SMOKING REDUCTION AND NICOTINE PRELOADING: NEW APPROACHES TO CESSATION?

by

NICOLA LOUISE LINDSON

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Department of Primary Care Clinical Sciences
School of Health and Population Sciences
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ABSTRACT

The Department of Health aim to reduce smoking prevalence to 10% by 2020; however estimates suggest this shall not be achieved. One way to increase the decline may be to introduce new cessation interventions into NHS Stop Smoking Services. Literature reviews and meta-analyses were used to test the efficacy of smoking reduction and nicotine preloading in comparison to current NHS treatments (abrupt quitting and nicotine replacement therapy post-quit, respectively), in smokers who wanted to quit. Results of the two reviews suggest that both approaches produce similar quit rates to their comparators. We suggest that pre-quit reduction should be offered alongside abrupt quitting, to encourage more smokers to use cessation services. However the use of nicotine preloading would be premature, as evidence of benefit is inconclusive. The protocol for a randomised controlled non-inferiority trial using both approaches is presented. Trial participant interviews suggest that reduction methods are feasible and may have more enduring popularity than abrupt quitting, providing further support for this approach. Accounts also suggest potential mechanisms of preloading, although a literature review provided little evidence of these. Further research should establish the effect of preloading, its mechanisms of action, and the best way to advise smokers to reduce.

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ABBREVIATIONS

Abbreviation	Term
AChR	Acetylcholine receptor(s)
CDTS	Cut Down Then Stop
CI	Confidence interval(s)
CO	Carbon monoxide
cpd	Cigarette(s) per day
CRF	Case report form
DA	Dopamine
DoH	Department of Health
FTND	Fagerstrom Test for Nicotine Dependence
GP	General Practitioner
HR	the Hierarchical Reduction method
HR-D	the Hierarchical-Difficult Reduction method
HR-E	the Hierarchical-Easy Reduction method
ICI	Inter-cigarette interval
ITT	Intention-to-treat
mCEQ	Modified Cigarette Evaluation Questionnaire
mg	milligram
MHRA	Medicines and Healthcare Regulatory Authority
MPSS	Mood and Physical Symptoms Scale
NA	Nucleus accumbens
NCSCT	NHS Centre for Smoking Cessation and Training
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NRT	Nicotine replacement therapy
OR	Odds ratio
OTC	Over-the-counter
PCCRTU	Primary Care Clinical Research and Trials Unit
PCT	Primary Care Trust
PI	Principal Investigator
PIS	Participant information sheet
ppm	Parts per million
RCT	Randomised controlled trial
RR	Risk ratio
RRT	The Rapid Reduction Trial
Rx	On prescription
SAE	Serious adverse event
sfp	Smoke-free periods
SFP	the Smoke-Free Periods Reduction method
SPC	Summary of Product Characteristic(s)
SR	the Scheduled Reduction method
SRNT	Society for Research on Nicotine and Tobacco
SSS	Stop Smoking Service
STS	Smoking Toolkit Study
SUSAR	Suspected unexpected serious adverse reaction

CHAPTER 1: INTRODUCTION TO THE THESIS

1.1 Prevalence and predictions

Since 1970, when around 55% of the population smoked cigarettes, the prevalence of smoking in adults, in England, has been reducing (Cancer Research UK 2011). Between 1980 and 2009 it decreased from 39% to 21% (Office for National Statistics 2011) (Figure 1).

In February 2010 the Department of Health (DoH) published its new tobacco control strategy for England (Department of Health 2010). One of the goals stated is to reduce adult smoking prevalence to 10% or less by 2020, which it claims will reduce hospital admissions due to smoking related illnesses by over 50,000 each year and save over 400,000 lives.

The DoH will assess whether this goal has been achieved using figures from the Office for National Statistics annual Integrated Household Survey. This survey is made up of a number of questionnaires, including the General Lifestyle Survey. This contains questions about smoking behaviour, which are used to establish prevalence (Office for National Statistics 2010). At the time of writing the most up to date smoking prevalence data available from this survey is the 21% recorded in 2009. Therefore at least an 11% decline would be required to meet this target. The DoH admit that to achieve this the decline will need to be among the best in the world (Department of Health 2010). Norway achieved a decline of over 1% per year from 2000-2010 that has been attributed to public health measures to prohibit the advertising of tobacco, health warnings on cigarette packets and a ban on smoking in indoor public spaces (Statistics Norway 2011). These have all also taken place in the UK, however

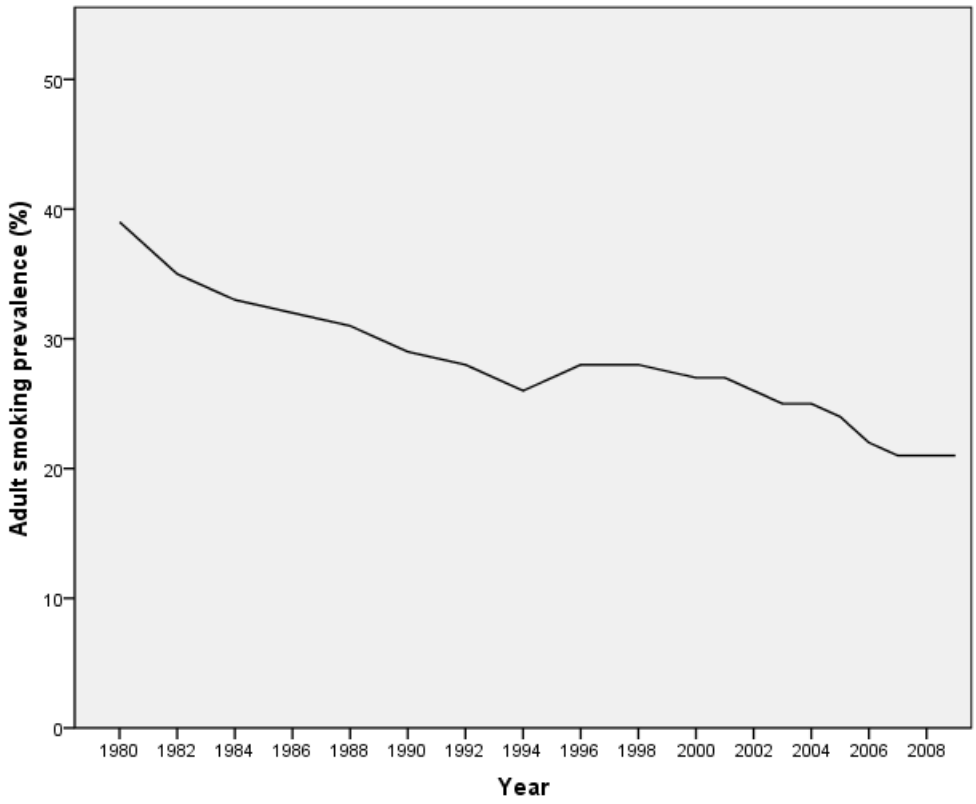

Figure 1: Adult smoking prevalence in England from the General Lifestyle Survey 1980 to 2009 (Office for National Statistics 2011)

unlike the UK the use of snus (moist smokeless tobacco placed inside the mouth, under the lip) is common in Norway and is rising in young people; so that now 25% of men from the age of 16-24 use it daily (Statistics Norway 2011). This suggests that the decline in cigarette smoking is due, to some extent, to the substitution of cigarettes for this less harmful tobacco product (Foulds et al. 2003). However snus is illegal in the European Union, as despite posing a reduced risk in comparison to cigarettes it is still classed as a carcinogen and outside of regulation (Gray 2005), and so is currently unlikely to be used as part of a public health strategy in the UK. Therefore reducing smoking to the extent suggested by the DoH may be a challenge and in order to reach this target tobacco control will need to be prioritised.

To make a rough estimate of how prevalent smoking may be in the future we carried out a projection analysis using existing prevalence data from the General Lifestyle Survey 2003 to 2009 (Office for National Statistics 2011). We did this by carrying out a regression analysis on the existing data, and using the resulting formula to calculate an estimate of prevalence in 2020. This analysis can provide only a crude estimate, as it does not account for short-term fluctuations in prevalence. This could only be accounted for by a times series analysis; however analysis such as this is beyond the scope of the introduction of this thesis. We strive only to provide a rough idea of the trend in prevalence, and how this may impact on future rates if this continues, using methods that have previously been used in the field (West 2010). Based on our analysis we predict that, based on the previous rate of decline, in 2020 12% of adults in England will be smokers (Figure 2).

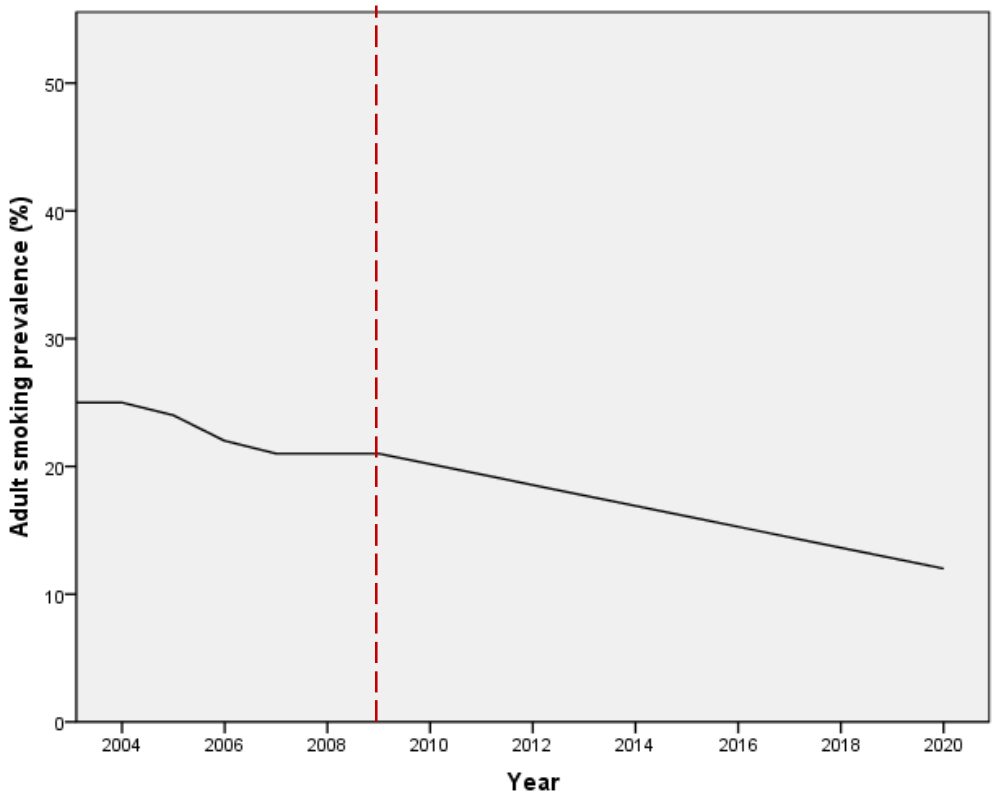

Figure 2: A forecast of adult smoking prevalence rates in England up to 2020 based on actual rates from the General Lifestyle Survey 2003 to 2009 (Office for National Statistics 2011).

Therefore using current practice and at the current rate of decline it looks like it will not be possible to reach the DoH's target. In addition, it could become progressively harder to achieve a reduction in smoking prevalence as time goes on. As more people quit it is likely that the smokers remaining will be those that do not wish to quit or have found it hardest in the past (Hughes 2011). Another smoking prevalence survey (The English Smoking Toolkit Study (STS), which has taken monthly reports of smoking prevalence up to as recently as September 2010, also shows that in more recent times (September 2008 to September 2010) the rate of the decline has diminished and remained relatively stable (West 2010); so that forecasts based on these data (calculated as outlined above) predict prevalence will have dropped to only 16% in 2020 (Figure 3).

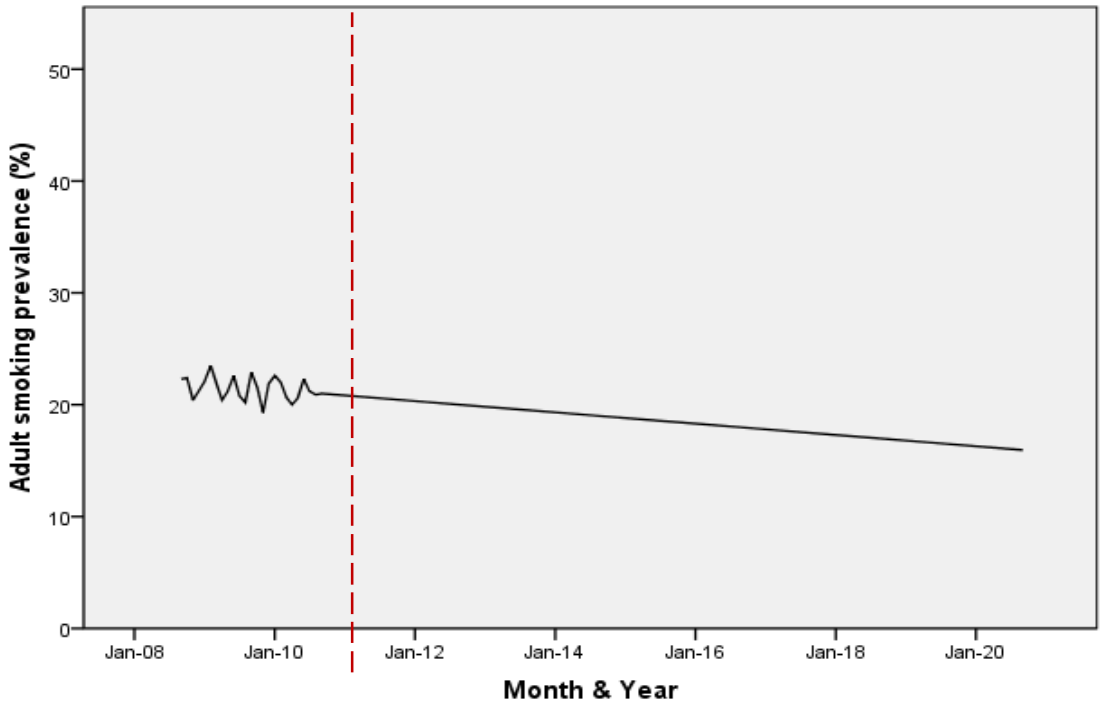

Figure 3: A forecast of adult smoking prevalence rates in England up to September 2020, based on actual rates from the Smoking Toolkit Study from September 2008 to September 2010 (West 2010)

Robert West created and carries out the STS and has hypothesised that this change in the rate of decline may be due to the global economic recession (Roberts 2010), which began in 2008 (Baldwin 2009). This is supported by a survey, which found that smokers do not see financial problems as a reason to quit; they would rather continue to smoke to help them cope with stress, and cut back on other spending during these times (West 2009). During a recession there are several causes of stress, such as unemployment, a reduction in wages and decreased job stability; as well as cutbacks in community and health services.

In the light of these obstacles to reaching the DoH target it is important to consider new ways to reduce smoking prevalence. Smoking prevalence is a function of both the rate of uptake of smoking by young people (the inflow) and the number of smokers who successfully quit (the outflow). The focus of this thesis shall be on increasing the outflow. There are three main ways that this could be addressed:

1) By increasing the number of smokers who wish to quit smoking;
2) Increasing the number of smokers who access treatment services to quit, as these services result in higher quit rates than unsupported quit attempts (Section 1.3); and
3) Improving the services available to aid a smoker to quit.

The following outlines ways that the third objective could be achieved, thereby perhaps indirectly contributing to objectives 1) and 2); the availability of new, potentially more effective treatment services may increase both a smoker's motivation to quit and the likelihood that they will access these services to do so. The first suggestion is the introduction of a completely new intervention- reducing smoking to quit- into the UK National Health

Service (NHS) Stop Smoking Services (SSS), and the second is to endeavour to increase the efficacy of nicotine replacement therapy (NRT) by implementing its use before quit day, as well as after (nicotine preloading). According to anecdotal evidence both of these methods are already being used tentatively by some individuals, outside and inside the NHS SSS. Therefore formal investigation is needed to see whether they do offer a benefit, and as a result whether they should be recommended to smokers, and rolled out across the entire NHS SSS.

1.2 Using the neural mechanisms of addiction to inform treatment

One of the primary motivators for suggesting these two interventions relates to the neurobiological mechanisms thought to underlie nicotine addiction, and the ways that these could be capitalised upon to aid and maintain abstinence.

1.2.1 The neurobiology of nicotine addiction

One of the key neural pathways thought to be responsible for the addictive properties of most drugs of dependence, including nicotine, is the mesolimbic dopamine (DA) system. Experiments with animals have found that when electrodes are inserted into dopaminergic pathways in their brains, they will learn to stimulate these through lever pressing. This lever pressing is reduced if the animals are also treated with nicotine, as less is required to achieve reinforcement (Bozarth et al.1998).

When inhaled the nicotine in cigarettes acts on the mesolimbic dopaminergic reward system. It does this by binding with acetylcholine receptors (AChR) on dopaminergic neurones in the ventral tegmental area, leading to the release of DA in the nucleus accumbens (NA)

(Cummings & Hyland 2005). Experimental evidence suggests that repeated exposure to nicotine results in neuroadaptation, and a sensitisation to its effects, leading to an overflow of DA in the NA (Benwell & Balfour 1992). Although these effects have been associated with reward and thus the reinforcement of smoking behaviour, the reinforcing psychological effects of nicotine are subtle when compared with other drugs of dependence. Therefore, these effects of nicotine do not seem to reflect the difficulty that many smokers have attaining and maintaining abstinence (Caggiula et al. 2001). This suggests that other factors contribute. Balfour (2009) has hypothesised that there are two routes to dependence on nicotine, facilitated through the overflow of DA in the NA. The NA incorporates two structural subdivisions: 1) the core, and 2) the shell. Balfour hypothesises that it is DA overflow in the shell that results in reward and thus leads to drug seeking in the pursuit of pleasure (as outlined above); whilst DA overflow in the core plays a complementary role. This is supported by evidence that when food (Hall et al. 2001) and cocaine (Ito et al. 2004) rewards are provided as a result of responses to a co-presented, conditioned stimulus, lesions of neurones in the core of the NA have been found to reduce the number of responses to the stimulus. Evidence such as this is not available specifically for nicotine; however Goldberg et al. (1981) found that squirrel monkeys responded significantly more to intravenous nicotine when visual stimuli were also presented. These studies suggest that sensory stimuli play an important role in drug addiction. This is supported by Rose et al.'s (1993) findings that humans regulate their smoking behaviour to maximise the sensory intensity of cigarettes, rather than primarily to maximise nicotine intake. Balfour (2009) suggests that this mechanism will enhance drug seeking behaviour in response to stimuli or cues associated with nicotine administration, which may explain cue-induced urges to smoke during abstinence (Miranda Jr. et al. 2008; Liu et al. 2010). There is evidence that urges such as these

are likely to lead to lapsing and relapse (Abrams et al. 1988, Doherty et al. 1995; Killen & Fortnum 1997).

Another way that nicotine is thought to exert its effects to ensure continuation of use is through the aversive abstinence syndrome (Balfour 2009). Kenny & Markou (2001) have theorised that when an individual stops taking a drug this may lead to a decrease in the overflow of DA in the NA, and that it is this decrease which mediates the aversive abstinence syndrome. However they are only able to speculate about the exact nature of this mediation. Some withdrawal symptoms commonly experienced as a result of the nicotine abstinence syndrome are irritability, restlessness, difficulty concentrating, impaired task performance, anxiety, hunger, weight gain, sleep disturbance, cravings and drowsiness (American Psychiatric Association 1994). Therefore it has been suggested that many smokers continue smoking to avoid these negative effects of abstinence (Balfour & Fagerstrom 1996). If this is the case then even if smoking abstinence were attempted the experience of these withdrawal symptoms may be enough to drive an individual to return to smoking.

For a more detailed discussion of the mechanisms of nicotine addiction highlighted here see Balfour (2009).

1.2.2 The potential effects of smoking reduction on neural mechanisms to facilitate and maintain abstinence

There appears to be two ways that reducing smoking before quitting could influence the neural mechanisms above, and therefore improve the likelihood of abstinence. The first is

based on the aforementioned neuroadaptation in the form of up-regulation of nicotinic AChR, and sensitisation of DA pathways. If neuroadaptation to high doses of nicotine has occurred, then neuroadaptation in the reverse direction may occur in response to reducing doses of nicotine. Once abstinence is attempted, this may reduce craving and withdrawal symptoms. Benowitz & Henningfield (1994) suggested that it would be good public policy to mandate a gradual reduction in the nicotine content of cigarettes. To support this proposal Benowitz et al. (2007) tested the feasibility of the approach with 20 participants, and found that after a reduction in nicotine content over six weeks 25% of participants had spontaneously quit smoking four weeks later, and those participants who had returned to their usual brand of cigarettes were smoking fewer, suggesting lower levels of dependence. However these results are preliminary and should be treated with caution. Due to the lack of a control group it is difficult to tell whether the observed cessation/reduction was as a result of the reduction in nicotine content or other factors, such as general participation in a smoking intervention or the switch to cigarettes of a different brand.

Benowitz and Henningfield (1994) also observed that smokers known as chippers, who smoke five or fewer cigarettes per day (cpd), appear not to be as dependent as heavier smokers. They do not seem to experience withdrawal symptoms and can avoid smoking for long periods without emotional distress. However, as Henningfield et al. (1998) also recognise, due to the neuroadaptation that is likely to have occurred, we cannot assume that the low levels of nicotine, to which chippers are exposed, would not be addictive to smokers who have been exposed to higher doses of nicotine in the past. Nevertheless, a study investigating the use of a nicotine conjugate vaccine, which has been found to reduce the distribution of nicotine to the brain (Hieda et al. 1999; Pentel et al. 2000; Cerny et al. 2002;

Lindblom et al. 2002; Meijler et al. 2003; Sanderson et al. 2003), found that rats trained to self-administer nicotine and given the vaccine were less likely to maintain self-administration than controls (LeSage et al. 2006). This suggests that a reduction in the dose of nicotine received could reduce dependence in smokers who have previously received higher doses. Further research in humans, examining the specific effects of reducing cpd on the neural mechanisms of addiction and markers of dependence would be beneficial.

