be maintained but neither predicts an increased nor decreased probability of future cessation. Of subjects who did not reduce smoking at year 1, 6% had quit at year 2 and 3% by year 5. Figures for quit rates at years 2 and 5 for reductions at year 1 were as follows: 1-24%: 4% at year 2, 1% at year 5 25-49%: 5%, 2% 50-74%: 7%, 2% 75-99%: 10%, 4% Smokers who used gum had more reduction at year 1 than those who did not ($p<0.001$). **Attrition:** Across years 2-5 194 (11%) smokers missed a visit. Where data were missing the subject was assumed to be smoking.	**Limitations (author):** Reduction was not a focus of the Lung Health Study. **Limitations (review team):** Secondary analysis of a smoking cessation not a cut down to quit trial. **Evidence gaps:** Report reduction as well as cessation outcomes from cessation studies; Compare reduction advice versus no reduction advice. **Funding sources:** National Heart,Lung and Blood Institute. National Institute on Drug Abuse. **Applicable to UK?** Quite likely - a huge multicentre US study.

APPENDIX I – Statistical analyses (See Sections 2.6 and 4.9 for commentary)

Figure 1 – Gradual versus abrupt reduction

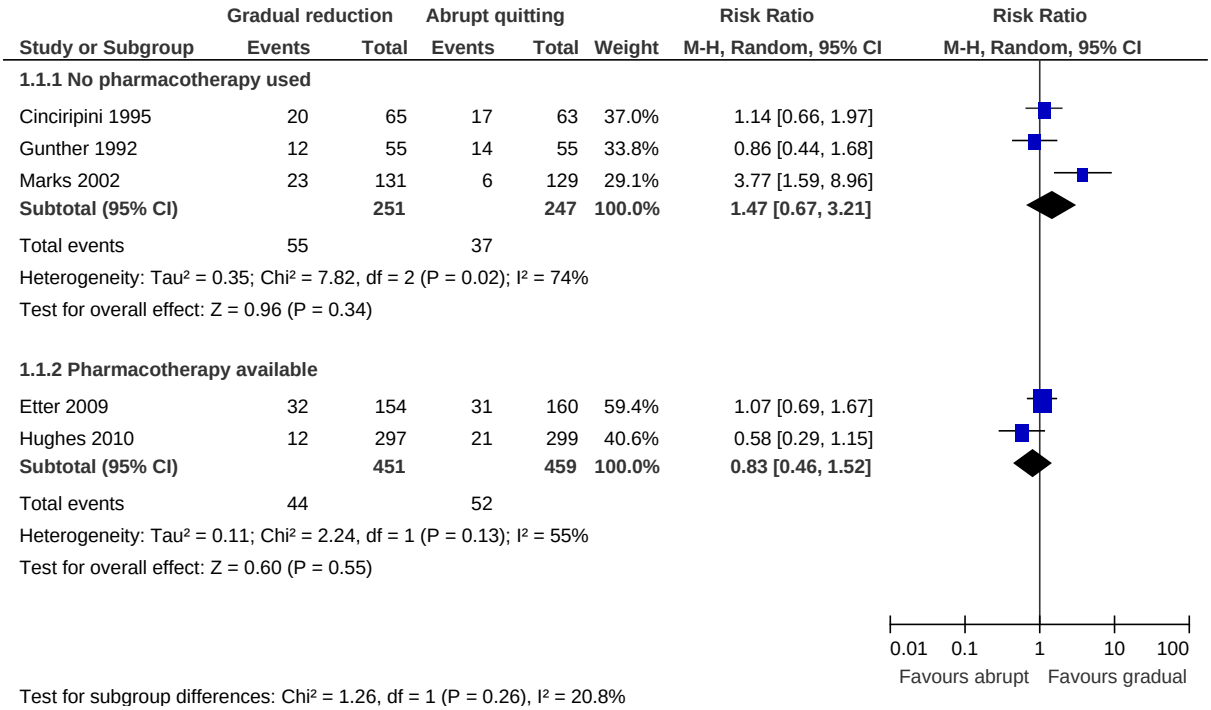

Figure 2 – Scheduled vs non scheduled reduction