The second reason that smoking reduction may aid quitting is based on Balfour's (2009) hypothesis that DA overflow in the core of the NA leads to conditioned relationships between environmental stimuli and smoking. Smoking reduction is likely to lead to a deconditioning of some of these relationships; as, at least in some cases, smoking will not take place when environmental stimuli create the urge to do so. Some smoking reduction methods have been specifically designed with this in mind. For example, Cinciripini et al. (1995) asked smokers to reduce their smoking before quitting using the inter-cigarette interval (ICI) method. Using this method the time in the day is divided by the number of cpd smoked at baseline, giving the baseline ICI. Over the reduction period this interval is gradually lengthened, so that less cigarettes are smoked each day. Smoking on a schedule, such as this, means that smokers are unlikely to ever be smoking in response to the environmental cues that would usually trigger their smoking, thus breaking the association between the stimuli and the behaviour. If all associations are broken in this way prior to the quit day, then the appearance of these cues when abstinent is unlikely to result in an urge to smoke, which should in turn reduce the likelihood of relapse.

1.2.3 The potential effects of nicotine preloading on neural mechanisms to facilitate and maintain abstinence

The nicotine present in NRT acts as an agonist by binding to the same AChR as the nicotine present in tobacco smoke. When NRT is administered after all smoking has ceased abruptly then the aim is to ameliorate withdrawal (Balfour & Fagerstrom 1996). However, using NRT in this way means that the learned associations between smoking cues and the reward experienced from smoking will still exist on the quit day; for example, as a result of usually smoking when drinking a cup of tea or coffee the smoker may still feel the urge to smoke when they drink tea or coffee post-quit. By using NRT in parallel to smoking before quitting (preloading), an attempt can be made to break these associations before the smoker stops smoking altogether (as suggested in Section 1.2.2), making it easier to manage their cravings post-quit (Hajek 2006).

Evidence suggests that depending on the type of NRT preparation AChR are activated or desensitised by the nicotine they deliver (Balfour 1994). Faster acting forms of NRT such as gum and nasal spray, most closely mimic the nicotine delivery of cigarettes, are more likely to mirror directly the effects of smoking, and so activate receptors. As nicotine patches are typically worn for 16-24 hours a day they provide a constant low stream of nicotine which keep nicotine levels constant and are more likely to desensitise nicotinic receptors. This means that receptors cannot respond to exogenous nicotine and this will undermine reward and reinforcement of smoking (Balfour 1994). This is likely to decondition the relationship between smoking cues and the smoking behaviour. If acute NRT is being used to preload (for example, if smoking is also reduced pre-quit) an urge to smoke can be partly satiated with the use of NRT rather than smoking a cigarette. This means the reinforcement in response to

nicotine should still be present, but the link between the smoking cue and smoking behaviour should weaken. This could lead to a fear that the smoker will become addicted to the NRT itself, however despite acute NRT mimicking the effects of cigarette smoking more closely than patches, nicotine is still delivered at a much slower rate than through smoking, and so does not have the same abuse potential (Balfour et al. 2000).

The theories and evidence from non-human animal studies described above argue that smoking reduction and nicotine preloading could be effective treatments for nicotine addiction, and therefore that their adoption by the NHS SSS may be beneficial. In the following sections I shall present further evidence to suggest that this is the case, and identify where further research is necessary.

1.3 Current smoking cessation services

In response to the DoH's White paper- Smoking Kills (1998) NHS SSS were implemented for the first time in 1999; firstly in those areas with greatest deprivation (Health Action Zones) and later across the whole of the UK. In 2009 the DoH aimed to optimise and ensure the quality of the support available through these services by commissioning the NHS Centre for Smoking Cessation and Training (NCSCT), led by University College London, to support the NHS SSS by developing training standards and delivering accredited smoking cessation training (NCSCT 2010[a]). As a result the NCSCT have produced a Standard Treatment Programme, which reflects the current accepted and evidence-based practice for cessation advisors in the NHS (NCSCT 2010[b]). Some of the key features of these guidelines are:

- The NHS SSS treatment programme is six to seven weeks, but can vary across services;
- Weekly contact between the service and the client is extremely important for the full duration of the course of smoking cessation support;
- The NHS SSS support smokers to stop smoking completely and abruptly, and not to cut down smoking before quitting;
- A quit date is set through agreement between the smoker and the practitioner, usually one to two weeks after the first appointment with the service;
- The 'not a puff rule'- the client is informed that stopping smoking through the service involves a rule of not smoking even one puff after their quit date;
- Regular carbon monoxide (CO) monitoring to measure the amount of CO (a by-product of smoking) in the client's blood;
- The discussion of withdrawal symptoms and cravings to smoke and how these can be dealt with;
- The identification and discussion of strategies to counteract any potential high risk situations which could arise and compromise the quit attempt;
- Prompting a commitment from the client to quit smoking;
- The provision of information about and medication to aid smoking cessation, in the form of NRT, varenicline or buproprion.

Based on data from the STS (West 2010), using the NHS SSS in partnership with smoking cessation medication appears more successful than medication on prescription (Rx) or over-the-counter (OTC) alone, and was almost four times more effective than no medication or support in assisting smokers to quit during 2009/2010. However over the same time period

the number of quit attempts by smokers, supported by attendance of these services was very low (2%), with 52% of quit attempts carried out with no support, 31% supported by over-the-counter NRT, and 15% using cessation medication on prescription. As using the NHS SSS results in higher quit rates than not, in the interest of raising quit rates overall, it would be beneficial to increase the number of smokers who approach the NHS SSS for help.

1.4 Improving the reach of the NHS SSS

Abrupt quitting is the only behavioural approach to smoking cessation treatment available through the NHS. The SSS are now encountering a number of individuals who have been through this same system a number of times without success. It would not be surprising if these individuals were disillusioned with the approach and therefore unenthusiastic about using it again. Nevertheless surveys suggest that the majority of smokers who use the NHS SSS are both satisfied with the service and willing to recommend it to others (May et al. 2009; May & McEwen 2011). However these participants may not consider that reduction is an option, and so responses may not take into account the possibility of an alternative treatment. In any case even if users do continue to use the SSS it seems nonsensical to keep providing the same treatment to people who it has not worked for in the past. Providing an alternative behavioural treatment to abrupt quitting, and therefore offering smokers a menu of quitting options may improve the appeal of the NHS SSS.

1.4.1 Interest in gradual cessation

The STS has found that although the NHS SSS advise that people stop smoking abruptly only 61% of those smokers who make a quit attempt actually do it in this way; 39% quit gradually

by reducing first (West 2008). Additionally Hughes and colleagues found, using surveys carried out in the US, that significantly more smokers were interested in gradual than abrupt cessation (Hughes et al. 2006), and that those who chose gradual cessation were as motivated to stop and as confident of success in their quit attempt as those who chose abrupt cessation (Hughes 2007). This suggests that there is a demand for gradual cessation services that is not being fulfilled by the NHS SSS, and as a result that there is a pool of smokers who are unlikely to seek treatment, but who may do so if gradual reduction were offered. The best proof for this untapped demand would be to conduct a trial advertising these services within the NHS SSS, and to monitor the effects of this on uptake to the services. However to do this now would be premature; it is important that we first establish the efficacy of the method, particularly in the light of previous fears about its use.

1.4.2 Reluctance to adopt gradual cessation

In the 1970s, smoking reduction was used as a method to accomplish cessation, and studies testing different behavioural interventions were conducted (Levinson et al. 1971; Marston & McFall 1971; Katz et al. 1977). However discovery of the central role of nicotine in tobacco addiction, and the efficacy of abrupt cessation seemed to have rendered this older literature obsolete.

The NHS SSS implementation of the abrupt quitting method is based on the Maudsley Hospital's Smokers Clinic, withdrawal-orientated therapy treatment model (Hajek 1989) and is in agreement with National Institute for Health and Clinical Excellence (NICE) recommendations (2008). These state that there is not enough evidence available to endorse

reducing smoking before quitting, and so gradual quitting should only be used in *"properly designed and conducted research studies"* (p.17). Abrupt quitting is the treatment of choice as it is based on the traditional model of addiction, which suggests that smokers are addicted to nicotine (as described in Section 1.2.1), that drug addiction is a disorder, and addicts need to abstain from all psychoactive drugs for the rest of their lives, or this disease may prove fatal (Denning 2002). Therefore treatment begins with discontinuation of drug use before dealing with any other concomitant psychological issues. This is because addicts are believed to be unreliable and to have no control over their drug use, making them unable to carry out a more complex treatment regimen, such as the reduction of drug use before stopping completely. However, Denning (2002) believes that in reality drug users are no more impaired in their ability to adhere to a medical treatment than those who do not use drugs.

Observational studies (Cheong et al. 2007; West & Fidler 2011) have shown that smokers who reduce their smoking before quitting are less likely to succeed. One reason for this may be that abrupt quitting is by its nature quite a structured straightforward way to quit, providing less of a need for behavioural support. Reduction on the other hand offers a lot of potential for variation in how it is carried out and perhaps provides more opportunity to put-off quitting altogether. However if a structured behavioural support programme were available it would limit the opportunity for this variation and for avoiding the quit day altogether. Thus there may be reason to believe that reduction, when offered alongside support and some structure, would result in better quit rates, as hypothesised by Cheong et al. (2007).

1.4.3 Reduction- a feasible approach to quitting

There is some evidence to suggest that reducing smoking is a feasible approach to quitting. A review by Hughes and Carpenter (2005) found that whereas little spontaneous reduction occurs in smokers- offering support for the observational studies (Cheong et al. 2007; West & Fidler 2011) - it is possible for a smoker to reduce their smoking and maintain that reduction when part of a treatment programme. Evidence was also found that using NRT aids reduction more so than placebo (Hughes & Carpenter 2005; Moore et al. 2009). Although some compensatory smoking occurred, for example by taking bigger, longer puffs, reduction in CO levels still occurred (Hughes & Carpenter (2005). This also supports Denning's (2002) view - that an addict is able to deal with more complex treatment regimens than abrupt stopping only.

There has been substantial concern that if a smoker aims to reduce initially rather than stop abruptly this could undermine their attempt at complete cessation, as reduction will be seen as a favourable alternative (Hatsukami et al. 2004). However there is evidence to suggest this is not the case and that reduction actually increases the likelihood of later cessation. In their systematic review Hughes & Carpenter (2006) found 19 studies that reported on both changes in cpd and whether future cessation had occurred. Participants were smokers who had either spontaneously reduced or not in observational studies, or who had been instructed to reduce or not in randomised controlled trials (RCTs). None of the 19 studies found that reduction was associated with a lower rate of future quitting, and 16 of the studies found that reduction was associated with higher rates of later quitting. A more recent review of 10 RCTs by Asfar et al. (2011) supports this. All included trials compared either a pharmacological, behavioural or combined smoking reduction intervention, in smokers not yet ready to quit, to at least one

control group, defined as placebo, no treatment, or minimal psychological intervention. Meta-analysis results for the pharmacological and combined interventions showed that in both cases the reduction interventions increased the likelihood of long-term abstinence (six months or over). However there was insufficient evidence available to reach a conclusion as to whether behavioural support for reduction alone enhanced future abstinence.

Additionally, as well as the reasons cited earlier regarding manipulation of addiction pathways in the brain (Section 1.2.2), there are a number of psychological hypotheses for why reduction could help a smoker to stop smoking completely. Firstly, Michie (2009) proposed that reducing cigarette consumption provides a goal which is more in-line with the smoker's current behaviour than complete abstinence. Therefore the eventual behavioural change may appear more achievable and desirable, encouraging more people to consider quitting in the first place. The second hypotheses concerns 'shaping': a type of operant conditioning. Shaping involves making successive approximations of a target behaviour, which are positively reinforced, encouraging the desired final behaviour (Skinner 1953). In this case gradually quitting individual cigarettes would induce intermittent reinforcement, offering encouragement to, and increasing the likelihood of quitting altogether. This links to the final hypothesis, relating to the cognitive psychology principle of self-efficacy- a person's belief in their ability to succeed. The positive reinforcement that smokers may experience when quitting individual cigarettes could increase their self-efficacy, as they can see that change is possible. Increases in self-efficacy such as this are thought to increase the likelihood that the final goal- in this case abstinence- will be achieved (Bandura 1977).

This evidence suggests that reduction could be a feasible alternative to abrupt quitting within treatment services. It could draw more people into the SSS by offering an option which appeals to a number of smokers (Section 1.4.1), who may not have had the opportunity to try this approach in a supportive context in the past. As a result, and despite scepticism (Section 1.4.2) there seems to have been some revival in interest in this method and the Medicines and Healthcare Regulatory Authority (MHRA), in the UK, have now licensed NRT for use alongside smoking reduction regimes, following findings that this is both safe (Moore et al. 2009) and cost-effective (Wang et al. 2008).

1.5 Making treatment more effective

1.5.1 The use of pharmacotherapies for smoking cessation

Of the three types of smoking cessation pharmacotherapy available through the NHS SSS (NRT-in the form of gum, lozenge, transdermal patch, nasal spray, inhaler and sublingual tablet- varenicline and bupropion), NRT is the most popular (Table 1).

Of smokers seeking assistance through the SSS between April and September 2010 monitoring reports show 91% received some form of pharmacotherapy, mainly NRT (62%) (The NHS Information Centre 2011). Data from the STS assesses the use of medication in smokers quitting mainly without NHS SSS support (only 7% of attempts to quit were made with their support). Forty-seven percent of total quit attempts made use of pharmacotherapy, and this was again predominantly NRT (44%) (West 2008).

NRT used post-quit has been found to produce abstinence rates 58% higher than when using no medication (Risk Ratio (RR) = 1.58, 95% Confidence Intervals (CI) = 1.50, 1.66) (Stead et al. 2008). However if the use of NRT before quit day were also introduced, and had the effects hypothesised in Section 1.2.3, then there may be the potential to improve abstinence rates further. Nicotine preloading could be used either when quitting abruptly or when reducing first, and when using NRT, varenicline or bupropion post-quit.

Table 1: The percentage of smokers using different types of pharmacotherapy to support their quit attempt: from a sample utilising NHS Stop Smoking Service support, and a sample quitting with and without behavioural support

Type of pharmacotherapy used	Smokers quitting through NHS SSS (The NHS Information Centre 2011)	Smokers quitting predominantly without NHS SSS support (West 2008)
No pharmacotherapy	6%	53%
NRT	62%	44% (34% OTC, 10% Rx)
Varenicline	26%	1%
Bupropion	1%	3%
NRT & varenicline	1%	N/A
NRT & bupropion	<1%	N/A
Treatment unknown	3%	N/A

NHS – National Health Service; SSS – Stop Smoking Service; NRT – Nicotine replacement therapy; OTC – over-the-counter; Rx – on prescription; N/A – option not included in survey.

Both bupropion (Electronic Medicines Compendium 2011[a]) and varenicline (Electronic Medicines Compendium 2011[b]) are licensed to be taken by smokers for up to two weeks before they quit, whilst still smoking. Current NHS SSS practice is usually to ask smokers to begin taking either medication one week before their scheduled quit day; however when using

NRT clients start using their chosen application on quit day and do not smoke whilst doing so (NCSCT 2010[b]). Historically there have been two reasons for this:

1) Smoking just one puff after quit day can sabotage the maintenance of abstinence (Kenford et al. 1994), and
2) Rose et al. (2006) notes that smoking whilst using NRT has been feared to lead to health problems. In particular, a telephone survey carried out in smokers in the US found this to be the case (Bansal et al. 2004). .

1.5.2 The safety of concomitant smoking and use of NRT

There has been no evidence of nicotine overdose when nicotine intake has been moderately increased (Stead et al. 2008; Moore et al. 2009), and a review by Fagerstrom & Hughes (2002), assessing the safety of using cigarettes and NRT concurrently found that although in some cases using nicotine patch and smoking raised nicotine concentrations to two to three times their usual level, this was accompanied by few and mild adverse effects. This favourable safety profile means NRT is now licensed for use whilst smoking, as part of harm reduction strategy. In 2010 the MHRA announced that it had extended the license of the nicotine inhalator, in response to a request, to include a harm reduction element (MHRA 2009). Therefore the following is now included in the product information:

"Nicorette Inhalator relieves and/or prevents craving and nicotine withdrawal symptoms associated with tobacco dependence. It is indicated to aid smokers wishing to quit or reduce

prior to quitting, to assist smokers who are unwilling or unable to smoke, and as a safer alternative to smoking for smokers and those around them." (MHRA 2009; p. 5)

The Commission on Human Medicines Working Group, who made this decision, also recommended that this harm reduction element was appropriate for all the other authorised forms of NRT, suggesting that if the manufacturers were to request that the indications of their products be changed to include this then it would most likely be granted. Additionally, as previously mentioned in Section 1.4.3., the Summary of Product Characteristics' (SPC) for all of the current forms of NRT (gum (Electronic Medicines Compendium 2010[a]), patch (Electronic Medicines Compendium 2010[b]), lozenge (Electronic Medicines Compendium 2010[c]) inhalator (Electronic Medicines Compendium 2010[d]) and microtab (Electronic Medicines Compendium 2009[a]), apart from the nasal spray (Electronic Medicines Compendium 2009[b]), carry instructions on how to use the products, both when quitting abruptly or when quitting gradually.

1.5.3 Preloading as aversion therapy

As well as the possible motivations for preloading treatment referred to in Section 1.2.3, it has also been suggested that preloading could work by making smoking less attractive, with an aim to extinguish the behaviour (Hajek 2006). Rapid smoking is an aversion technique that was used largely in studies in the 1970s and 1980s and involved asking participants to puff on a cigarette every 6-10 seconds. Smoking in this way leads to a rapid rise in blood nicotine concentration and generally results in unpleasant sensations, such as nausea, and participants were asked to concentrate on these (Hajek & Stead 2010). It is possible that preloading could

invoke similar feelings and experiences as it could also substantially increase nicotine concentrations in the body (Fagerstrom & Hughes 2002). A Cochrane Review investigated the effects of rapid smoking in comparison to a control of either inactive treatment matched for therapist contact, or active treatment of a different type or severity, and summarised that the positive results obtained could not be used to strongly conclude that rapid smoking was beneficial in smoking cessation, due to methodological flaws of the included studies (Hajek & Stead 2010). However the results were promising and further investigation is needed. Using a method such as rapid smoking is unlikely to be very popular with health services at the current time. Firstly, because smoking in enclosed public places is illegal, and therefore asking smokers to smoke rapidly in a clinic is out of the question, and secondly, it would involve asking smokers to smoke more when we know that smoking is damaging to health. However it may be possible to implement this aversive principle in a legal and safe way, deemed more acceptable to the health service, using preloading.

1.5.4 Acclimatisation to NRT

A final reason why preloading may improve abstinence rates in smokers who wish to use NRT post-quit day is that it could acclimatise quitters to the use of NRT (Hajek 2006; Shiffman & Ferguson 2008; Bullen et al. 2010). This may mean that by the time they reach their quit day quitters will have have got used to the taste (in the case of acute NRT) and side effects of NRT, will have increased confidence in its effects, and so feel comfortable with using it and have ironed out any initial problems; therefore using it effectively to maximise success. If this is the case then even if previously mentioned theories as to why preloading could be successful (Section 1.2.3 & Section 1.5.3) are not supported then efficacy could be

increased indirectly by improving post-quit adherence to treatment. However any benefit would most likely be greater in smokers who have not used NRT previously. Previous users are already likely to have at least an idea of how to use NRT and what works best for them from previous attempts.

1.5.5 Preloading- evidence of efficacy

Theories that preloading could make smoking less rewarding and less attractive are supported by evidence that smokers spontaneously reduce their smoking behaviour (Bolliger et al. 2000; Fagerstrom et al. 2000), and rate cigarettes as less rewarding when using NRT (Levin et al. 1993; Rose at al. 1994; Rose & Behm 2004).

Two meta-analyses have estimated the overall effect of nicotine preloading on abstinence rates in smokers trying to quit (Shiffman & Ferguson 2008; Stead et al. 2008). The studies included in both reviews compared smokers preloading with nicotine patches, for two to four weeks pre-quit, with smokers using a placebo pre-quit or starting NRT on their quit day. They both found a significant favourable effect of preloading with a nicotine patch. Shiffman and Ferguson's (2008) analysis resulted in odds ratios (OR) of 1.96 (95% CI= 1.31, 2.93) for 6 weeks abstinence, and of 2.17 (95% CI= 1.46, 3.22) for 6 months, and Stead et al.'s (2008) produced a RR of 1.79 (95% CI= 1.17, 2.72) for long-term abstinence (6 or 12 month). These results are promising, however both of the reviews failed to include an available study (Rose et al. 1994 in the case of Shiffman & Ferguson 2008; Rose et al. 2009- for which only short-term data were available at the time of the review (Rose et al. 2007)- in the case of Stead et al. 2008), and neither review included any studies that utilised acute forms of NRT for

preloading, such as gum or nasal spray, or investigated the possible mechanisms by which preloading may have its effects. Also since they were conducted further data has become available meaning these efficacy estimates are now outdated (Etter et al. 2009; Bullen et al. 2010; Hughes et al. 2010).

1.6 Plan of the thesis

In order to achieve national targets for smoking prevalence it may be important to focus on two new strategies to increase rates of smoking cessation. Neurobiological addiction theory and the way that associated neural pathways could be manipulated to aid and maintain cessation suggest that both smoking reduction to quit and nicotine preloading could improve abstinence; both directly as aids to cessation, and indirectly by drawing into treatment those who would not otherwise have used treatment services. As quit attempts through the SSS result in higher success rates, this could lead to higher population level quit rates.

Anecdotal evidence suggests that some advisors within the NHS SSS already support clients to use these methods, and that smokers may be trying these things themselves outside of the service. Therefore we need to ascertain whether these approaches are beneficial or whether they may be less effective than the treatments already available. As well as looking at quit rates, it is important to look at the experiences of smokers who use these methods to ascertain the optimal way to implement them and to show whether and how they would be used if provided. Using these experiences we may also be able to gain insights into the potential mechanisms of action of the methods. These are the objectives of this thesis.

Chapter 2 is the published research protocol (Lindson et al. 2009[a]; Appendix 1) for the Rapid Reduction Trial (RRT) - a non-inferiority RCT- developed to compare the success of a reduction to quit smoking method and abrupt quitting. Participants in the reduction arm of the study are able to choose one of three different ways to reduce their smoking, and participants in both arms use NRT for two weeks prior to their quit date. This protocol was developed when there was strong evidence for the efficacy of preloading (Shiffman & Ferguson 2008; Stead et al. 2008), which is why the decision was made to implement preloading in both arms; however since then further evidence has to come to light on this subject, which is the topic of Chapter 4. Although the quantitative results of this trial are not the subject of this thesis, as these are not yet available, the results of the qualitative interviews conducted with trial participants are the subject of Chapter 5. Therefore the inclusion of Chapter 2 provides the context for these results. The interview element of the trial, and the resulting amendment to the trial protocol, was added after the initial publication of the protocol. This was as a result of my attendance at the UK Society for Behavioural Medicine (UKSBM) conference 2009, hosted by the University of Southampton, where a large emphasis was placed on the importance of user input in successful intervention development (for example Anderson 2009; Miller et al. 2009; Morrison et al. 2009). As noted in the acknowledgements of this thesis this Chapter was the result of collaborative work. My role was to adapt the basic trial proposal- developed by Paul Aveyard- into a full trial protocol, suitable for submission to regulatory authorities and for publication. The sections describing the RRT interview study were the result of my own original idea. I also developed trial documents to support the protocol, and applied for and obtained regulatory approvals.

Chapter 3 outlines and implements further methods to investigate the efficacy of reduction to quit methods when compared to abrupt quitting; including a published systematic review of the literature (Lindson et al. 2010; Appendix 2) to identify all of the RCTs relevant for inclusion, and a meta-analysis to combine these data to estimate an overall treatment effect. The review was carried out on behalf of the Cochrane Collaboration and therefore conforms to the standards of the Cochrane Handbook for Systematic Reviews of Interventions (Higgins & Green 2009) and the Tobacco Addiction Group. This review was a collaborative work inspired by and building on the literature review carried out to develop the RRT protocol, reported in Chapter 2 (Section 2.1.1). My role was to develop the review protocol, identify and collect literature, conduct study eligibility assessment, extract data, assess risk of bias, conduct analyses and to draft the manuscript for publication.

The published literature review and meta-analysis (Lindson & Aveyard 2011[a]; Appendix 3) reported in Chapter 4 utilises similar methodology to that used in Chapter 3. Quit rates achieved when nicotine preloading is used by smokers prior to a quit day is compared to placebo treatment or starting NRT use on the quit day. Due to the availability of substantial additional data this updates previous reviews of the literature (Shiffman & Ferguson 2008; Stead et al. 2008), that have found a significant positive effect of preloading, and also goes further than the existing reviews by separating the studies in terms of the type of NRT used, and by investigating the mechanisms by which preloading may have its effects. Chapter 4 also includes our response (Lindson & Aveyard 2011[b]; Appendix 4) to a Letter to the Editors (Rose 2011) inspired by our review. This review was carried out to update previous reviews, to support a funding application for a new trial of nicotine preloading commissioned by the NIHR. My role was to develop a search strategy, identify and collect literature not included

in the original reviews, conduct study eligibility assessment, extract data, assess risk of bias, conduct analyses, draft the manuscript for publication, and draft the response to Rose's (2011) letter.

Chapter 5 builds on Chapters 3 and 4 by assessing the experiences of the RRT trial's (described in Chapter 2) participants, when using the behavioural abrupt or reduction to quit methods, and preloading. I feel that it is important to gain insight into the perspectives of the individuals taking part in these interventions, as when deciding to implement an intervention it is important not only to take into account whether these are successful in controlled circumstances, but whether people would be likely to use and remain engaged with that intervention throughout the entire programme, if it were available. The efficacy of a treatment is irrelevant if people will not enrol onto the programme in the first instance. By asking participants directly it is possible to gain sometimes unexpected insights into why an intervention may or may not be successful beyond that which could be achieved through examining quantitative data. As mentioned above this collaborative work was the result of my idea outlined in Chapter 2. My role was to design the study, create study documents, identify, contact and interview participants, arrange transcription, carry out analyses, identify exemplary quotations, and draft the manuscript.

Finally Chapter 6 discusses the findings presented in the previous Chapters, drawing them together and relating them back to the original objectives of the thesis. Based on this, conclusions are drawn about the potential impact of the results on future policy and practice in the field of smoking cessation, and how future research could be carried out to build on these.

The Chapters in this thesis are ordered chronologically, based on the emergence of research findings and resulting ideas over a period of time. It may seem logical that the description of the new RCT (RRT; Chapter 2) should come after the literature reviews and meta-analyses of the existing studies (Chapters 3 and 4); however when the protocol was developed the reviews had not been carried out, and so trial justification and design decisions were not based on these, but a more informal non-systematic review of the literature (Section 2.1.1).

CHAPTER 2: RAPID REDUCTION VERSUS ABRUPT QUITTING FOR SMOKERS WHO WANT TO STOP SOON: A RANDOMISED CONTROLLED NON-INFERIORITY TRIAL

2.1 Background

Without help, most smokers who try to stop smoking relapse within one week and only 4% of quit attempts sustain abstinence for one year (Hughes et al. 2004). The NHS SSS achieve around 15% one year abstinence (Ferguson et al. 2005), and NHS support in primary care achieves around 7% one year prolonged abstinence (Aveyard et al. 2007). Thus, while treatment improves substantially the number who achieve abstinence, whatever method of stopping is used, return to smoking is the norm for the majority, and even with treatment the majority of relapsers resume smoking during active treatment. Thus there are a cadre of patients who have been through treatment services many times. Currently, as addressed in Section 1.4, the NHS gives the same treatment on repeated attempts to stop as on the first attempt- abrupt quitting. Patients can choose different pharmacotherapies, but in other respects, the treatment is the same every time. As previously mentioned in Chapter 1 there are principles that suggest that reducing smoking before quitting might be as, if not more, effective than abrupt cessation, and could provide a new option for those who have failed to quit abruptly in the past. These include, setting a goal more in keeping with current behaviour, the cognitive psychology self-efficacy principle, decreasing the association between environmental cues and behaviour, and reducing biological dependence by lowering the dose of nicotine an individual receives. In addition, smokers feel that cutting down is an

appropriate way to stop smoking. However, before a programme such as this is introduced it is important to ensure it is at least as effective as abrupt quitting, otherwise smokers may choose to reduce who would otherwise have quit abruptly, putting themselves at a disadvantage.

2.1.1 Literature Review

We conducted a search to find randomised trials comparing gradual to abrupt cessation using MEDLINE, Google Scholar, PsychINFO, Society for Research on Nicotine and Tobacco (SRNT) abstract search, a citation search, and contact with key authors.

Identified trials (with relevant data) all resulted in RRs with CIs spanning one for 6 or 12 month abstinence (Flaxman 1978; Cummings et al. 1988; Gunther et al, 1992; Cinciripini et al. 1995), suggesting that neither abrupt quitting or reducing smoking to quit resulted in superior quit rates in any of the studies. Cinciripini et al. (2006) have recently completed a three arm study with participants randomised to cutting down with nicotine patch, nicotine patch pre-cessation treatment without reduction, or usual post-cessation patch only. The results are unpublished, but preliminary data show improved cessation for the reduction arm at four weeks, with no evidence of difference at six months. The reduction arm had lower craving, fewer lapses, and less negative affect (personal communication). These studies are reviewed in more detail in Chapter 3.

A second group of studies have led to a new use for NRT as an aid to gradual cessation in a programme called Cut Down Then Stop (CDTS). Critically, the CDTS trials enrolled smokers

who wanted to reduce their smoking but did not intend to stop it in the next one or six months. They were randomised to either NRT (used in acute and patch preparations) or placebo. The treatment programme gives NRT over six to nine months for reduction and for a further three months post-cessation. The CDTS NRT programme led to improvements in six month prolonged abstinence over placebo (7% versus 3%), with an RR (95% CI) of 2.06 (1.34, 3.15) (Wang et al. 2008). Six months prolonged abstinence is a standard accepted for evidence of effectiveness in smoking cessation (West et al. 2005). Half of those who sustain abstinence for six months remain abstinent for their whole lives (Etter & Stapleton 2006). These cessation rates are lower than those achieved by the NHS SSS (Ferguson et al. 2005); however the key point is that these were rates achieved in smokers who said that they did not intend or want to stop imminently (and who were on average highly addicted). It is possible that the differing intentions of smokers enrolled in CDTS trials and those that use the abrupt quitting method offered by the NHS explain the difference in prolonged abstinence rates. The CDTS studies demonstrate that reduction with NRT is more effective than without, but cannot show whether reduction or abrupt cessation is more effective. The positive effect of pre-quit nicotine patch found in the CDTS trials has also been discovered in trials utilising the abrupt method of cessation, as outlined in Section 1.5.5. However, two studies using nicotine gum pre-quit, for four days and four weeks respectively, have appeared to show less of an effect (Herrera et al. 1995; Etter et al. 2009).

There is evidence that reduction should be much more rapid than used in the CDTS trials. In one CDTS trial (Haustein 2002) participants were randomised to rapid (four week) versus slow reduction (12 month). Despite enrolling people who said they did not intend to stop smoking in the next month, rapid reduction outperformed slow reduction at all follow-ups. In

addition, a pilot study randomised 31 smokers, ready to stop, to reduce over two weeks or three (Blalock et al. 2003). The quit rates were slightly higher in the two week group and qualitative data indicated that rapid reduction helped demarcate the boundary between reducing and quitting. Further detail about these trials can be found in Section 5.1.2.1.

The studies comparing rapid reduction with abrupt quitting typically had small sample sizes and took place before a common standard had been introduced for both reporting RCTs in general (Moher et al. 2001), and carrying out and reporting the results of smoking cessation focused trials (West et al. 2005). Little consideration was given to the mechanisms by which these methods have their effects, which could provide insight into the best ways to implement them, and who they might benefit the most. Therefore there is a need for a further correctly powered trial to compare rapid reduction and abrupt quitting, incorporating the use of pre-quit NRT, and investigating these mechanisms.

2.1.2 Trial Objectives

2.1.2.1 Aim

To confirm or refute the non-inferiority of smoking reduction to quit in comparison to abrupt cessation, in smokers who wish to quit.

2.1.2.2 Objectives

1) To measure smoking abstinence at four week, eight week and six month follow-up, in smokers who wish to quit, in both the abrupt and reduction treatment arms.

2) To investigate possible mechanisms by which the behavioural advice to reduce prior to quit day achieves its effects in smokers who wish to quit.

2.1.2.3 Hypothesis

A behavioural intervention to reduce smoking before quitting completely will result in abstinence rates non-inferior to a behavioural intervention to quit smoking abruptly in smokers who want to quit.

2.1.2.4 Null Hypothesis

A behavioural intervention to reduce smoking before quitting completely will not result in abstinence rates non-inferior to a behavioural intervention to quit smoking abruptly in smokers who want to quit.

2.2 Method

All methods outlined below are in compliance with the Declaration of Helsinki (World Medical Association 2008) as approved by the National Research Ethics Service (Reference: 08/H0408/213)

2.2.1 Why a non-inferiority trial?

Given that reduction is both intuitive and appealing; it is likely to attract smokers who would have used abrupt quitting had reduction not been available. It is imperative to show that such smokers would not be worse off if they opted for a reduction programme rather than an abrupt quitting programme. Therefore we propose a non-inferiority, unblinded, pragmatic trial, large enough to show the non-inferiority these methods, to test this. Non-inferiority trials can show superiority but conventional superiority trials cannot show non-inferiority (Piaggio et al. 2006).

2.2.2 Inclusion criteria

Participants must meet all of the following inclusion criteria to be eligible for enrolment into the trial:

1. Male or female;
2. 18 years or older;
3. smokes at least 15 cigarettes, or 12.5 grams of loose tobacco daily as roll your own cigarettes, or blows 15 parts per million (ppm) or above on exhaled CO reading;
4. willing to stop smoking completely in two weeks;
5. able to understand and consent to all pertinent aspects of the study;
6. willing to be randomised to either trial arm;
7. willing and able to comply with all other study procedures.

2.2.3 Exclusion criteria

Subjects presenting any of the following exclusion criteria will not be included in the trial:

1. currently using NRT, bupropion, nortriptyline, mecamylamine, reserpine, or varenicline, or undergoing any treatment for tobacco dependence (e.g. acupuncture);
2. unstable angina pectoris, myocardial infarction, or cerebrovascular accident during the last three weeks;
3. severe cardiac arrhythmia;
4. currently uncontrolled hyperthyroidism;
5. active phaeocromocytoma;
6. pregnancy, lactation or intended pregnancy;
7. suspected alcohol or drug abuse;
8. participation in other medicinal trials within the last three months and during study participation;
9. previous severe skin reactions to nicotine patches, or severe eczema, or other skin diseases that make patch use hazardous or undesirable;
10. a severe acute or chronic medical or psychiatric condition or previously diagnosed, clinically important renal or hepatic disease, that may increase the risk associated with study participation or may interfere with the interpretation of study results, and in the judgment of the investigator, would make the subject inappropriate for entry into this study.

These exclusions were developed based on contra-indications to NRT use (2, 3, 4, 5, 6, 9, 10), to reduce the likelihood that observed effects may be due to a source other than those controlled in the trial (1, 8), or to limit the burden of quitting on smokers who may find

participation in the trial difficult, taking into account the intensity of data collection and visits (7, 10).

2.2.4 Withdrawal criteria

Trial Withdrawal: It is standard practice in smoking cessation trials to regard those who fail to attend for support and treatment as having relapsed, which is based on evidence (West et al. 2005). Therefore, failure to attend will not count as withdrawal from the trial and the only withdrawals will be those where a patient asks to be withdrawn. Such patients will not be replaced and, unless s/he refuses permission, data available up to that point will be used. Such withdrawals are expected in fewer than 5% of participants.

Treatment withdrawal: One of our exclusion criteria is previous adverse reactions to NRT. Given that many smokers have used NRT recently, the established safety profile of NRT and the evidence from trials of combination NRT (for example Bohadana et al. 2000), we do not expect any serious adverse events (SAE) due to the medication. Nevertheless, there will be a detailed work instruction for the trial that will detail the weekly assessment of side-effects, and the procedure for SAE and suspected unexpected serious adverse reactions (SUSAR). In the event of an SAE or SUSAR that is judged either possibly, probably, or definitely related to NRT, the prescription for NRT will be withdrawn and not re-instituted in that person.

2.2.5 Participant Recruitment

We will recruit participants through South Birmingham, Solihull, Heart of Birmingham and Warwickshire and Worcestershire Primary Care Trusts (PCTs) in the first instance; extension

to other sites will be considered if necessary. We will request that general practitioner's (GP) practices write to patients on their practice lists recorded as smokers and offer them treatment, using a provided RRT study template. We will also request that the NHS SSS write to people on their databases who have tried to stop and failed. The letters sent out will ask those individuals who wish to take part in the trial to respond to the research team. In our experience, 5–10% will respond. Following telephone screening for preliminary eligibility, potential participants will be booked in for an assessment visit and sent a participant information sheet (PIS), giving them more information about the study (Appendix 5). Written informed consent will be obtained from participants, using a consent form (Appendix 6), at the first assessment session before they have been randomised to a treatment arm.

Participants in both treatment arms will be seen weekly for two weeks prior to quit day (visits -2 & -1), on quit day (visit 0), and weekly for four weeks post-quit (visit +1, +2, +3, +4). A further follow-up visit will take place eight weeks post-quit day (visit +8) and a final follow-up phone call at six months post-quit. Therefore all participants will be enrolled in the trial for six months and two weeks.

It is not unusual for people to delay their quit day, once committed, for a variety of reasons, e.g. death of a close family member or friend. In this situation we will allow participants to delay their quit attempt for a maximum of two weeks. They will be advised to carry on with their pre-quit NRT regime as prescribed and their actual quit date appointment will be recorded as their visit three appointment. Extra visits in between week two and week three will be recorded in the case record form (CRF; Appendix 7) and extra diaries and NRT will be issued to the participants to cover their delay period. Participants wishing to delay their quit

day by more than two weeks will be classified as abandoning this quit attempt, NRT will be ceased and the participant will be advised to contact their local NHS SSS (name and number will be provided) when they are ready to set a new quit date.

2.2.6 Allocation to trial arms and treatments

2.2.6.1 Randomisation

Participants will be seen at an assessment session, similar to that used by the NHS SSS, where participants will be randomised 1:1 to reduction or abrupt cessation. We will use Stata software to accomplish stratified randomisation by therapist with blocking within each stratum to ensure balance. The blocks will be randomly ordered blocks of two, four, and six. Each therapist will open sealed numbered envelopes in turn after consent and initial procedures, to determine allocation to abrupt cessation or rapid reduction.

Participants in the reduction arm will be offered a choice of three ways to reduce and asked to choose the method they feel is right for them. Those without strong preferences, who feel they can not choose between methods, will be randomised to one of the three reduction methods. We expect this to occur rarely, and will analyse those who choose their method and those randomised to it together (See Section 2.2.9.3). Again, we will use Stata to accomplish stratified randomisation by therapist with blocking within each stratum. Blocks will be randomly ordered blocks of three and six. The therapist will open sealed numbered envelopes in turn to determine allocation to reduction method.

It is quite likely that we will see couples, friends, or relatives who want to quit together and attend clinic as a group. In this situation they will be randomised together so they go into the same arm, and given the same study number, made individually identifiable by adding a letter, for example A or B. We hope that this will reduce the risk of contamination between behavioural methods. This has the potential to introduce cluster effects, however we expect joint randomisation to occur rarely and so to have little effect. Nevertheless we will bear this in mind when carrying out analysis and allow for clustering if it takes place.

2.2.6.2 Behavioural intervention in the abrupt cessation (control) arm

Participants randomised to abrupt cessation will have a brief discussion with the nurse about smoking and about the nicotine patch treatment. Participants will be informed that the rationale of wearing the patch is to divorce the cigarette smoking behaviour from its reward (the delivery of nicotine), as discussed previously (Section 1.2.3). We hope that this instruction will encourage the smoker not to reduce consumption at all, even if they feel like smoking fewer cigarettes, because this will work against the stated rationale (addressed in Section 2.2.7.1).

At the first and second clinic visits patches will be provided for use until the next visit and homework given to identify critical cigarettes, which will provide the basis for the pre-quit session discussion, used in standard behavioural support. This will be followed by five weekly sessions on quit day and weekly thereafter, following the typical seven session UK withdrawal orientated therapy programme (Hajek 1989). Should a participant resume smoking during this treatment they will be allowed to renew their quit day following the new NHS

standards (Department of Health 2007). From quit day onwards participants in this arm will receive combination NRT, meaning patch plus top-up acute product of their choice (for example gum, inhalator). They will be advised to use generous doses of their acute NRT, because dose is related to outcome (Shiffman 2007), and combination treatment is more effective than patch alone (Stead et al. 2008). Combination NRT is standard in SSS clinics, and advised by NICE (2008) for dependent smokers.

Participants will also be provided with diaries from week -2 to week 0. In weeks -2 and -1 (Appendix 8) these will be used to record the number of cigarettes smoked per day, whether patches are being used, and any free-text comments. In week 0 this will be extended to include the amount of acute NRT product used per day.

2.2.6.3 Behavioural intervention in the rapid reduction (intervention) arm

The rapid reduction arm differs from the control arm only in the advice given in the pre-quit period- the two weeks before quit day. Two of the three reduction methods offered (Section 2.2.6.1) will focus on cpd, and aim to reduce consumption to less than 50% of baseline by the end of the first pre-quit week and less than 25% by quit day. The final method will focus on smoke-free periods (sfp), and aim to reduce the number of time periods when smoking takes place to less than 50% of baseline by the end of the first week and less than 25% by quit day.

The three methods are as follows:

a) Scheduled reduction (SR) method: A median ICI is calculated and then altered to achieve the gradual reduction in cpd. For example, if a person is typically

awake for 16 hours per day and smokes 16 cpd, then the median ICI is one hour. To achieve a 50% reduction, the ICI needs to increase to two hours. In this method, a person is advised to smoke every two hours whether or not they want to do so. If they cannot smoke, that cigarette is missed and the next opportunity takes place two hours later. At visits -2 and -1 each participant and their nurse will calculate their ICIs for the week, and record these on a smoking schedule (See Appendix 9 for an example of a completed SR schedule), which the participant can then refer to during the week. This method is potentially difficult in a country with smoke-free laws and for people with jobs where it is not possible to take cigarette breaks at the allotted times.

b) Hierarchical reduction (HR): There are two variants of this approach- hierarchical reduction- difficult (HR-D) and hierarchical reduction- easy (HR-E). Participants classify their usual cigarettes as either habitual cigarettes or particularly rewarding cigarettes. The HR-D method aims to get participants to reduce smoking by removing the most rewarding and therefore difficult cigarettes first. The rationale is that getting rid of the hardest ones is the most difficult and if this can be accomplished well before total abstinence, this will enhance confidence and reduce the chance of a slip. Using the HR-E method participants seek to avoid smoking habitual, less rewarding cigarettes that they judge easier to forgo first. The rationale is that this gives participants early initial success and allows them the confidence to tackle more difficult cigarettes later. If HR is allocated or chosen participants will be able to choose between HR-E and HR-D. Again participants will work with their nurse to create a reduction schedule (See Appendix 10 for an example of a completed

HR schedule) at visits -2 and -1, which will detail the cigarette(s) they should knock out each day.

c) Smoke free periods (SFP): This method is different to the previous methods as it does not focus on cpd as the marker of reduction. Participants map out their typical day on a reduction schedule (see Appendix 11 for an example of a completed SFP schedule), marking the times they would usually smoke (their smoking periods). In a country with smoke free laws, smoking behaviour is generally concentrated into smoking breaks, except perhaps when at home. The SFP procedure will concentrate on reducing these smoking breaks over the reduction time. In a smoking period, participants will be able to smoke as much as they want, but they will be asked not to smoke outside of the smoking periods. The rationale for this is that anecdotally smokers typically report few urges to smoke in places where smoking is forbidden, but find not smoking when it is allowed more difficult. This method provides clear boundaries about when smoking is and is not allowed. It also focuses participants on what is being achieved- sfp- and not on what is being forgone- cigarettes not smoked.

In methods that focus on cpd, participants will be asked to put aside the next day's cigarettes into a separate pack to encourage adherence to the target. Participants will be instructed to replace cigarettes missed with a type of acute NRT (for example nicotine gum) and encouraged to use this sufficiently to avoid smoking more cigarettes than the quota or smoking in a sfp. Reduction participants will also complete a diary from week -2 to week 0 (Appendix 12), recording patches and acute NRT used, and the number of cigarettes smoked. In a current trial we find most participants complete the diary reliably.

2.2.7 Trial Medication

The trial takes place within the context of NHS smoking cessation clinics, which provide behavioural support and medication to assist smoking cessation. The majority of smokers in these clinics use NRT as their medication to assist quitting (Section 1.5.1). This is the only pharmacotherapy that will be available to participants in this trial to ensure that any observed differences in efficacy are due to behavioural instructions, rather than medication choice.

As previously mentioned (Section 2.2.6.2) current best practice is to use NRT in combination, which has been endorsed by the MHRA, and is recommended by NICE (2008). Therefore in this study, we propose using both nicotine patch and an acute form of NRT in combination (See Table 2). We will use Niquitin, Nicotinell, Wockhardt, and Nicorette NRT products, including 24 hour patches, which are also licensed for 16 hour use (there is no evidence that the effectiveness of 16 hour patches or 24 hour patches is different (Stead et al. 2008).

Table 2: Daily medication regimes

	Rapid reduction	**Abrupt cessation**
Pre-quit period (-2 weeks to quit day)	21mg/24 hour patch, 1mg of absorbed nicotine per cigarette forgone as a minimum from acute NRT.	21mg/24 hour patch, No acute NRT.
Quit day onward	21mg/24 hour patch, Minimum of 6mg of absorbed nicotine from acute NRT. As much as needed to feel comfortable.	21mg/24 hour patch, Minimum of 6mg of absorbed nicotine from acute NRT. As much as needed to feel comfortable.

NRT – Nicotine Replacement Therapy; mg–milligram

These patches provide about 1 milligram (mg) of nicotine per hour. Participants will be advised to wear the patch 24 hours per day, but will be advised to wear it only during day time should they experience sleep disturbance or vivid dreams. Although the medications provide the same amount of nicotine delivery with similar pharmacokinetics, the license dosing advice differs. Niquitin CQ recommend the 21mg patch for smokers who smoke 10 or more cpd, while Nicotinell recommend the 30cm^2 (= 21mg) patch for smokers of 20 or more cpd. The evidence is that most smokers who smoke 10 or more cpd get less nicotine from their patch than they did from their cigarettes (Tonnesen et al. 1999; Johnstone et al. 2004). We have therefore chosen a cut-off of 15 cpd. In addition, all participants will be offered additional intra-nasal or oral nicotine replacement (gum, microtabs, lozenges, or inhalator), with the choice of delivery system left to personal preference. The dose of these products used will vary, but participants will be advised to take at least 1mg of absorbed nicotine for each cigarette forgone in the reduction phase, because each cigarette delivers about 1.2mg on average, though this is highly variable (Perez-Stable et al. 1998). A 2mg oral product, for example gum, delivers about 1mg available systemically, and a 10mg inhalator cartridge yields about 3mg of nicotine that is systemically available. In the cessation phase, participants in both arms will be given identical dosing instructions and advised to use at least 6mg of absorbed nicotine daily from acute NRT, which is the minimum dose associated with improved outcomes (Stead et al. 2008).

2.2.7.1 Rationale of the pre-quit NRT in the abrupt and rapid reduction arms

By utilising pre-quit NRT in both arms of the trial we will ensure that any effect is caused by the difference in reduction rather than differences in nicotine intake. Smoking and using a

patch gives higher concentrations of nicotine than just smoking, whereas smoking and using an acute form of NRT does not (Fagerstrom & Hughes 2002). As explained in more detail in Section 1.2.3, it is thought that high levels of nicotine dissociate the cigarette from its reward and this is responsible for the effectiveness of nicotine pre-treatment (Hajek 2006), which does not appear to occur when only acute forms of NRT are used (Herrera et al. 1995; Etter et al. 2009). Consequently, we have chosen a nicotine patch for both study arms. However, gradual reduction could undermine the nicotine preloading effect so we will attempt to keep nicotine levels high by replacing foregone cigarettes with acute NRT, alongside the patch.

2.2.7.2 Duration of medication use and discontinuation

At the time of writing, the license for NRT allows continued use for up to nine months, however patch use will be phased out using the step down doses between two and three months after quit day. For participants who are still lapsing but showing determination to stop smoking, the patch will be phased out more slowly, providing no signs of overdose are evident. The dose reduction regimes vary in the SPCs and in any case the dose reduction is individual, based upon confidence in reducing the patch dose and occurrence of urges to smoke. Oral NRT is commonly continued for several months in abstinent smokers (Hajek et al. 1988; Hughes et al. 1991; Sutherland et al. 1992; Hajek et al. 2007) and there are reasons to assume this is beneficial; again we will apply clinical judgement in deciding on length of treatment of oral/intranasal NRT. The advice on patch duration and oral NRT discontinuation will be the same in both arms. At week +8 participants will be given a months supply of NRT and advised to contact either their GP or local SSS should they need further support and/or prescriptions beyond week +12.

2.2.7.3 Stopping rules/modification of medication regime

The following stopping rules or modifications to the medication regime will be exercised:

- Participants who have problems with insomnia or difficulties with vivid dreams will use the patch for 16 hours daily, not 24 hours;
- Participants who have skin reactions to the patch that are not controlled by switching preparations, emollient and hydrocortisone cream will switch to acute NRT only;
- Participants who become pregnant may have their dose adjusted in line with NICE (2008) guidance, and in accord with the wishes of the participant;
- Participants who show symptoms of overdose will have their dose reduced;
- Participants who do not quit or give up on their quit attempt will cease using NRT.

2.2.7.4 Evidence of the safety of concomitant smoking and NRT use

The safety of using transdermal NRT whilst smoking was investigated in reviews by Fagerstrom & Hughes (2002) - summarised in Table 3- and Wang et al. (2008). Wang et al. (2008) systematically reviewed the CDTS studies mentioned in the literature review (Section 2.1.1), and also conducted a meta-analysis of adverse events in people smoking and using NRT versus those smoking and using placebo NRT. Overall, 1384 predominantly middle-aged smokers were treated with NRT for 6 to 18 months, while 1383 were treated with placebo. Four deaths occurred in those randomised to NRT and four in those randomised to placebo (OR=1.00, 95% CI=0.25, 4.02). SAEs occurred in fewer than 8% of participants in both arms (OR=1.09, 95% CI=0.79, 1.50). In no cases were these judged likely to have been due to treatment. Discontinuation of treatment due to adverse events was rare with 1.7% and

Table 3: Summary of Fagerstrom & Hughes (2002) review of the safety of smoking and concomitant NRT use

Study reviewed	Nicotine intake	Blood nicotine concentrations	Safety conclusions
Foulds et al. (1992)	16+ cpd & 15mg TP over 16hrs	Baseline: 37ng/ml, Placebo: 36ng/ml, 15mg TP: 44ng/ml.	Participants experienced almost no subjective toxic effects whilst wearing the patch
Pickworth et al. (1994)	13+ cpd & 22mg, 44mg TP over 24hrs	Baseline: 30ng/ml, Placebo: 19ng/ml, 22 mg TP: 39ng/ml, 44 mg TP: 63ng/ml.	No adverse subjective experiences were reported.
Mahmarian et al. (1997)	8+ cpd & 14mg, 21mg TP over 24hrs	Baseline 16ng/ml, 14mg TP: 24ng/ml, 21mg TP: 30ng/ml.	Only adverse effects noted were nausea & vomiting in 2 patients.
Zevin et al. (1998)	Smoking ad libitum & 21mg, 42mg, 63mg patch over 8hrs	Placebo: 20ng/ml, 63mg TP: 60ng/ml.	No additional haemodynamic effects of TP on heart rate, blood pressure, noradrenaline, white blood cell count, fibrinogen, haematocrit, cortisol, or lipids. No adverse reactions.
Carpenter et al. (2000)	11+ cpd & TP, gum or inhaler	Lower than 22mg TP: 54% increase, Higher than 22mg TP: 190% increase.	Not applicable

cpd – cigarettes per day; mg – milligrams; TP – transdermal patch; ng/ml – nanograms per millilitre; hrs–hours

1.3% in the NRT and placebo groups respectively (OR=1.27, 95% CI=0.64, 2.51). Nausea was selected as an index symptom to indicate possible nicotine overdose. It was slightly and significantly more common in the NRT group with 8.6% versus 5.3% on placebo experiencing nausea (OR=1.69, 95% CI=1.21, 2.36).

2.2.7.5 Lifestyle advice

There is no special dietary or life-style advice warranted for NRT use, and the associated regimes proposed in the protocol. However, participants using oral NRT will be advised to avoid acidic drinks 15 minutes prior to using oral NRT, as acidic conditions in the mouth have been found to hinder nicotine absorption (Henningfield et al. 1990).

2.2.8 Concomitant Medication

All medications will be permitted for use concurrently, except those that are proven to help smoking cessation (bupropion, nortriptyline, mecamylamine, reserpine, varenicline), and medications that are unlicensed, for which no interaction data with NRT are available. No rescue therapies will be permitted in treatment, in accordance with NICE (2008) guidance on smoking cessation pharmacotherapy. The NRT itself is aimed at the relief of symptoms of nicotine withdrawal. Should adverse skin reactions occur with the use of the patch, advice will be given on the use of OTC emollients and 1% hydrocortisone cream, as is standard. Data on all concomitant medications will be recorded.

2.2.9 Trial Outcomes

2.2.9.1 Primary trial outcome

- Abstinence at four weeks, measured according to the Russell standard for clinical practice, outlined in the NHS SSS Service and Monitoring Guidance (Department of Health 2007). The Russell standard definition of abstinence allows a two week grace period from quit day for slips, and is CO validated.

2.2.9.2 Secondary trial outcomes

- Point prevalence abstinence at each follow-up and prolonged abstinence at eight weeks and six months. Half of those sustaining abstinence for six months sustain it for life- the goal of treatment (Stapleton 1998; Etter & Stapleton 2006).
- Urges to smoke and nicotine withdrawal symptoms will be measured after cessation. Urges to smoke are an important proxy of return to smoking (Doherty et al. 1995; Killen & Fortmann 1997).

2.2.9.3 Other trial outcomes (non-efficacy)

- Exhaled CO, using CO monitors. This is a measure of smoke exposure, which we will compare before quit day between study arms.

- Cotinine levels- to show whether nicotine intake rises from normal when smoking in both arms, as we expect, and whether the rise in cotinine relates to the success of treatment. We propose measuring cotinine at baseline, week -1, quit day, and at week +1 in all participants to examine whether reduction leads to higher self-medication with nicotine. It could be that reduction treatment gets people used to using high doses of NRT and therefore some of the effect of treatment could be explained by post-quitting NRT dose. These data will also provide valuable evidence on nicotine consumption while smoking and using NRT.

- Participant rating of the reward from their cigarette while smoking using the modified Cigarette Evaluation Questionnaire (mCEQ) (Westman et al. 1992; Capelleri et al.

2007). The mCEQ measures satisfaction, taste, mood, and cognitive and sensory sensations to smoking particular cigarettes. Twice each week, prior to quitting, we will ask participants to rate satisfaction from smoking, for the first cigarette of the day and one other key cigarette. We will routinely ask participants to rate cigarette satisfaction in one specimen day so as to anticipate danger periods for lapsing after cessation. For example, typical rewarding cigarettes are after dinner. Additionally, participants will be asked to rate a cigarette smoked in a negative affect situation. It is possible that the mechanism of benefit may be the reward from smoking, and this study will allow investigation of this. We will also rate satisfaction from smoking after cessation, should slips occur.

- Confidence in quitting- self-efficacy- is a predictor of abstinence (McIntyre et al. 1983), which may be modified by reduction, and so will be used in mediation analysis. This will be measured by the single question:

How high would you rate your chances of giving up smoking for good at this attempt? (Circle one response):

Extremely high

Very high

Quite high

Not very high

Low

Very low

- Smoking stereotypy is a measure of the degree to which smoking is prompted by cues to smoke (Shiffman et al. 2004). Reduction may work by disrupting stimulus control, as hypothesised in Section 1.2.2, and the stereotypy scale could measure this. Only two questions from this scale will be used to measure smoking stereotypy because the other questions are either forced to change with reduction, or could not be assessed over a short period.

There are no specific outcomes proposed when comparing methods of reduction, hence why randomisation to method of reduction was not obligatory. Participants who chose their method of reduction and those randomised to it shall be analysed together. This analysis will focus on the above measures and is exploratory. See Table 4 for a breakdown of which outcomes are to be measured at specific time-points.

2.2.10 Trial Statistics

2.2.10.1 Power calculation

We propose a non-inferiority trial, following the Consolidated Standards of Reporting Trials (CONSORT) statement for such trials (Piaggio et al. 2006). A one-sided alpha of 0.05 will have 80% power to detect inferiority of 9.5% in the quit rate at four weeks, if 343 participants are enrolled in each arm, assuming 50% four week abstinence. This is roughly the percentage of people who achieve four week abstinence when quitting through the NHS SSS (The NHS Information Centre 2011). Therefore the trial sample size shall be N = 700. Analyses will be carried out on an intention-to-treat (ITT) basis, according to the Russell Standard, where participants lost to follow up are assumed to be smokers (West et al. 2005). Arguably,

Table 4: Schedule of trial measures

Follow-up	Trial measures
Baseline (wk -2)	-Smoking history, demographics, nicotine dependence using FTND (Heatherton et al. 1991), urges and withdrawal using MPSS (West & Hajek 2004), confidence in quitting, smoking stereotypy (Shiffman et al. 2004), cigarette satisfaction (Cappelleri et al. 2007), exhaled CO, salivary cotinine. -Give out diaries.
Pre-quit visit (wk -1)	-CO, cotinine, MPSS, confidence, smoking stereotypy, cigarette satisfaction, adverse events. -Collect diaries with daily smoking, NRT use, the two urge to smoke questions from the MPSS, and once a week cigarette satisfaction. -Give out diaries.
Extra pre-quit visit (wk -1a)	**Only applicable if delays quit date by 1 week** -CO, MPSS, confidence, smoking stereotypy, cigarette satisfaction, adverse events. -Collect diaries with daily smoking, NRT use, the two urge to smoke questions from the MPSS, and once a week cigarette satisfaction. -Give out diaries.
Extra pre-quit visit (wk -1b)	**Only applicable if delays quit date by 2 weeks** -CO, MPSS, confidence, smoking stereotypy, cigarette satisfaction, adverse events. -Collect diaries with daily smoking, NRT use, the two urge to smoke questions from the MPSS, and once a week cigarette satisfaction. -Give out diaries.
Quit day (wk 0)	-CO, cotinine, MPSS, confidence, smoking stereotypy, cigarette satisfaction, adverse events. -Collect diaries with daily smoking, NRT use, the two urge to smoke questions from the MPSS, and once a week cigarette satisfaction. -Give out diaries
One week after quit day (wk +1)	-CO, cotinine, MPSS, confidence, cigarette satisfaction if lapsed, adverse events -Collect diaries with daily smoking, NRT use, the two urge to smoke questions from the MPSS, and once a week cigarette satisfaction.
Post-quit visits (wks +2, +3, +4)	-Smoking in past week, CO, MPSS, confidence, cigarette satisfaction if lapsed, NRT use, adverse events
+8 wk visit	-Smoking in past 4 weeks, CO, MPSS, cigarette satisfaction if lapsed, confidence, NRT use, adverse events
6 month telephone call	-Smoking status over past 5 months, NRT use, SAEs. Those claiming 7-day abstinence will be invited to a validation visit for exhaled CO.

FTND - Fagerstrom Test for Nicotine Dependence, MPSS – Mood and Physical Symptoms Scale, CO – carbon monoxide, NRT – nicotine replacement therapy, SAEs - serious adverse events.

differences of 5% at four weeks would be worthwhile detecting (West 2007), but a trial would need to enrol 2500 participants for this, which would make it impractical and unlikely to be funded. If the reduction arm produced abstinence rates not worse than 9.5% less than the abrupt arm at four weeks, then it would still result in an abstinence rate of at least 40% at 4 weeks. This is almost twice as effective as basic support for smoking cessation in primary care, measured at 4 week follow-up (22%; Aveyard et al. 2007) and therefore, in the judgement of the authors, is probably sufficient for NHS SSS to implement the programme.

This trial is powered to make a comparison between the abrupt quitting and reduction to quit arms of the study, and not to make comparisons between reduction methods. This will be kept in mind during analysis, and any comparison made between reduction methods will be purely exploratory.

2.2.10.2 Analysis

The analysis will compare the proportions stopping smoking, calculating the RR and CIs. If the upper and lower limits of the CIs lie above the non-inferiority margin (0.9) then reducing smoking to quit will be judged non-inferior to quitting abruptly, in accord with Piaggio et al. (2006). We will calculate differences in withdrawal scores using regression, controlling for baseline differences, as is standard using the Mood and Physical Symptoms Scale (MPSS) (West & Hajek 2004). We will investigate possible mechanisms of action (NRT dose, cigarette satisfaction, withdrawal, self-efficacy) using mediation analysis within a regression framework. Mediation analysis is outlined in more detail by the Research in Prevention Lab (RIPL) research group at the Arizona State University (RIPL 2008).

In comparing methods of reduction, we have no specified hypotheses. We will compare changes in confidence, stereotypy, and urges to smoke, calculating differences in mean changes and confidence intervals for the difference. We will compare the proportion abstinent, using point prevalence and prolonged abstinence as in the comparison between reduction and abrupt cessation. The primary analysis of abrupt cessation versus reduction will not be adjusted by method of reduction used.

2.2.11 Qualitative Interviews

Qualitative interviews will be conducted during the trial to investigate participants' experiences and opinions about the methods they used to make their quit attempt. These views could be used in the future to refine quitting methods, and to provide insight into how the methods may work. Interviews will be conducted over the phone for a maximum of 30 minutes per participant, and not necessitate a further visit in order to encourage participants to take part. Interviews will be carried out by a researcher (NL), using a semi-structured interview schedule consisting of open questions (Appendix 13). As this research is largely exploratory there are no pre-conceived ideas of the answers that participants may provide. The semi-structured schedule means we will be able to ask participants to elaborate on topics which arise and appear to be of interest. All of the interviews will be digitally recorded and then transcribed, and analysed as the interviews progress. These recordings and transcripts will be filed with no identifying information and so will be anonymous. We will carry out interviews with consenting patients (in all arms) until no new themes emerge and we have deemed theoretical saturation to have been reached. Analysis of interview transcripts shall be

carried out using principles of the framework approach (indexing, charting, mapping and interpretation), developed and outlined by Ritchie & Spencer (1994).

At the first visit when the research nurse explains the study participants will be given information about these interviews. There will be an option included on the consent forms (Appendix 6), which will allow participants to opt out of taking part if they wish. If participants agree to take part they will be asked to provide a phone number and convenient times to contact them, so that we can call them to conduct the interviews around week +5. They will also be provided with a sheet providing information about the interviews and the topics that they will be asked about (Appendix 14). There will be room for participants to make notes on these topics as they proceed through the study, so that these can be used as prompts for participants whilst they are being interviewed. Hopefully this will encourage participants to think about their method of quitting throughout the study, so that they can provide richer data when interviewed.

2.2.12 Trial schedule

With two full-time nurses who will also act as trial co-ordinators and liaise with practices, and do follow ups, and the support of a PhD student, we can see the 700 participants in 24 months (bearing in mind that clinical contacts span 10 weeks).

2.2.12.1 Definition of end of trial

End of trial is defined as the final six month patient follow-up, measuring CO level of the last participant undergoing the trial.

2.2.13 Safety Reporting

2.2.13.1 Assessment of safety

Potential participants' safety will be ensured by screening for eligibility using a structured form (included in the CRF- Appendix 7), completed by the trial nurse. This will record evidence of eligibility and exclusion criteria. In addition, the nurse will take a general medical history to assess for other complicating diseases. Any queries remaining as a result of this process will be resolved by discussion between the trial nurse, principal investigator (PI) and the relevant physicians providing routine medical care (usually the participant's GP). Such concerns are not rare and typically arise from a participant's hazy knowledge or understanding of their past medical history, but can usually be readily resolved. No blood or further medical testing will be necessary to ensure safety.

NRT has been investigated in several hundred previous clinical trials and is widely prescribed worldwide. It is subject to safety monitoring, and is replacing a product- nicotine- which the participants are already consuming, and will most likely have consumed for many years in cigarettes. Thus, there is every reason to expect that treatment in this trial will be safe. Participants will be warned about the side-effects of NRT and advised not to stop taking the medication without consulting with an NHS professional; preferably the trial team. To this end, all participants will be given a credit card-sized card including the trial team's contact details that will allow participants to receive advice on medication or to report perceived SAEs as required. Participants will record the occurrence of side-effects of medication, as specified on the SPC for relevant NRT preparations, by completing a checklist. The checklist will be given to the trial nurse and the nurse will enquire about recorded adverse events, so as

to determine the severity of any adverse event and ensure that appropriate advice is given for its management (such as rotating the patch site or use of emollients for skin reactions). For each known side-effect listed in the SPC, the trial nurse will have a definition of clinical severity. For example, a mild skin site reaction to the patch will be defined as burning sensation that does not interfere with normal activities, redness or swelling at the site of application, or mild blistering. Any reaction beyond that will be classified as potentially moderate or severe and will be reported to and discussed with the PI. A decision on stopping therapy will then be made with the participant, attending clinician, PI, and other relevant parties as appropriate. Nicotine has a short half-life (two hours), meaning that the blood concentration will not build up during the course of treatment, so that new side-effects are not expected after the first few weeks. In addition, with reactions relating to local use, such as skin discomfort from patches, or bad taste from oral use, either treatment will have been switched or people will have become accustomed to the side-effects within a short time of using the preparation. At their last clinic visit (week +8 of the quit attempt) participants will be advised to phone the provided trial contact number to report any side-effects that occur after this. The advice given will depend upon the severity of the reported reaction, and those with moderate reactions will be invited to an ad hoc consultation.

Participants will also complete a schedule of nicotine overdose symptoms at each visit. On completion of this questionnaire, the schedule will be handed to the nurse and thus any symptoms of overdose will be assessed. Based on this enquiry the nurse will make an assessment of whether the NRT dose is too high or not, and then take appropriate action, such as continue with prescribed dose, or direct the participant to use a lower dose, which will be recorded.

The SPC for the relevant NRT products contain no warnings about serious adverse reactions, except rare allergic reactions, such as angioedema, and cardiac arrhythmias- occurring in less than 1/1000 users. This and the long history of NRT use in and outside of trials means that no or very few SUSARs are expected in this trial. On the reverse of the trial card providing the contact number for advice on side-effect management, there will be instructions for the reporting of SAEs. Therefore, we expect to become aware of these through direct contact with the participant or their attending physician. If any member of the trial team becomes aware they will inform the PI within 24 hours. The PI will then assess the seriousness, causality, expectedness and severity of the adverse effects. An immediate decision will be made on the interim use of medication for that participant. If an event is judged severe, it will be reported to the trial sponsor, who will report the event to the Research Ethics Committee and MHRA. Participants will be asked weekly to report inter-current illnesses and the response recorded. If any of these inter-current illnesses contraindicates NRT, this will be immediately reported to the PI and a decision made about continued use of the NRT product. The reporting procedures and definitions for adverse events are presented in Appendix 15.

2.2.13.2 Monitoring and audit

The progress of the trial will be monitored by a quarterly review of records. This will ensure that consent is being obtained and the inclusion and exclusion criteria are adhered to. The medication dispensed and the instructions for using it will also be assessed.

Data cleaning will take place by a series of logical checks on the electronic data. (For example, a person cannot be recorded as prolonged abstinent smoker at six months if they

were not in such a state at eight weeks). Discrepant records will be checked with the source documents, and the database amended if necessary.

The trial will be potentially subject to audit by the appropriate regulatory authorities and therefore participants will be asked to consent to allow their records to be viewed.

2.2.14 Data management

The trial is being run as part of the portfolio of trials in the Primary Care Clinical Research and Trials Unit (PCCRTU), a National Institute for Health Research (NIHR) recognised trials unit in Primary Care Clinical Sciences at the University of Birmingham. The data management will be run in accord with the standard operating procedures, which are fully compliant with the Data Protection Act (Great Britain 1998) and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP) guidance (European Medicines Agency 2002). The source documents for the trial will be the CRFs, which will be stored in the trials unit, in a locked cabinet, in a locked office, in a locked department. The trial database will be securely held and maintained by the PCCRTU. On completion of the trial and data checking, the CRFs will be transferred to Modern Records, a secure archiving facility at the University of Birmingham, where they will be held for 15 years and then destroyed. The database will be anonymised and a secure compact disc containing the link between identification number and patient identifiable information will also be stored in Modern Records.

2.2.14.1 Data protection and confidentiality

Data will be kept in accordance with the Data Protection Act (Great Britain 1998), and the trial registered with the Data Protection Act website at the University of Birmingham. The standard operating procedures of the PCCRTU will be followed, which are designed to protect patient confidentiality. Patient identifiable data will be shared only within the clinical team on a need-to-know basis, to provide good and appropriate clinical care and follow-up. Patient identifiable data will also be shared with GPs, and approved auditors from the Research Ethics Committee, NHS Research and Development, or the MHRA. Otherwise, confidentiality will be maintained and no one outside the trial team will have access to either the CRFs or the database.

2.2.15 Ethics and Research Governance

We will conduct the trial in compliance with the principles of the Declaration of Helsinki (World Medical Association 2008), the principles of ICH-GCP (European Medicines Agency 2002), including recommendations for the reporting of adverse events, SAEs and SUSARs, in accord with the EU Clinical Trials Directive (The European Parliament and the Council of the European Union 2001), and all of the applicable regulatory requirements. The study protocol and other documentation have been reviewed and approved by the National Research Ethics Committee (08/H0408/213), the MHRA (2008-006433-28), and local NHS Research & Development offices. Any subsequent protocol amendments will be submitted to the Research Ethics Committee for approval, and the other bodies if necessary. In addition the Research Ethics Committee will be provided with progress reports as well as a copy of the Final Study Report.

2.2.16 Finance

The study will be funded by the British Heart Foundation and service support costs will be claimed via the Comprehensive Clinical Research Network.

2.2.17 Publication

The trial is registered with www.controlled-trials.com, and results will be written up for submission to a peer reviewed journal. No data relating to individuals will be identified in these publications.

CHAPTER 3: A COCHRANE REVIEW OF REDUCTION VERSUS ABRUPT CESSATION IN SMOKERS WHO WANT TO QUIT

3.1 Background

As previously described in Section 1.4.2, surveys carried out across England and Wales (West & Fidler 2011) and the UK, US, Canada and Australia (Cheong et al. 2007) have investigated the success of quit attempts, and found that abrupt quitting was almost twice as successful as quitting gradually (by reducing first), in those sampled. However, there is reason to believe that this may not be the case when support is provided, as the provision of increased structure may benefit quitters who reduce more than those who quit abruptly (Cheong et al. 2007). Therefore with a goal to establish the relative efficacy of abrupt and reduction to quit services (Section 2.1), it is important that an attempt is made to compare these approaches when support is available to the quitters using them.

Although British (NICE 2008) and American (Fiore et al. 2008) national guidelines for smoking cessation services do not recommend reducing smoking before quitting, both conclude that further research is needed into whether it could be used as a successful intervention to help those who have tried unsuccessfully to quit in the past. The RRT described in Chapter 2 is one attempt to do this, and this review is another. It builds on the narrative review in Section 2.1.1, by carrying out a systematic search and amalgamating the

existing data from RCTs, to come up with an overall conclusion about the relative efficacy of the two approaches.

3.2 Objectives

- To compare the success of smoking cessation interventions that instruct the smoker to reduce the amount they smoke before quitting with interventions that instruct the smoker to stop smoking abruptly, in smokers who want to quit soon.
- To compare adverse events by intervention type (reduction to quit versus abrupt quitting), stratified by whether they use pharmacotherapy.

3.3 Methods

All methods were carried out as specified in the protocol for this review (Lindson et al. 2009[b]).

3.3.1 Criteria for considering studies for this review

3.3.1.1 Types of studies

Randomised controlled trials (RCTs). We included one trial where allocation to treatment arms was cluster randomised, and carried out a sensitivity analysis to adjust for this clustering. To meet the second objective we examined adverse events, only in those trials which had a reduction arm utilising pre-quit pharmacotherapy, and an abrupt quitting arm that did not utilise pre-quit pharmacotherapy (the only trials for which adverse events data was available).

3.3.1.2 Types of participants

Cigarette smokers of any age who intended to stop smoking soon. Participants demonstrated their commitment to quitting by enrolling in a smoking cessation programme. Trials that enrolled smokers who did not intend to quit soon were excluded, as they are covered by the Cochrane review of harm reduction (Stead & Lancaster 2007).

3.3.1.3 Types of interventions

We compared any instruction to participants to reduce the amount of cigarettes smoked before quitting, with any instruction to stop smoking abruptly without prior reduction. We did not include trials with arms where participants spontaneously reduced before quitting without being advised to do so, versus arms where participants stopped abruptly.

Interventions included anything from no behavioural support to extensive behavioural support, but studies were excluded if behavioural support differed substantially in type or duration between arms. Behavioural support pre- and post-quit could vary between the reduction and abrupt quit arms as long as overall contact was roughly equal. Trials could also include concomitant pharmacotherapy to support cessation, as long as it was equivalent in all trial arms after cessation. Pharmacotherapy used prior to quit day could vary as a necessary component of the intervention i.e. to support smoking reduction.

3.3.2 Types of outcome measures

3.3.2.1 Primary outcomes

The primary outcome was abstinence from smoking at least six months after the quit day. We excluded trials with a follow-up of less than six months.

In trials with more than one measure of abstinence, we preferred the measure with the strictest criteria. We used prolonged or continuous abstinence over point prevalence abstinence, and preferred biochemically validated abstinence, such as exhaled CO, over self-report.

3.3.2.2 Secondary outcomes

The secondary outcome was the type and number of adverse events recorded.

3.3.3 Search methods for identification of studies

We searched the Cochrane Tobacco Addiction Review Group specialised register, which has been developed from electronic searches of MEDLINE, EMBASE and PsycINFO, together with hand searching of specialist journals, conference proceedings and reference lists of previous trials and overviews. We also searched MEDLINE, EMBASE, PsycINFO and the reference lists of relevant trials for possible trials to include in the review. Where necessary we contacted the authors of ongoing trials.

We searched MEDLINE (Ovid, 1966 to 5th November 2009), EMBASE (Ovid, 1980 to 2009 week 44) and PsycINFO (Ovid, 1967 to 23rd November 2009) using the following topic-specific terms:

- cold turkey.mp
- (schedul* adj3 smok*).mp
- (cut* down or cut-down).mp
- (({Gradual* or abrupt*}) adj3 (reduction or reduce* or quit* or stop* or abstin* or abstain* or cessat*)).mp
- fading.mp
- taper*.mp
- (controlled adj smoking).mp

[mp=title, original title, abstract, name of substance word, subject heading word]

combined with the standard terms used to identify trials of tobacco addiction interventions for the Tobacco Addiction Review Group specialised register. Full strategies are shown in Appendix 16. We also searched the specialised register in November 2009 using the following terms: Cold turkey or schedul* or Cut* down or cut-down or Gradual* or abrupt* or fading or reduction or reduce* or taper* or controlled smoking.

3.3.4 Data collection and analysis

3.3.4.1 Selection of studies

One author (NL) checked the titles and abstracts of studies identified by the search strategy for relevance, and obtained copies of papers reporting relevant trials. Two authors (NL & PA) then independently assessed the reduced trials list for inclusion in the review. Any disagreements were resolved through discussion with the remaining review author (JH). We based eligibility decisions on the following questions:

1. Is the study described as randomised or quasi- randomised?
2. Were the participants cigarette smokers who wanted to quit?
3. Did the study include at least two groups, i.e. one group advised to reduce their smoking before quitting and one advised to quit abruptly on their quit day?
4. If the intervention includes behavioural support with or without pharmacotherapy, is the intensity of overall contact for behavioural support (throughout the intervention), and post-quit pharmacotherapy, similar between groups?
5. Is the intervention an instruction to reduce the number of cigarettes smoked, rather than an instruction to reduce harm, e.g. smoking cigarettes with lower levels of nicotine?
6. Does the study report smoking abstinence at least six months after the quit date?

If the answer to any of the above questions was 'No' then the trial was not included in the review. Study eligibility, as well as the data extraction outlined below, was piloted on one

study initially, to establish the suitability of our criteria, before full eligibility assessment and extraction took place.

3.3.4.2 Data extraction and management

Only one non-English language article met the inclusion criteria and this was translated from Spanish for this review (Roales-Nieto & Fernández Parra 1992). For each included trial one author (NL) extracted the data and another author checked them (PA). The following information was extracted:

Methods:

- The design of the trial, for example randomised or quasi-randomised
- Country and setting
- Method by which participants were selected
- The definition of a smoker used
- Duration of the study
- Time to follow up(s)

Participants:

- The number of participants randomised to each intervention group
- Demographics of participants (age, gender, ethnicity)
- The average number of cpd, and number of past quit attempts
- Average Fagerstrom Test for Nicotine Dependence (FTND) or equivalent score
- Preference for abrupt or gradual cessation

Interventions:

- The method of rapid reduction intervention used
- The method of abrupt quitting intervention used
- Whether pharmacotherapy was used as part of the intervention, and if so details of use
- Details of any behavioural support provided
- Duration of reduction period
- Who delivered the intervention?

Outcomes:

- Did the trial examine whether the reduction arm reduced as instructed, and that the abrupt arm did not reduce?
- Outcomes measured
- The strictest definition of abstinence used
- Whether abstinence was biochemically verified, and if so, how?
- Whether data was available for an intention-to-treat analysis
- The proportion of quitters in each intervention arm
- The number of adverse events in each arm
- Amount of reduction in cpd in each arm (self report and/or chemical biomarkers)
- Additional outcome results
- Drop-out rates
- Information about withdrawals
- Further information about adverse events
- Missing data in both arms

3.3.4.3 Assessment of risk of bias in included studies

Risk of bias for each trial was assessed within the domains of sequence generation, allocation concealment and incomplete outcome data, using the risk of bias table, as outlined in the Cochrane Collaboration Handbook (Higgins & Green 2009). Blinding of participants and investigators was not assessed, as it is not possible to keep these concealed when administering behavioural interventions, as was the case in the included trials. Selective reporting was also unlikely to be a problem as in smoking cessation trials abstinence is generally the main outcome, and therefore unlikely not to be reported. However during the risk of bias analysis we kept an open mind as to potential sources of bias outside of the tool, and reported those that were apparent (Section 3.4.4).

3.3.4.4 Measures of treatment effect

All quantitative analysis of abstinence data was carried out using the RevMan 5.1 computer programme, developed by the Cochrane Collaboration to carry out systematic reviews and meta-analyses. We compared quit rates between the abrupt cessation and reduction groups, calculated on an ITT basis, including all participants originally randomised to a trial arm. Any participants lost to follow-up were treated as relapsed, excluding any deaths. We used RR as the summary statistic in all meta-analyses, using the Mantel-Haenszel fixed-effect model for pooling results, checking for no significant heterogeneity. Had heterogeneity been detected we would have considered the use of a random-effects model.

We also compared the number of adverse events between arms; however no meta-analysis was carried out for this outcome as data was sparse and not consistently measured across studies.

3.3.4.5 Assessment of heterogeneity

Any inconsistency across study results was identified and assessed by examining forest plots for poor overlap of confidence intervals, and by examining the I-squared statistic.

3.3.4.6 Sub-group analyses

We conducted a sub-group analysis comparing trials which used pharmacotherapy as part of the interventions with those that did not. We also grouped interventions by whether or not the instruction on how to quit smoking was given alongside behavioural support or self-help methods.

3.3.4.7 Sensitivity analyses

We investigated the sensitivity of the main effect, when adjusting for the only cluster randomised trial eligible for inclusion in the meta-analysis. This adjustment to Jerome , Behar et al. (1999) used an intra-class correlation of 0.0105 (as recommended by Martinson et al. (1999) for an outcome of percentage quit in the work place) and an average number of people per group of 18.3 (design effect = 1.18). We also carried out a sensitivity analysis to see whether the exclusion of studies where non-validated, self-report data were used influenced the outcome of the meta-analysis.

3.4 Results

3.4.1 Description of studies

3.4.1.1 Results of the search

The searches of the Cochrane Specialised Register, MEDLINE, EMBASE and PsycINFO resulted in 543 unduplicated references (See Appendix 17 for study inclusion flow diagram). Additionally, at the time of writing, a co-author of this review (JH) has just completed a study comparing reduction to abrupt quitting, and written a study report (Hughes et al. 2010) citing two further studies possibly relevant for inclusion. These 546 references were screened for eligibility based on their titles and abstracts, resulting in a reduced total of 30 studies. These studies were then independently assessed by two authors (NL & PA) for eligibility, based on the questions specified in Section 3.3.4.1. We found 10 studies which were relevant for inclusion in the review based on these criteria (further detail available in Appendix 18); seven of these took place within the USA (Flaxman 1978; Cummings et al. 1988; Curry et al. 1988; Cinciripini et al. 1995; Jerome, Behar et al.1999; Riley et al. 2005; Hughes et al. 2010), and the remaining three were situated in Austria (Gunther et al. 1992), Switzerland (Etter et al. 2009) and Spain (Roales-Nieto & Fernández Parra 1992). We also discovered three ongoing studies (Riley et al. 2001; Cinciripini et al. 2006; Lindson et al. 2009[a]) which, when completed, may also be relevant for inclusion (further details available in Appendix 19). The authors of eight of the aforementioned studies (Cummings et al. 1988; Curry et al. 1988; Jerome, Behar et al.1999; Riley et al. 2001; Riley et al. 2005; Roales-Nieto & Fernández Parra 1992; Cinciripini et al. 2006; Etter et al. 2009) provided additional information when contacted.

The inclusion of Hughes et al. (2010) may be deemed a potential source of selection bias, as the study was yet to be published when the searches were carried out, and results were obtained through one of the review authors. In addition one of the ongoing studies is being carried out by two of the review authors (Lindson et al. 2009). However every attempt was also made to identify studies eligible for inclusion in the review, published or not, from authors outside of the review team (identified through conference proceedings included in the Cochrane Tobacco Addiction Review Group specialised register). This is evidenced by the fact that neither of the trial reports for Jerome, Behar et al. (1999) or Riley et al. (2005) had been published, and were obtained through contact with the authors. We also tried to obtain unpublished data from Riley et al. 2001 and Cinciripini et al. 2006, however this is not yet available, and so these studies are classed as ongoing. Therefore we feel that we made every effort to obtain relevant and available data. As Cochrane Reviews are updated every two years, emerging data will be periodically incorporated into the review.

3.4.1.2 Included studies

3.4.1.2.1 Characteristics of participants

The 10 included studies all recruited adult cigarette smokers with an aim to quit. Seven studies recruited participants from the community using advertisements (Flaxman 1978; Cummings et al. 1988; Curry et al. 1988; Cinciripini et al. 1995; Riley et al. 2005; Etter et al. 2009; Hughes et al. 2010). One study recruited work-sites to take part, and then recruited their employees by posting advertisements and internal memos (Jerome, Behar et al.1999). Another recruited students using advertisements at a university (Roales-Nieto & Fernández Parra

1992), and another recruited patients consulting a hospital based, smoking counselling service (Gunther et al. 1992).

In one study these participants were then randomised in clusters (work-sites) to study arms (Jerome, Behar et al.1999), however for all other included studies participants were individually randomised. In the eight studies where participant gender was reported participants were on average evenly split between males and females, and the average reported age of participants (averaged across seven studies) was 42.8 years. Eight studies reported average baseline cpd in all participants, and this ranged from 23 to 28 cpd, with an average of 25.4.

3.4.1.2.2 Sample sizes

The total sample size across the 10 included studies ranged from 23 to 1895, with a mean sample size of 487. However not all study arms in all of the trials were used in the meta-analysis. When only the conditions relevant to this review were taken into account, sample sizes ranged from 14 to 1277, with a mean of 376. In five of the included studies all conditions randomised were relevant to the current review and were therefore included in the meta-analysis, however five of the studies randomised participants to interventions which were not relevant. Cummings et al. (1988); Jerome, Behar et al. (1999) and Hughes et al. (2010) all included a control condition, which did not provide specific advice on how to quit, but provided information about the health implications of smoking, praise for quitting, and material emphasising the importance of a general programme of physical health (including quitting smoking) respectively. Flaxman (1978) included an immediate quit condition where participants were asked to quit the day after enrolling in the study and received substantially

less behavioural support than the other conditions. Roales-Nieto & Fernández Parra (1992) included two conditions where the participants' goal was to reduce their smoking and control it rather than to reduce and quit completely. All of these conditions were deemed not relevant to this review and were excluded from any meta-analyses.

3.4.1.2.3 Interventions

All of the included studies had at least one group of participants who were instructed to reduce the amount they smoked before they quit, and at least one group instructed to quit smoking abruptly. In four of the studies, participants were advised on either abrupt or gradual cessation by self-help manuals or a handheld computer programme (Cummings et al. 1988; Jerome, Behar et al.1999; Riley et al. 2005; Etter et al. 2009). Participants in another five studies were given face-to-face (Flaxman 1978; Gunther et al. 1992; Roales-Nieto & Fernández Parra 1992; Cinciripini et al. 1995) or telephone based (Hughes et al. 2010) behavioural support as a means to assist either reduction or abrupt cessation. In the remaining study one reduction arm and one abrupt arm consisted of self-help therapy, and participants in the other reduction and abrupt arms were provided with behavioural support (Curry et al. 1988). The behavioural support varied in terms of the overall length of time for which support was provided, the length of support sessions, number of support sessions, whether these were provided to individuals or groups, and who provided the support; however they all included pre-quit sessions where participants were taught strategies to help them avoid smoking when tempted, such as strategies to maximise self-control, and post-quit sessions focusing on relapse prevention. Most of the self-help interventions consisted of information booklets, some of which provided the participants with written activities. However for the reduction interventions in Jerome, Behar et al. (1999) and Riley et al. (2005) participants were given the

LifeSign handheld computer (PICS Inc). LifeSign structures a gradual reduction schedule, prompts users to smoke and allows them to record each cigarette they smoke. In the Jerome, Behar et al. (1999) study this computer was provided, with a 48 page manual, which consisted of instructions on how to use the computer and information about behaviour modification strategies and relapse prevention. In the Riley et al. (2005) study participants only received brief instructions on how to use the device and no further information. This was designed as a minimal contact intervention, which matched the minimal instructions provided to the abrupt quitting intervention group members, who received a calendar log to record their smoking.

The abrupt quitting method advised for participants did not vary much across the ten studies. Participants were either given a quit date or asked to choose one themselves, and then asked to smoke as normal and quit abruptly on this date, with no prior cutting down. Quit dates ranged from zero to five weeks following baseline assessment. The smoking reduction methods all culminated in a quit day but varied considerably across studies as follows:

- Cummings et al. (1988) gave participants unspecific advice on how to quit; they were simply advised to reduce the amount smoked over two weeks before quitting. Suggestions were provided on how they could reduce, such as setting daily goals, switching brands, changing habits and delaying the first cigarette; but ultimately it was left to participants to choose by how much to reduce and which, if any, strategies to use to achieve this.
- Three studies asked participants to reduce cpd by a certain quota over a set time interval without providing participants with any particular strategy to do so. Etter et al. (2009) asked participants to reduce their smoking to 50% of baseline over four

weeks and then quit completely. Gunther et al. (1992) asked participants to reduce their smoking by five to ten cigarettes per week (depending on how much they were smoking at baseline), over five weeks until they were not smoking at all. Roales-Nieto & Fernández Parra (1992) instructed participants to reduce by 25% of baseline in week one, 50% in week two, 75% in week three and to quit completely in week four.

- In the Cinciripini et al. (1995) study two groups of participants were asked to reduce their smoking; one of the groups reduced smoking by a set quota but did not use a specific technique to achieve this, as in the three studies above. Participants cut down to 66% of their baseline smoking rate in the first week of reduction, to 33% of baseline in the second week, and to 22% of baseline in the third week, until they reached two to four cpd. The second reduction group reduced by the same quota of cigarettes, but this was structured. Each week the advised smoking rate was divided by the number of hours in the participants' waking day, to calculate an ICI. Participants were then able to smoke only in the first five minutes of each interval, and any missed cigarettes could not be accumulated for later use. Both groups quit in the week following the third week of reduction, and were combined for the purposes of our meta-analysis.
- Jerome, Behar et al. (1999) and Riley et al. (2005) also used ICIs to reduce smoking to zero. They implemented this using a handheld computer called LifeSign, which developed a smoking reduction schedule, lasting between 10 to 28 days, depending on each individual's baseline smoking rate and progress through the programme. The machine beeped and put a reminder on its screen to prompt participants to smoke.
- Hughes et al. (2010) advised participants to reduce their smoking by 25% of baseline in week one, 50% in week two and 75% in week three, before quitting completely.

They were also provided with three structured ways to do this, which they could choose between. The first was scheduled reduction where participants were advised to gradually increase the time between cigarettes (the ICI). The second asked participants to rate each cigarette of the day in terms of how difficult it would be to give up and then eliminate each in turn starting with the most difficult first. The third was the same as the second but participants started with the easiest first. Abstinence results did not appear to differ across the methods and so the data was pooled.

- Flaxman (1978) differed from the previous approaches as participants were not asked to reduce by a certain quota of cigarettes, but to identify situations that caused them to smoke. They were then asked to rate these situations in terms of how difficult it would be to abstain from smoking, and then to eliminate smoking in one situation every three days, starting with the easiest situation and proceeding to the most difficult. In one reduction group participants continued this until they were not smoking at all and in the other they reduced until they were smoking in 50% of their baseline smoking situations, and then quit abruptly. These two reduction groups were combined into an overall reduction group for our meta-analysis.
- One study gave very limited information as to how reduction took place (Curry et al. 1988); the method was described as cigarette tapering and a gradual acquisition of coping skills. The authors confirmed that this was a reduction method relevant for inclusion in this review, however no further detail could be provided.

3.4.1.2.4 Pharmacotherapy

Three of the studies included in this review gave participants pharmacotherapy as a part of their interventions. In all cases this was in the form of NRT; one study used gum (Etter et al.

2009), another lozenges (Hughes et al. 2010) and the third nasal spray (Riley et al. 2005). In the reduction arm of each study participants used the NRT both pre- and post- quit, and in the abrupt quitting arm post-quit only. In the pre-quit period Etter et al. (2009) advised participants to use at least 10 pieces of 4mg nicotine gum per day, Hughes et al. (2010) requested that participants replace each cigarette missed with a 2mg or 4mg lozenge (4mg for those who smoked within 30 minutes of waking and 2mg for others). Riley et al. (2005) signalled when participants should use the nasal spray using the same LifeSign handheld computer as was used to signal smoking. The appropriate nasal spray dosage was determined for each individual user depending on their recorded baseline smoking rate.

3.4.1.2.5 Outcomes

Nine of the 10 studies reported smoking abstinence as an outcome at either six month follow-up (Flaxman 1978; Cummings et al. 1988; Hughes et al. 2010), 12 month follow-up (Gunther et al. 1992; Curry et al. 1988; Etter et al. 2009) or both (Cinciripini et al. 1995; Jerome, Behar et al. 1999; Riley et al. 2005). The remaining study (Roales-Nieto & Fernández Parra 1992) reported cpd over seven days at six month, nine month and 12 month follow-ups for individual participants; so it was possible to calculate abstinence rates from this information. Where abstinence was measured at 6 and 12 month follow-ups the 12 month rates were used in the meta-analysis. In three studies smoking abstinence was reported as point prevalence (Roales-Nieto & Fernández Parra 1992; Jerome, Behar et al. 1999; Riley et al. 2005) and in six studies as prolonged/continuous (Cummings et al. 1988; Curry et al. 1988; Gunther et al. 1992; Cinciripini et al. 1995; Etter et al. 2009; Hughes et al. 2010). Flaxman (1978) did not report how abstinence was defined. Abstinence was verified in eight of the included studies, by either expired carbon monoxide (Jerome, Behar et al. 1999; Riley et al. 2005; Etter et al.

2009; Hughes et al. 2010), saliva cotinine (Cinciripini et al. 1995; Etter et al. 2009), saliva thiocyanate (Curry et al. 1988), or asking a relative or friend to confirm the participant had stopped smoking (Cummings et al. 1988; Roales-Nieto & Fernández Parra 1992). However for the purposes of this review verified data were not used for one of the studies (Cummings et al. 1988), as there were problems with the naming of a friend or relative to verify participants' self report. If participants did not name a person to verify their self-report, or if their self-report contradicted their friend's/relative's then they were classed as smoking; however 20% of those claiming abstinence did not provide a friend/relative. Participants who lived alone were four times more likely not to name a person for verification than those who lived with others.

All of the study reports either reported ITT analysis or provided sufficient information to allow calculation of this, apart from Cummings et al. (1988) where the authors provided this information when contacted. Only two studies (Etter et al. 2009; Hughes et al. 2010) reported information about adverse events. Further information was obtained from these authors, and some limited information about adverse events was also obtained from the authors of Riley et al. (2005). Reporting was not consistent across studies and so it was not possible to carry out a meta-analysis; therefore these data are synthesised qualitatively.

3.4.1.3 Excluded studies

Studies which were identified as potentially relevant but later excluded are listed, with reasons for exclusion, in the characteristics of excluded studies tables (Appendix 20). The primary reasons for exclusion fell into one of three categories: 1) The goal of the intervention

was to reduce smoking and control it, rather than quit (Hatsukami et al. 1988; Bolliger 2000- Rosette trial); 2) the main outcome was smoking rates, and it was not possible to calculate abstinence rates from the data presented, or to get these from the authors (Marston & McFall 1971); or 3) both of the trial arms quit in the same way (Bernard & Efran 1972; Glasgow et al. 1989; Cinciripini et al. 1994; Herrera et al. 1995; Daughton et al. 1998; Jerome, Fiero et al. 1999; Rose et al. 1998; Bolliger 2000- CEASE trial; Schuurmans et al. 2004; Rose et al. 2006; Rezaishiraz et al. 2007; Bullen et al. 2010; Rose et al. 2009; Shiffman et al. 2009). Five of the excluded studies examined pre-treatment with NRT versus placebo prior to the quit date, and did not instruct smokers to reduce pre-quit (Rose et al. 1998; Schuurmans et al. 2004; Rose et al. 2006; Rose et al. 2009; Bullen et al. 2010). These studies are included in the meta-analysis of nicotine preloading treatment, reported in Chapter 4. Three of these reported that participants spontaneously reduced whilst using the NRT (Rose et al. 1998; Rose et al. 2006; Rose et al. 2009), two of which found that participants who reduced their smoking the most were more likely to achieve abstinence (Rose et al. 2006; Rose et al. 2009). However, as none of the studies instructed participants to reduce their smoking during the pre-cessation phase of the treatment, this success cannot be attributed to an instruction to reduce and so the studies were excluded from this review.

3.4.2 Effects of interventions

3.4.2.1 Abstinence Outcome

The main meta-analysis included 10 trials with a total of 3760 participants. There was evidence that reduction produced similar quit rates to abrupt cessation and that any difference in effectiveness was small. The overall RR for abstinence, for reduction versus abrupt

cessation was 0.94 (95% CI= 0.79, 1.13) (Figure 4). There was low heterogeneity (I^2 = 14%), suggesting that the effect of reduction relative to abrupt cessation did not differ across trials. For all studies CIs spanned one, indicating no study achieved statistically significant superiority of either gradual or abrupt cessation. We have not reported pooled quit rates because studies varied on a number of factors, such as definition of abstinence (point prevalence or prolonged), length of abstinence (6 months or 12 months), whether or not behavioural support was provided, and whether pharmacotherapy was provided, meaning that average rates would not be useful.

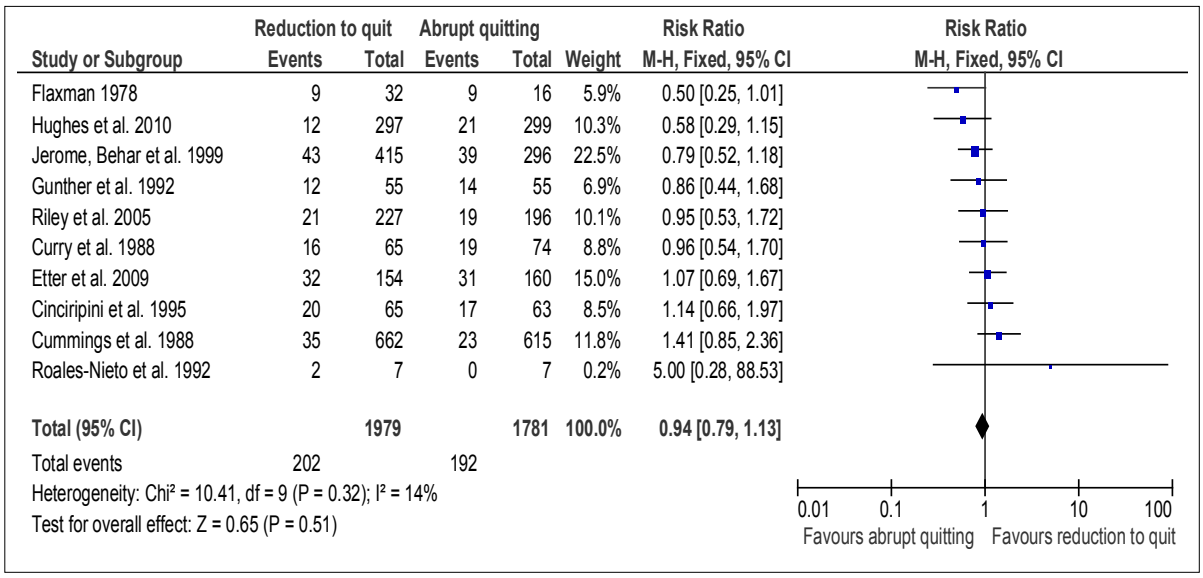

Figure 4: A forest plot illustrating the outcome of the reduction to quit versus abrupt quitting meta-analysis (abstinence outcome)

3.4.2.2 The effect of gradual versus abrupt cessation in participants using pharmacotherapy

The studies were split into two sub-groups to assess whether the effect of gradual cessation depended on whether people used smoking cessation pharmacotherapy or not. One sub-group

included studies that didn't use any pharmacotherapy as part of the interventions (Flaxman 1978; Cummings et al. 1988; Curry et al. 1988; Gunther et al. 1992; Roales-Nieto & Fernández Parra 1992; Cinciripini et al. 1995; Jerome, Behar et al. 1999). The other sub-group included the remaining studies (Riley et al. 2005; Etter et al. 2009; Hughes et al. 2010), which utilised NRT pre- and post-quit in the reduction interventions and post-quit in the abrupt interventions. There was no evidence of the superiority of either gradual or abrupt cessation whether NRT was used (RR= 0.89, 95% CI= 0.65, 1.22), or not (RR= 0.97, 95% CI= 0.78, 1.21), and neither was there evidence that pharmacotherapy modified the effect of reduction versus abrupt cessation (Figure 5).

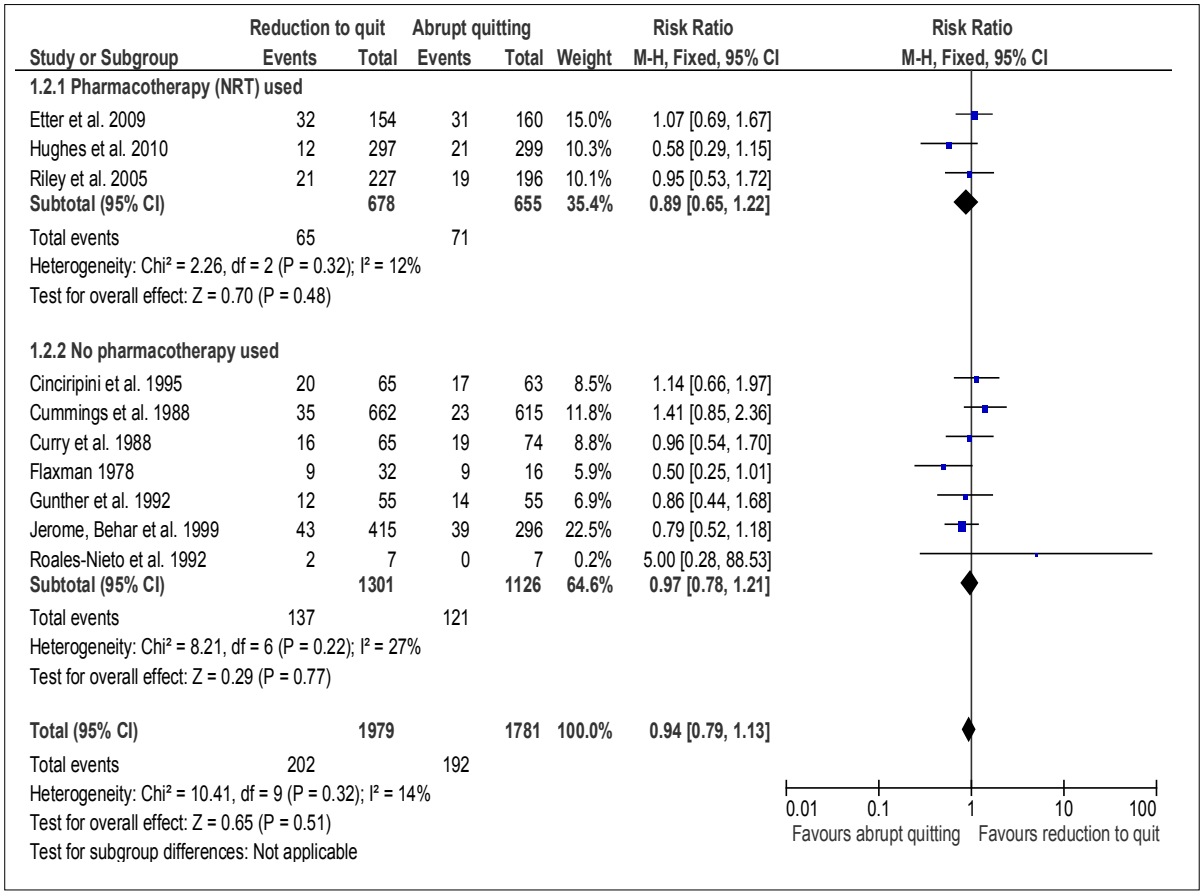

Figure 5: Forest plots illustrating the outcome of the sub-group analysis investigating the impact of pharmacotherapy use on the reduction to quit versus abrupt quitting meta-analysis (abstinence outcome)

3.4.2.3 The effect of the type of behavioural support utilised

We also conducted a sub-group analysis, splitting studies based on the type of therapy provided. Some of the included studies used self-help therapy (Cummings et al. 1988; Jerome, Behar et al. 1999; Riley et al. 2005; Etter et al. 2009), and some behavioural support (Flaxman 1978; Gunther et al. 1992; Roales-Nieto & Fernández Parra 1992; Cinciripini et al. 1995; Hughes et al. 2010). Curry et al. (1988) included study arms that were self-help and others that were behavioural, so these were split accordingly for the sake of this analysis. Again the risk estimates were similar whether the instruction of how to quit and support for achieving this was given by self-help (RR= 0.98, 95% CI= 0.78, 1.23) or by behavioural support (RR= 0.87, 95% CI= 0.64, 1.17), and neither reduction nor abrupt quitting resulted in superior quit rates in either case (Figure 6).

3.4.3 Adverse Events Outcomes

The secondary objective of this review was to compare adverse events between arms, however no attempt has been made to do this quantitatively as there was a lot of variation in the nature and depth of reporting. The seven studies that did not utilise pharmacotherapy did not report information about adverse events. Of the three studies using pharmacotherapy, Riley et al. (2005) reported no information on adverse events in the study report, but the authors kindly supplied further information for this review. Etter et al. (2009) and Hughes et al. (2010) also provided additional information, as well as data reported in the publications. Etter et al. (2009) and Riley et al. (2005) reported that no participants experienced SAEs. Etter et al. (2009) also provided data obtained in response to the question: "If you experienced undesirable effects due to the nicotine gum, please describe them" (open ended

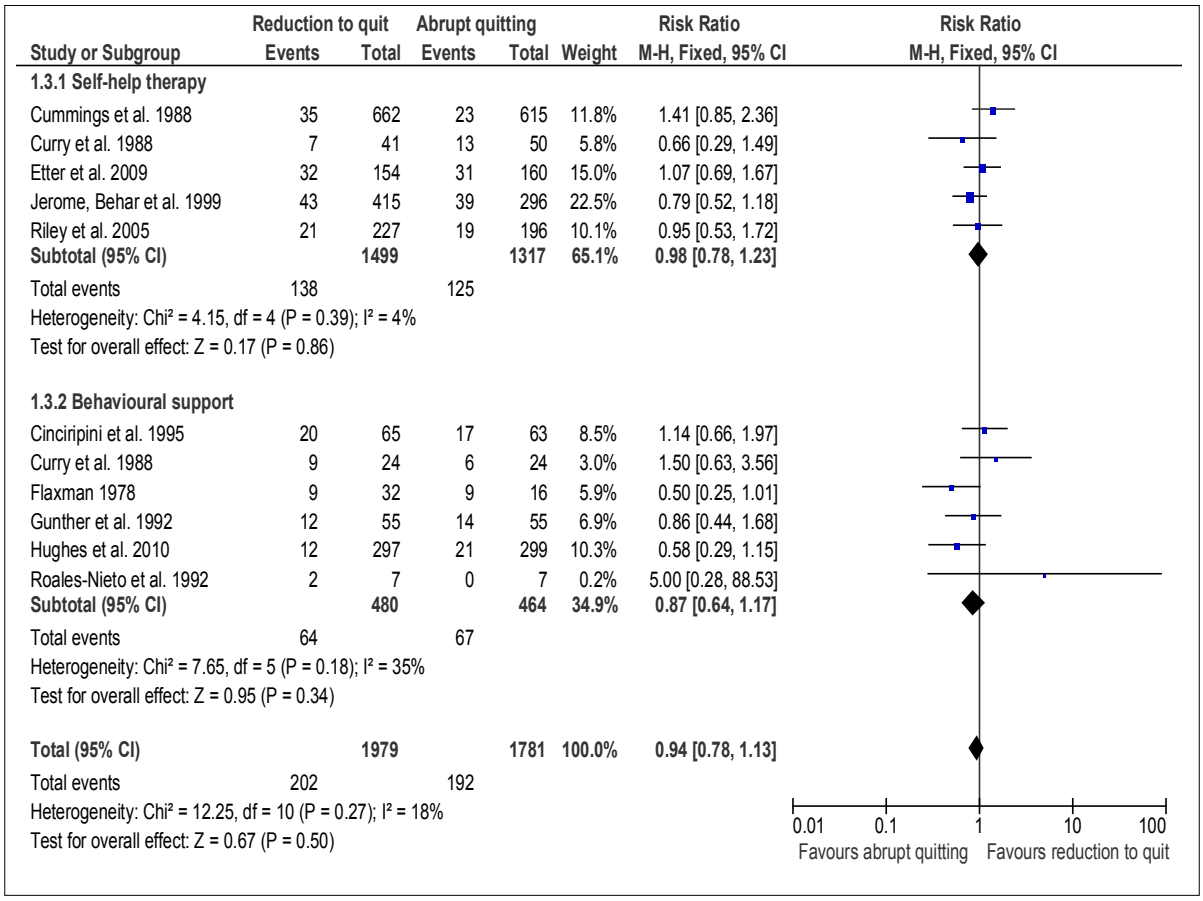

Figure 6: Forest plots illustrating the outcome of the sub-group analysis investigating the impact of type of support provided on the reduction to quit versus abrupt quitting meta-analysis (abstinence outcome)

question), asked two months after target quit day. Overall the most commonly reported symptoms were mouth pain/dry mouth/throat burns, hiccups, stomach pain/heartburn- the most common side-effects from oral NRT. Nine of the total symptoms reported occurred more frequently in the reduction group (mouth pain/dry mouth/throat burns, hiccups, stomach pain/heartburn, pain/cramp in jaws, mouth ulcers, headache, eructation, heart palpitations, cough), four in the abrupt group (nausea, bad taste, insomnia, vomiting), and three were reported as frequently in both groups (malaise, constipation, diarrhoea). Hughes et al. (2010) reported that the incidence of adverse events rated severe was small and similar across

conditions. 3% of participants randomised to the reduction to quit group reported severe adverse events and 5% of the abrupt quit group; the incidence of discontinuation was 1% for both groups.

3.4.4 Risk of bias

We extracted information from each study to assess the risk of biased randomisation, whether allocation concealment took place, and whether incomplete outcome data was addressed. This was assessed as either likely to cause bias, unlikely to cause bias, or unclear, if insufficient information was present to make a judgement (Figure 7).

- Randomisation sequence generation. Five studies reported adequate information on sequence generation, to be classified as having minimal chance of bias in this regard. Five of the studies (Flaxman 1978; Roales-Nieto & Fernández Parra 1992; Cinciripini et al. 1995; Jerome, Behar et al. 1999; Riley et al. 2005) did not describe the method of randomisation used, and so were classified as unclear in this category. All of the studies randomised individual participants, apart from Jerome, Behar et al. (1999) who randomised work-sites to trial arms. Trials that randomise clusters to treatment arms can be given a higher weighting than they should if data on individuals are entered into the meta-analysis. This is because the analysis assumes there is no connection between individuals in the same group, in the likelihood of them stopping smoking successfully. However, when an analysis was carried out to adjust for the clustering in Jerome, Behar et al. (1999), although the study weighting decreased from 22% to

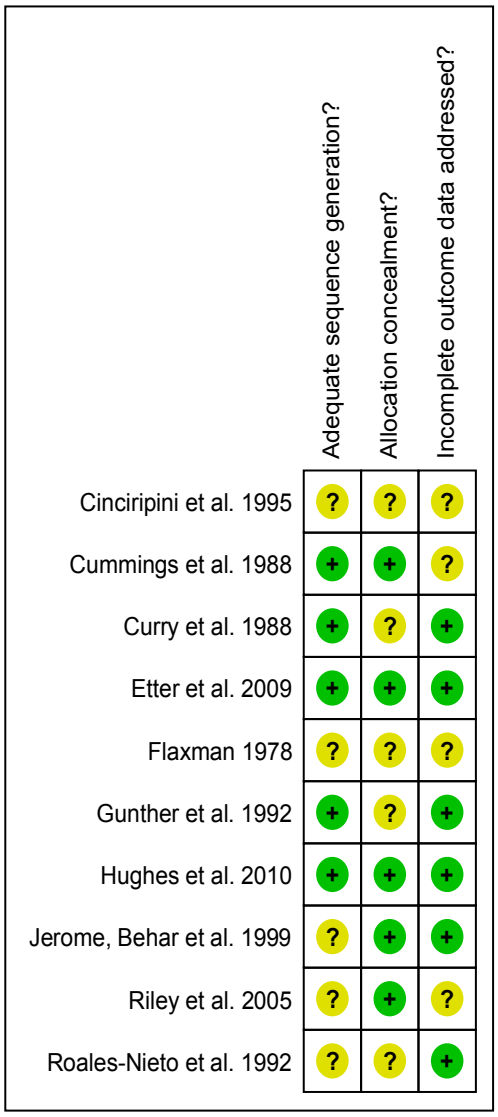

Figure 7: Risk of bias: a summary of judgements made about methodological quality for each study included in the reduction to quit versus abrupt quitting meta-analysis

17%, the main result was not sensitive to the adjustment; RR = 0.93, 95% CI= 0.78, 1.12 (Figure 8).

- Allocation concealment. When rated in terms of concealing allocation from clinicians enrolling participants into studies, four studies (Cummings et al. 1988; Jerome, Behar

et al. 1999; Riley et al. 2005; Etter et al. 2009) were rated as unlikely to cause bias, as all interventions consisted of self-help therapy and there was either no or minimal contact with investigators/enrolling clinicians. Consequently, participants' enrolment in the studies could not depend on knowledge of the allocation sequence, as there was no clinician deciding on whether to enrol, or which treatment to give. Hughes et al. (2010) was also rated as unlikely to cause bias in this category, as a statistician generated a concealed allocation sequence. The five remaining studies did not report on allocation concealment and were therefore classed as unclear.

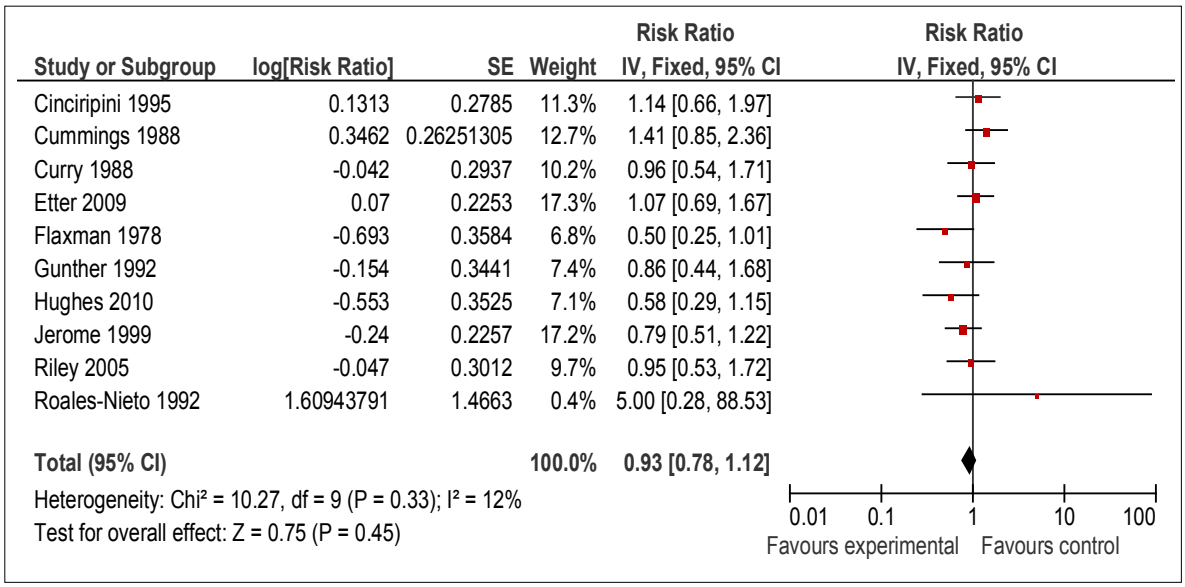

Figure 8: A forest plot illustrating the cluster randomisation sensitivity analysis, for the reduction to quit versus abrupt quitting meta-analysis (abstinence outcome)

- Incomplete outcome data. In the category of incomplete outcome data six studies were classed as unlikely to cause bias, as participant attrition was reported as similar in all trial arms. The four remaining studies were classed as unclear; three of the studies

(Flaxman 1978; Cinciripini et al. 1995; Riley et al. 2005) did not provide any information about participant attrition or missing data, and the abstinence rates table in the Cummings et al. (1988) report appeared to leave 18 participants unaccounted for. Due to the length of time since the study had been completed the authors could not clarify why this was the case, but did provide further information so that an ITT analysis could be carried out, in which the missing participants were classified as not abstinent. Participants' attrition in general was similar across arms, however the study was classified as unclear, as the allocation of the missing participants and whether this was similar across arms was unknown.

Two of the included studies (Flaxman 1978; Cinciripini et al. 1995) were rated as unclear for all three of the above bias categories and another two were rated as unclear for two (Roales-Nieto & Fernández Parra 1992; Riley et al. 2005). We carried out a sensitivity analysis to establish whether the main result was sensitive to the exclusion of these four studies and found that it was not (RR= 0.94, 95% CI= 0.76, 1.16; Figure 9).

Other potential sources of bias were failure to verify smoking abstinence by biochemical means and whether participants conformed to their allocated intervention.

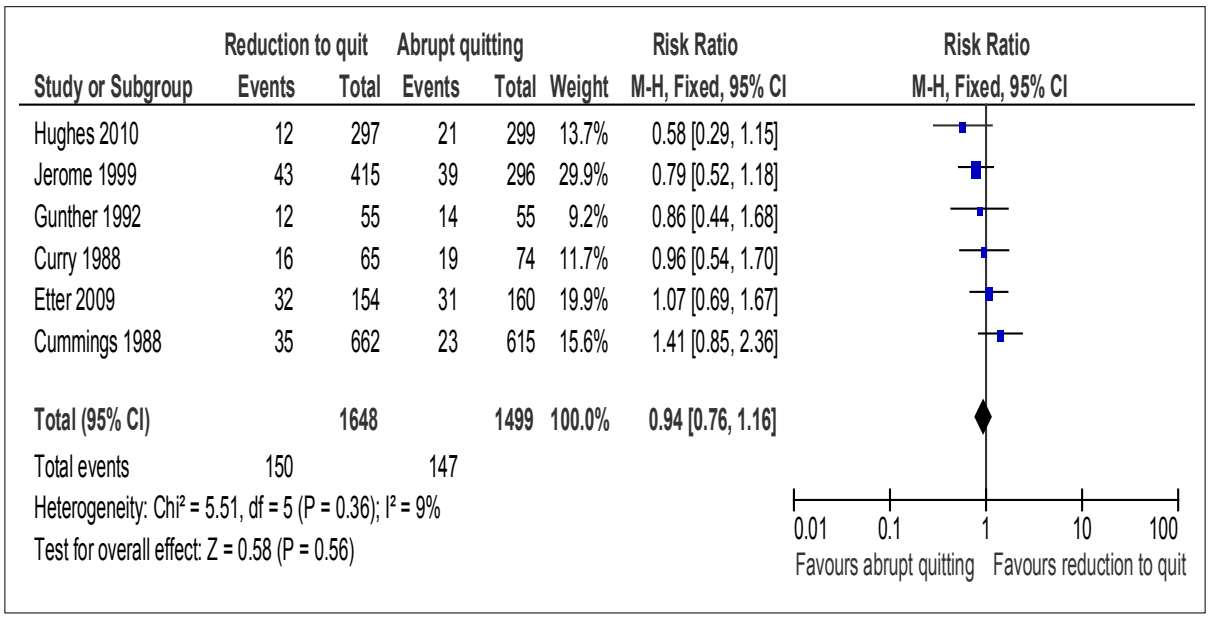

Figure 9: A forest plot illustrating the risk of bias sensitivity analysis, for the reduction to quit versus abrupt quitting meta-analysis (abstinence outcome)

- Biochemical verification. Studies that did not validate self reports of abstinence (Flaxman 1978; Gunther et al. 1992), or where validation was potentially flawed, and therefore not used in this review (Cummings et al. 1988) could potentially over-estimate abstinence. However we would not expect this to differ between arms, and a sensitivity analysis (Figure 10) confirmed that the main findings were not sensitive to the exclusion of studies where abstinence was not validated (RR= 0.91, 95% CI= 0.74, 1.12). The SRNT Subcommittee on Biochemical Verification (2002) concluded that population based studies with limited face to face contact, and where data collection is optimally by mail, telephone, or on the Internet are unlikely to benefit from biochemical verification. Population studies have much higher biochemical verification refusal rates than clinic based studies, if all participants who refused were classed as smoking then this would be likely to overestimate smoking rates. In reality the extent that self-reports inflate abstinence rates is small and rarely differs across

conditions. Also, in studies where there is very little contact with an investigator or therapist this reduces demand characteristics, meaning there is little incentive to lie.

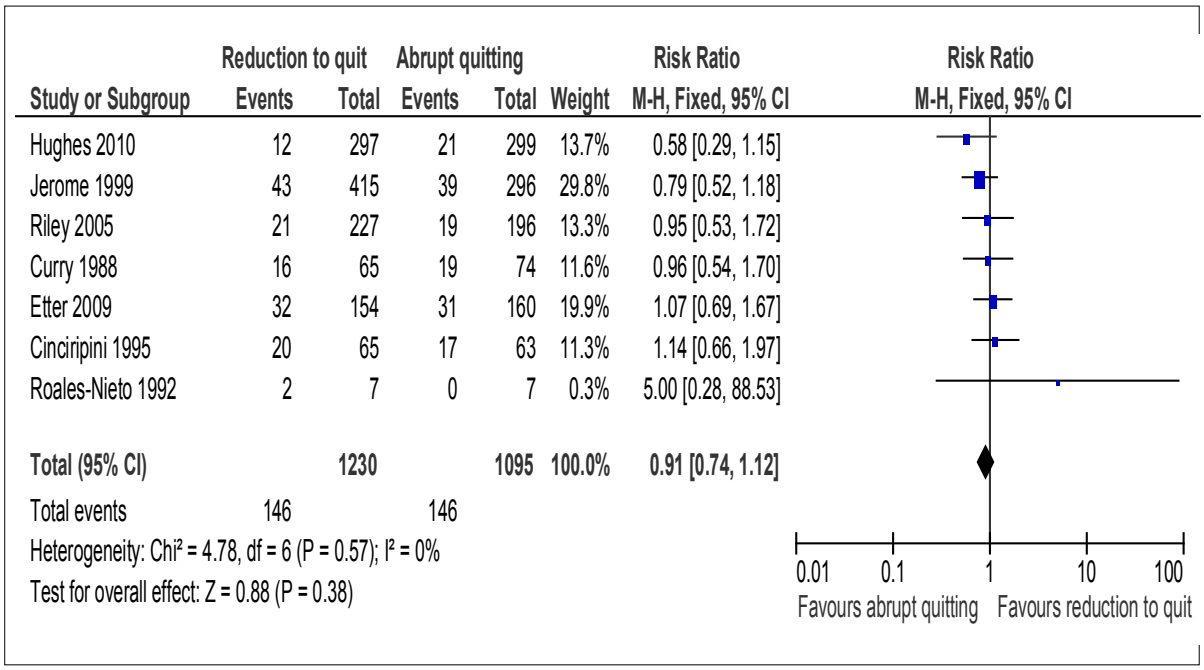

Figure 10: A forest plot illustrating the non-validated abstinence sensitivity analysis, for the reduction to quit versus abrupt quitting meta-analysis (abstinence outcome)

- Adherence to method of quitting allocated. Six of the 10 studies assessed whether participants followed the instructions they had been given on how to quit i.e. to reduce or quit abruptly without prior reduction. Three of these studies (Roales-Nieto & Fernández Parra 1992; Etter et al. 2009; Hughes et al. 2010) found that participants followed instructions; the participants in the reduction group reduced before quitting and the participants in the abrupt group quit abruptly with no prior reduction. Cinciripini et al. (1995) found that the reduction group complied well with their instructions but the abrupt group also reduced by seven to eight cpd before quitting.

However the reduction group smoked significantly fewer cigarettes than the abrupt group before quit day. The two remaining studies to report on adherence to the intervention allocation found that participants did not abide by intervention instructions. In Flaxman (1978) the group which reduced until they were not smoking at all reduced by a mean of 6 cpd, and the group who reduced to 50% of baseline then quit reduced by a mean of 3.5 cpd. However the abrupt quit group also reduced by an average of 3.4 cpd before they quit, meaning there was little difference between reduction in the partial reduction group and the abrupt quit group. Cummings et al. (1988) asked participants after quit day whether they had quit abruptly- 39% of participants in the abrupt group quit abruptly and 40% of the reduction group also quit abruptly- therefore there appeared to be little difference between the arms in the methods of quitting that were actually used. As is the case with all ITT analyses, it is only ever possible to examine the effect of allocation to a quitting method, not the effectiveness of actually following it.

3.5 Discussion

The 10 studies included in this review compared interventions that instructed participants to quit smoking gradually, by reducing the amount they smoked, with interventions that instructed participants to quit smoking abruptly without prior reduction, in smokers who wanted to quit. The results provide evidence that reduction to quit results in similar quit rates to abrupt quitting, with no evidence that one method is significantly superior to the other, in adults trying to quit smoking. This applies whether therapy is self-help or includes behavioural support, and whether the quit attempt uses NRT or not. The similarity of the result in the NRT sub-group and the non NRT sub-group suggests that the success of the

reduction interventions, relative to the abrupt quit interventions, is not due to the use of pre-quit NRT. We were unable to combine data on absolute quit rates as studies varied on a number of factors expected to influence quit rates, for example length of follow-up, and so cannot provide meaningful estimates of average quit rates as a result of reduction to quit and abrupt quit interventions.

We were unable to combine the adverse events data statistically, and therefore could not determine whether adverse events differed significantly between the intervention groups that reduced and used NRT pre- and post-quit, and the intervention groups where participants quit abruptly and used NRT post-quit. However a recent review conducted a meta-analysis (Moore et al. 2009) of seven placebo controlled RCTs, which used NRT to assist reduction to stop smoking, and found that there were no significant differences in deaths (OR= 1.00, 95% CI= 0.25, 4.02), SAEs (OR= 1.16, 95% CI= 0.79, 1.50), and discontinuation due to adverse events (OR= 1.25, 95% CI= 0.64, 2.51), between the placebo and NRT interventions. The only adverse event that was more common in the NRT interventions was nausea (OR= 1.69, 95% CI= 1.21, 2.36), which is a common side effect of NRT. Taken with other safety data on concurrent smoking and use of NRT (Fagerstrom & Hughes 2002), there appears to be no reason to recommend against the practice of gradual reduction assisted by NRT. At least one trial shows that among smokers trying to quit smoking by gradual reduction, using NRT is more effective than use of placebo in supporting abstinence (Shiffman & Ferguson 2008), and a Cochrane Review of smoking harm reduction (Stead & Lancaster 2007) found that people who did not originally want to quit smoking were more likely to be abstinent from cigarettes at long-term follow-up when NRT was used as an aid to reduction than when a placebo was used (OR= 1.90, 95% CI= 1.46, 2.47). On this basis, if reduction is to be used as a means of

quitting, use of NRT or other pharmacotherapy appears desirable. NRT is licensed for use in this way in the UK and Australia, however at the time of writing the US Medicines Regulator, along with other pharmaceutical regulators have not yet licensed NRT for this purpose.

An important limitation of any meta-analysis is that methods vary across studies and the underlying assumption that the meta-analysis is trying to estimate a single true rate ratio might not hold. In this instance patient populations, outcome definitions, provision of pharmacotherapy and the behavioural support provided varied across the included trials. Despite this, the measure of heterogeneity was low, suggesting that heterogeneity of these elements did not translate into heterogeneity of effectiveness of reduction. One of the studies also varied because it used cluster randomisation, but sensitivity analysis suggested that allowing for this or not had little influence on the result of the meta-analysis. Four of the studies included in the meta-analysis (Flaxman 1978; Cummings et al. 1988; Curry et al. 1988; Cinciripini et al. 1995) had more than one intervention that qualified as reduction and/or abrupt quitting, and these were combined to create one reduction arm and one abrupt quit arm per study. We considered entering data from each trial arm separately to see if this would give us any more detailed information about the relative success of different reduction methods, however the methods used differed in each study (scheduled, non scheduled, group behavioural support, individual behavioural support, reduction to zero cigarettes before quit, reduction to 50% of baseline before quit etc), so they could not be pooled for a sub-group analysis, and therefore would be no more informative than the original studies. There is however some evidence that structured methods of reduction are more effective than simple advice to cut-down without following specific methods (Levinson et al. 1971; Cinciripini et al. 1995).

Two of the 10 included studies (Etter et al. 2009; Hughes et al. 2010) were assessed as unlikely to cause bias for all three of the Cochrane risk of bias categories assessed. These studies were the most recent of the 10 studies, which may suggest that their increased reporting, relative to the other eight studies, is due to awareness of the revised CONSORT reporting guidelines (Moher et al. 2001), which were published in 2001, and advise reporting methods of sequence generation and allocation concealment, and a flow diagram illustrating the flow of participants through the study. Seven of the studies rated in at least one bias category as 'No' or 'Unclear' were published before 2001, and the remaining study was not written up for publication. Therefore lack of reporting may be for these reasons rather than because bias is present. This may also explain why the reporting of adverse events was only present in the most recent studies. The main results of the two most recent studies do not differ much from the main results of the eight older studies; therefore there is no evidence that studies reporting better randomisation procedures produced different results. Many of the older studies did not propose a hypothesis that favoured either a reduction or an abrupt quitting intervention (Flaxman 1978; Curry et al. 1988; Gunther et al. 1992; Roales-Nieto & Fernández Parra 1992; Cinciripini et al. 1995), so in the cases where allocation concealment was not reported, and so may not have occurred, there is no reason why allocation would have been carried out to favour any particular arm.

Whilst assessing studies for eligibility there were two studies (Curry et al. 1988; Jerome, Behar et al. 1999) where uncertainty arose about whether the intervention methods were abrupt or reduction to quit. Curry et al. (1988) reported that one method of quitting used in the study was "cold turkey" and that the other was "tapering and nicotine fading". There is no

further detail given on these methods so we contacted the authors who confirmed that one of these methods was an abrupt quit method and the other was a reduction to quit method, which met the inclusion criteria. Jerome, Behar et al. (1999) consisted of a study arm where participants reduced and then quit using a handheld computer, and an arm where participants were provided with an American Lung Association self-help booklet called "Freedom From Smoking For You and Your Family". The study report did not specify whether this booklet advised an abrupt quitting method or a reduction to quit method, and the authors and the American Lung Association were unable to provide additional information. However Davis et al. (1992) includes a table comparing the content of three self-help guides including this one, which reported that the topic of cutting down smoking is not covered. We therefore believe that including these studies in the review is appropriate. The failure of studies to clarify methods used to achieve abstinence does raise the possibility that studies could have been missed because authors described them in terms that were not expected. We followed-up included studies' reference lists to check for other studies that may not have come up in the search, and no other studies were found. Nevertheless, we could have failed to include all extant studies, but there is no reason why publication bias or failure to find less clearly described or less prominent studies would be expected to bias the results towards reduction or abrupt cessation methods.

Surveys carried out in the general population (Cheong et al. 2007; West & Fidler 2011) have found that gradual quitting isn't as effective as abrupt quitting, however these differ from the RCTs included in this meta-analysis in ways that may explain the difference in outcomes. The participants quitting gradually in the RCTs (whether support was behavioural or self-help) were all provided with some instructions as to how to quit, which included setting quotas of

cigarettes to reduce by, and setting time intervals at which participants could smoke. All of the included studies also appeared to require participants to set a target quit day, providing them with a goal to work toward. However, the participants included in the observational studies will have quit using a number of methods of gradual reduction, and it is likely that these will vary in their levels of success. The UK and US national guidelines do not recommend cutting down before quitting and therefore services such as the UK NHS SSS only offer abrupt quitting as a cessation method. This means that those participants who choose gradual cessation in the general population are less likely to have benefited from any kind of support whilst quitting (although this wasn't the case in the Cheong et al. 2007 and West & Fidler 2011 studies, where behavioural support was not used or used rarely respectively), which in the case of the NHS SSS has been found to increase quit rates by up to four times (Hughes et al. 2004; Ferguson et al. 2005). Therefore quitters choosing gradual reduction are automatically put at a disadvantage. A person who quits without support may also be more likely to use an unstructured method, with no reduction goals, no particular method of reducing, and no target quit day. Cinciripini et al. (1995) found that those participants that quit using unstructured reduction were less successful than those who used a more structured method.

Two previous meta-analyses (Law & Tang 1995; Fiore et al. 2008) have looked at nicotine fading as a smoking cessation intervention. These, however, differ from the current analysis, because as well as including studies where participants were asked to reduce nicotine intake by reducing the number of cigarettes they smoked, they also included studies where participants were asked to use graduated filters to remove progressively more nicotine from inhaled smoke, and studies where participants changed brands to cigarettes of successively

lower nicotine yield. We chose not to combine all of these approaches in the current analysis as there is reason to believe that the different methods do not all work by the same mechanisms. For example, one of the ways reducing cigarettes smoked may work is by weakening links between environmental cues (e.g. socialising) and smoking a cigarette (Section 1.2.2). This wouldn't be applicable to using nicotine filters as the person is still smoking in all of the same situations, and therefore still associates smoking with the same environmental cues. One of the reviews (Law & Tang 1995) compared the gradual quitting interventions with sudden or abrupt cessation, as in this review, however the second (Fiore et al. 2008) compared nicotine fading with untreated control conditions, and therefore the relative effectiveness of reducing nicotine intake and abrupt quitting was not reported. Fiore et al. (2008) found that there was no effect of using nicotine fading techniques when compared to no treatment, however Law & Tang (1995) found that gradual cessation was 5% (95% CI= 2% to 11%) more effective than abrupt quitting, although this difference was not significant ($p>0.10$). Therefore, as in this analysis neither abrupt quitting nor reducing to quit provided superior quit rates.

The result of this analysis suggests that public health messages on cessation and cessation services supporting individuals who smoke could advocate or offer reduction as a way to quit for people who intend to quit soon. They can be confident that if people choose to quit by reducing before stopping entirely, this would not put them at a disadvantage compared with those who choose to smoke as normal and then quit abruptly. Reduction to quit might help those who have tried to quit a number of times without success and are disillusioned with the abrupt quit method. Having a new way to quit could give renewed hope, especially as many smokers see reduction as an intuitive first step toward stopping smoking completely (Hughes

et al. 2006; West 2008). Offering reduction to quit may also appeal to those who would otherwise not seek behavioural support and pharmacotherapy because they want to pursue gradual cessation, and this is not currently supported. This would then enhance the proportion of the population that make assisted quit attempts and boost population cessation rates. The increase in success rates achieved when behavioural support is provided (Section 1.3) suggests that efforts should be made to encourage as many people as possible to use cessation services. Our sub-group analysis, however, suggests that reduction is as successful as abrupt quitting whether the intervention consists of behavioural support or is self-help. Therefore this result could also benefit people who want to quit smoking on their own, without behavioural support. If people who smoke are aware of an additional effective quitting method then this could also encourage more of those, who want to quit independently, to do so.

Although the statistical heterogeneity in this review was not significant reduction versus abrupt quitting RRs did vary to some extent across the studies included in this meta-analysis (from Flaxman (1978): RR= 0.50, 95% CI= 0.25, 1.01 to Roales-Nieto & Fernández Parra (1992): RR= 5.00, 95% CI= 0.28, 88.53). We may expect the effect of the abrupt interventions to be constant across studies as quit instructions did not vary, suggesting that there may be a difference in the success rates of different reduction methods. This is supported by the fact that gradual reduction has been found to be less successful than abrupt quitting in observational studies, but as successful in RCTs. The studies included in this review used a number of different methods, including scheduled reduction, non-scheduled reduction, reducing to zero cigarettes before quitting, and reducing to 50% of baseline before quitting. However a calculation of the 'risk' of quitting when quitting abruptly in each study suggests that this does vary to some extent across studies (Range = 0.04-0.56), and more so

than when quitting by reducing smoking first (Range = 0.04-0.33). Therefore this variation could be due to variation in study characteristics rather than the interventions used.

Nevertheless, there are conceivably many ways that people could reduce before going on to quit completely. Trials that have been carried out so far to compare different reduction methods are small and often participants aim to reduce rather than to quit completely. Therefore, further work is needed to identify the most effective reduction methods in those wanting to quit. Ideally this would be a review which amalgamates existing evidence and identifies literature gaps, leading to large-scale RCTs that directly compare different methods. In turn, this could inform policy and service development as to the most successful reduction to quit method or methods. If there are marginal differences in the effects of different reduction methods then quitters could choose from a number of options. However, if there are methods shown to be significantly less effective quitters should not be advised to use them, as this might put them at a disadvantage. It may prove useful to establish whether different quitting methods benefit different groups of smokers; for example, a particular method may benefit a highly addicted smoker more than a less addicted one. If so, then a person could use a quitting method tailored to their individual profile, to produce the optimal likelihood of abstinence. Further research also needs to be carried out to investigate the methods of gradual reduction that smokers in the general population are using, and whether they are using any type of support alongside. This could establish whether this accounts for the difference in results between observational studies and RCTs.

Finally, so far there has been no assessment of the cost-effectiveness of a reduction to quit cessation method. This is likely to be influenced by the intensity of the behavioural support

for the reduction method used, whether pharmacotherapy is used alongside behavioural support, and the length of the reduction period before the quit day. Now that there is efficacy evidence to suggest that reduction could be used alongside abrupt quitting economic data would also be useful to aid health care commissioners in their decision making. If reduction to quit is as cost-effective as abrupt quitting this would give further support for its use in the NHS.

In summary, we believe that the methods used in this review allow us to draw robust conclusions about the relative effectiveness of the two cessation methods compared. As with any meta-analysis there are concerns that a single rate ratio may not hold, however the heterogeneity in this meta-analysis was low, reducing this possibility. Despite the fact that some studies do not report interventions used clearly we are confident that we have identified existing studies, due to the fact that the literature review was systematic and that the reference lists of relevant studies were also searched. We believe another strength of this review to be that a thorough quality assessment and sensitivity analyses, where necessary, were carried out of included studies, to assess the risk of bias and allow the reader to make their own decisions. In all cases methods have been reported transparently allowing for replication and update of the review where necessary.

We found no big differences in effect when advising people who smoke, and want to quit, to quit abruptly or advising them to reduce cigarette consumption prior to quit day, i.e. gradual quitting. These results apply to gradual quitting methods that all employed a definite quit day, and it is not clear whether telling people to cut down and quit when they are ready would achieve the same results. Given these findings, it seems reasonable to offer smokers a choice

of whether to cut down in preparation for quitting or to continue to smoke as normal and quit abruptly.

3.6 Conclusions

3.6.1 Implications for research

- Further research should focus on methods of reduction that smokers in the general population use to quit, and whether they utilise behavioural or self-help support alongside these.
- A review of the existing literature on methods of smoking reduction is needed, and RCTs should be developed to determine which methods of reduction are the most effective.
- Research is needed to try and establish people who may benefit most from the abrupt and gradual approaches to quitting smoking, in order to tailor smoking cessation to individuals.
- Future research into reduction methods should include assessment of cost-effectiveness.

3.6.2 Implications for practice

- Smokers could be given a choice to quit smoking either by reducing cigarettes smoked before quitting or by quitting abruptly with no prior reduction.
- Reduction to quit could be implemented via self-help therapy or with the aid of behavioural support.
- NRT could be used to aid pre-quit reduction.

CHAPTER 4: AN UPDATED META-ANALYSIS OF NICOTINE PRELOADING FOR SMOKING CESSATION, IN SMOKERS WHO WANT TO QUIT: INVESTIGATING MEDIATORS OF THE EFFECT

4.1 Background

Nicotine preloading means using NRT prior to quitting smoking. As mentioned previously (Section 1.5.5) two meta-analyses of nicotine patch preloading, in comparison to no preloading or placebo patch preloading, reported very positive results. Shiffman and Ferguson (2008) gave an OR of 1.96 (95% CI= 1.31, 2.93) for six weeks abstinence, and an OR of 2.17 (95% CI= 1.46, 3.22) for six months, and a Cochrane review (Stead et al. 2008) a RR of 1.79 (95% CI= 1.17, 2.72) for long-term abstinence (6 or 12 month). Since these reviews were published the results of three more trials have become available (Etter et al. 2009; Bullen et al. 2010; Hughes et al. 2010), as well as six month quit rates from a study by Rose et al. (2009), which is cited as Rose et al. (2007) in Shiffman and Ferguson's (2008) review.

Neither previous review (Shiffman and Ferguson 2008; Stead et al. 2008) investigated possible mediators of the efficacy of preloading. However knowing the mechanisms of action could have clinical implications. For example, preloading could reduce the reward from smoking, help extinguish the learned need to smoke, and lead to reduced withdrawal intensity after cessation of smoking (Section 1.2.3). One hypothesis that flows from this is that lengthening the preloading period might enhance efficacy. Furthermore, a clinician could

measure reward from smoking and lengthen preloading or advise quitting depending upon responses of individual patients.

We developed three mediational hypotheses to test in this review. The first is that preloading reduces reward from smoking which facilitates the extinction of learned associations between cues to smoke and smoking, as outlined in Section 1.2.3. This would lead to reduced dependence, reduced withdrawal symptoms and craving on stopping smoking, and enhance the likelihood of cessation success. If this mechanism holds, we would expect nicotine patches to be more effective than short-acting forms of NRT. This is because nicotine patches used concurrently with smoking lead to supra-normal blood nicotine concentrations (Fagerstrom and Hughes 2002), that we expect would blunt reward, reduce the need to smoke to avoid withdrawal, and hence undermine the learned basis of tobacco addiction. Short-acting NRT, such as gum, used concurrently with smoking produces blood nicotine concentrations similar to those while smoking only (Fagerstrom and Hughes 2002). We expect in this situation that the natural fall in blood nicotine concentrations will mean that smoking is more rewarding than on a patch and that preloading with a short-acting form of NRT will be less effective. It follows from this that higher blood nicotine concentrations (usually measured by cotinine) will be associated with greater cessation efficacy. It also follows that we would expect reduced exhaled CO concentrations, as preloading reduces smoking intensity due to reduced reward.

The second mediational hypothesis is that preloading accustoms smokers to using NRT, which leads to greater use of NRT after quit day. Greater use of NRT after quit day is associated with increased likelihood of abstinence (Shiffman 2007; Stead et al. 2008). If this

hypothesis holds we would expect to see higher use of NRT in the intervention arm than the control arm. However, NRT use after quit day is contingent on participants' intentions. Once a participant decides continuing to quit is futile or no longer desired, s/he usually stops NRT. A trial showing higher abstinence in one arm than another could show higher use of NRT for this reason alone, so we need to account for this.

Our third mediational hypothesis is that smoking while using NRT leads to reduced cigarette consumption, based on findings reported in Section 1.5.5, which will increase a person's confidence that he or she can stop smoking. Confidence or self-efficacy is associated with increased likelihood of cessation (Gwaltney et al. 2009).

In addition to these mediational hypotheses, we also examined the evidence that behavioural support modifies the effectiveness of preloading. Until recently, smokers were warned even by the package inserts that smoking while wearing the nicotine patch was dangerous, and there is no intuitive reason for people to assume that smoking while using a patch would help. Behavioural support is assumed to be effective partly by enhancing adherence to medication, as users are able to voice their doubts and be directly reassured by therapists. If this is the case, we hypothesise that more intensive pre-quit behavioural support would be associated with better adherence in the pre-quit period. However, if adherence is high during preloading, even without behavioural support, we would expect behavioural support not to modify the effectiveness of preloading.

Finally, we also assessed evidence of any additional moderation in trial reports.

4.2 Method

4.2.1 Inclusion criteria

Studies were included if they were RCTs, if participants were cigarette smokers attempting to quit, if the intervention was a smoking cessation intervention with a pre-quit phase during which participants were randomised to receive active NRT daily for at least a week or a control of either placebo or no NRT, if the nicotine content of cigarettes smoked pre-quit were comparable across conditions, if post-quit NRT and overall behavioural support was comparable across conditions, and if abstinence was reported at six month follow-up or later.

4.2.2 Search strategy

Studies relevant for inclusion were sought from already published reviews of preloading, and from the MEDLINE, EMBASE and PsycINFO databases, using the following topic-specific terms: nicotine or NRT, combined with any of the following: pre-cessation, precessation, pre cessation, pre-loading, preloading, pre loading, pre-treatment, pretreatment, pre treatment, pre-quit, prequit, pre quit, before treat*, before quit*, before cessation (See Appendix 21 for complete search strategies).

4.2.3 Study eligibility assessment

The titles and abstracts generated from the search strategy, as well as the reference lists of relevant papers, were checked for relevance using the inclusion criteria above (see Appendix 22 for the study eligibility form used to do this).

4.2.4 Data extraction

Data on the following were then extracted from each relevant paper: study design, setting of study, method of participant recruitment, type of NRT, type of support/participant contact, follow-up point, number of participants randomised to each group, participant characteristics at baseline, definition of abstinence, whether abstinence was biochemically verified, the number of quitters in each arm, and secondary outcomes.

4.2.5 Outcomes

Primary outcomes were both short-term abstinence and long-term abstinence at least six months after quit day. In trials with more than one measure of abstinence, we preferred the measure with the strictest criteria. We used prolonged or continuous abstinence over point prevalence abstinence, and biochemically validated abstinence over self-report, for both short-term outcomes and abstinence at least six months from quit date. We also extracted data on the possible mediators and moderators of the effect of preloading.

4.2.6 Quality assessment

The quality of each included study was assessed within the domains of randomisation sequence generation, concealment of allocation to study arm, blinding to study arm allocation, and incomplete outcome data. This assessment was carried out according to procedure outlined in the Cochrane Collaboration Handbook (Higgins and Green 2009). Whether studies validated self-reported abstinence was also considered. A sub-group analysis was used to compare the effect of preloading in double-blinded studies using placebo NRT in the control

groups, with studies that were unblinded. We also examined funnel plots to investigate possible publication bias.

4.2.7 Analysis

With an aim to establish the efficacy of preloading we compared both short- and long-term quit rates between treatment arms using pre-quit NRT and the arms using placebo/no pre-quit NRT, calculated on an ITT basis. Participants lost to follow-up were classified as smokers. This meta-analysis was carried out using the RevMan 5.1 computer programme developed by the Cochrane Collaboration. RR was used as the summary statistic in all meta-analyses, using the Mantel–Haenszel fixed-effect model. We checked for heterogeneity by examining forest plots for poor overlap of confidence intervals and using the I^2 and the chi-squared Q statistics.

In order to establish how preloading may work and in which circumstances it may be most effective we tested our hypotheses, by carrying out the following a priori analyses. Where analysis is qualitative this is because insufficient quantitative data was provided to conduct meta-analyses.

4.2.7.1 Hypothesis 1. Efficacy is mediated through reduced reward and hence reduced dependence

We synthesised the data qualitatively to examine the effects of preloading on reward, negative reinforcement, cigarette smoking, and post-quit withdrawal intensity. Furthermore, we split the studies into those providing two and four weeks preloading, and those using patch and gum consistent with the hypotheses reported in Section 4.1, using meta-analyses.

4.2.7.2 Hypothesis 2. Efficacy is mediated through increased post-quit adherence

We synthesised the data qualitatively to examine whether post-quitting adherence was higher, in participants who continued to try to quit, in those who had carried out preloading in comparison to those who had not.

4.2.7.3 Hypothesis 3. Efficacy is mediated through increased confidence

We examined qualitatively whether confidence before quitting increased more in the preloading groups relative to the control groups.

4.2.7.4 Hypothesis 4. Behavioural support modifies the effect of preloading

We qualitatively examined whether the degree of behavioural support provided was associated with enhanced adherence to pre-quit NRT. We also investigated whether studies that provided less support in the pre-quit period were associated with reduced smoking cessation efficacy, using meta-analysis.

Finally we examined baseline individual differences, as potential moderators of the effect of preloading on abstinence, and synthesised the available data.

4.3 Results

4.3.1 Included studies and participants

Our database searches retrieved 129 references and after title and abstract searches we were left with 15 full-text papers (See Appendix 23 for study inclusion flow diagram). After checking the full-text against the inclusion criteria, we found eight studies relevant for inclusion (Rose et al. 1994; Rose et al. 1998; Schuurmans et al. 2004; Rose et al. 2006; Etter et al. 2009; Rose et al. 2009; Bullen et al. 2010; Hughes et al. 2010) (Table 5). Four of these were included in Stead et al.'s (2008) review (Rose et al. 1994; Rose et al. 1998; Schuurmans et al. 2004; Rose et al. 2006), and four were included in Shiffman and Ferguson's (2008) review (Rose et al. 1998; Schuurmans et al. 2004; Rose et al. 2006; Rose et al. 2009). We found three studies published since these reviews were conducted (Etter et al. 2009; Bullen et al. 2010; Hughes et al. 2010). The total sample size in the preloading arms was 1,403 across the eight studies, ranging from 24 to 549 in individual studies. In the control arms total sample size was 1,410, ranging from 24 to 551 across studies. All of the studies recruited participants attempting to quit smoking. On average participants were evenly split between males and females, their mean age was 42 years, average cpd ranged from 19 to 30 across studies, with a median of 24 cpd, and a median FTND of 6. In all but one of the studies (Hughes et al. 2010) all trial arms were relevant and included in the analyses; however Hughes et al. (2010) included a third arm where participants were randomised to a minimal treatment condition. As this trial arm received a different level of behavioural support to the preloading condition this could impact on the resulting effect, and so it was not included in the analyses.

Table 5: Characteristics of studies included in the preloading meta-analyses

Study ID	Total N	Preloading N	Control N	Mean age	% female	Mean baseline FTND	Mean baseline cpd	Length of preloading (weeks)	Pre-quit NRT	Preloading smoking instructions	Measure of short-term abstinence	Measure of long-term abstinence
Bullen et al. (2010)	1100	549	551	40	60	6	19	2	Patch +/or gum	Smoke freely	12 week self-reported, continuous	6-month self-reported, continuous
Etter et al. (2009)	314	154	160	Preloading = 42 Control= 44	Preloading = 35 Control= 47	Preloading = 5.5 Control= 5.4	Preloading = 24 Control= 23.4	4	4mg gum	Reduce	8 week self-reported continuous	12 month, cotinine & CO verified, 4 week prolonged
Hughes et al. (2010)	596	297	299	48	54	5.9	23	3-5	2 or 4mg lozenge	Reduce	12 week self-reported, prolonged	6 month CO verified, prolonged
Rose et al. (1994)	48	24	24	34	60	6	28	2	21mg/24 hr patches	Smoke freely	7 week CO verified, continuous	12 month CO verified, continuous
Rose et al. (1998)	80	40	40	41	49	6.4	29.9	4	21mg/24 hr patches	Smoke freely	6 week CO verified, continuous	6 month CO verified, continuous
Rose et al. (2006)	96	48	48	45	53	6.5	28.6	2	21mg/24 hr patches	Smoke freely	4 week CO verified, continuous	6 month CO verified, 7-day point prevalence
Rose et al. (2009)	379	191	188	42	57	5.9	23.1	2	21mg/24 hr patches	Smoke freely	6 week CO verified, continuous	6 month CO verified, continuous
Schuurmans et al. (2004)	200	100	100	44	44	6.1	24.8	2	15mg/16 hr patches	Smoke as normal	6 week, CO verified, continuous	6month, CO verified, continuous

FTND- Fagerstrom Test for Nicotine Dependence, cpd- cigarettes per day, NRT- nicotine replacement therapy, CO- carbon monoxide, mg- milligram, hr- hour, N- number of participants

4.3.2 Excluded studies

The seven studies that were excluded at this stage were excluded for the following reasons: participants were not asked to preload as defined for the purposes of this review (Powell et al. 2004; Chan & Davenport 2010); the nicotine content of cigarettes was varied across study arms pre-quit (Rezaishiraz et al. 2007); the NRT treatment was not comparable across study arms post-quit (Becker et al. 2008; Shiffman et al. 2009); participants were not asked to preload as part of a smoking cessation intervention (Braur et al. 1999); and finally Herrera et al. (1995) was excluded as a small sub-group of the participants were allocated to preloading as defined here, however the quit rate data was not available at long-term follow-up for this group.

4.3.3 Interventions

All studies included at least one group randomised to receive NRT before quitting smoking; three included another group who received a preloading placebo pre-quit (Schuurmans et al. 2004; Rose et al. 2006; Rose et al. 2009), and five studies included a group who received no placebo preloading intervention, and so were unblinded (Rose et al. 1994; Rose et al. 1998; Etter et al. 2009; Bullen et al. 2010; Hughes et al. 2010). Preloading was carried out for two weeks in five studies (Rose et al. 1994; Schuurmans et al. 2004; Rose et al. 2006; Rose et al. 2009; Bullen et al. 2010), four weeks in two studies (Rose et al. 1998; Etter et al. 2009), and three to five weeks in the remaining study (Hughes et al. 2010). Four studies provided participants with 21mg/24hr patches pre-quit (Rose et al. 1994; Rose et al. 1998; Rose et al. 2006; Rose et al. 2009), one with 15mg/16hr patches (Schuurmans et al. 2004), and Bullen et

al. (2010) gave participants a choice of nicotine patch only, patch and gum, or gum only, where the dose depended on the advisor's assessment. Another study provided participants with 4mg gum pre-quit (Etter et al. 2009), and the final study (Hughes et al. 2010) sent participants 2 or 4mg lozenges depending on how soon they smoked their first cigarette on waking. Post-quit day NRT was provided for 4-12 weeks, varying across studies.

In addition to NRT treatment three included studies provided participants with mecamylamine (a nicotinic antagonist) or placebo either pre and post-quit (Rose et al. 1994; Rose et al. 1998) or post-quit only (Rose et al. 2006), and two studies provided participants with cigarettes with manipulated nicotine content (Rose et al. 2006; Rose et al. 2009). Five studies asked participants to smoke freely whilst preloading (Rose et al. 1994; Rose et al. 1998; Rose et al. 2006; Rose et al. 2009; Bullen et al. 2010), one asked participants to smoke as they normally did (Schuurmans et al. 2004), and two asked participants to reduce their smoking in the preloading arm and quit abruptly in the control arm (Etter et al. 2009; Hughes et al. 2010).

4.3.4 Outcomes

The follow-up point for short-term abstinence varied across studies from 4 to 12 weeks, with a median of 6.5 weeks. Seven of the eight studies reported short-term continuous abstinence: two as self-report only (Etter et al. 2009; Bullen et al. 2010) and five studies using CO validation to confirm self-report (Rose et al. 1994; Rose et al. 1998; Schuurmans et al. 2004; Rose et al. 2006; Rose et al. 2009). The eighth study (Hughes et al. 2010) defined short-term abstinence as self-reported prolonged abstinence.

Six studies reported long-term abstinence at six month follow-up (Rose et al. 1998; Schuurmans et al. 2004; Rose et al. 2006; Rose et al. 2009; Bullen et al. 2010; Hughes et al. 2010), one at 12 month follow-up (Etter et al. 2009), and the remaining study reported abstinence at both 6 and 12 month follow-up (Rose et al. 1994); in this case 12 month abstinence was used. Four of the included studies supplied continuous abstinence rates, verified by either CO and/or cotinine (Rose et al. 1994; Rose et al. 1998; Schuurmans et al. 2004; Rose et al. 2009), one prolonged CO-verified rates (Hughes et al. 2010) and another defined abstinence as seven day point prevalence at six months, verified by CO measurement (Rose et al. 2006). Etter et al. (2009) provided four week prolonged abstinence rates verified by cotinine and CO, as well as continuous self-reported rates at 12 month follow-up. In this case the verified rates were used as these were most stringent. Bullen et al. (2010) only attempted cotinine verification in a sample of participants, for point prevalence rates. For this study self-reported continuous abstinence was used.

4.3.5 Effect of preloading on abstinence

There was a very weak positive effect of preloading on short-term abstinence (RR=1.05, 95% CI= 0.92, 1.19), however the effect was not significant (p=0.49) (Figure 11). There was marked heterogeneity with an I^2 of 69%, p=0.002. The effect on long-term abstinence gave a slightly larger RR of 1.16 (95% CI= 0.97, 1.38) (Figure 12), and there was less heterogeneity with an I^2 of 39%, p=0.12. However, again the effect was non-significant. Based on the large amount of heterogeneity in the short-term analysis we re-ran the analyses using random-effects models; however the results were similar to the fixed-effect models for both short- and long-term abstinence (Appendix 24).

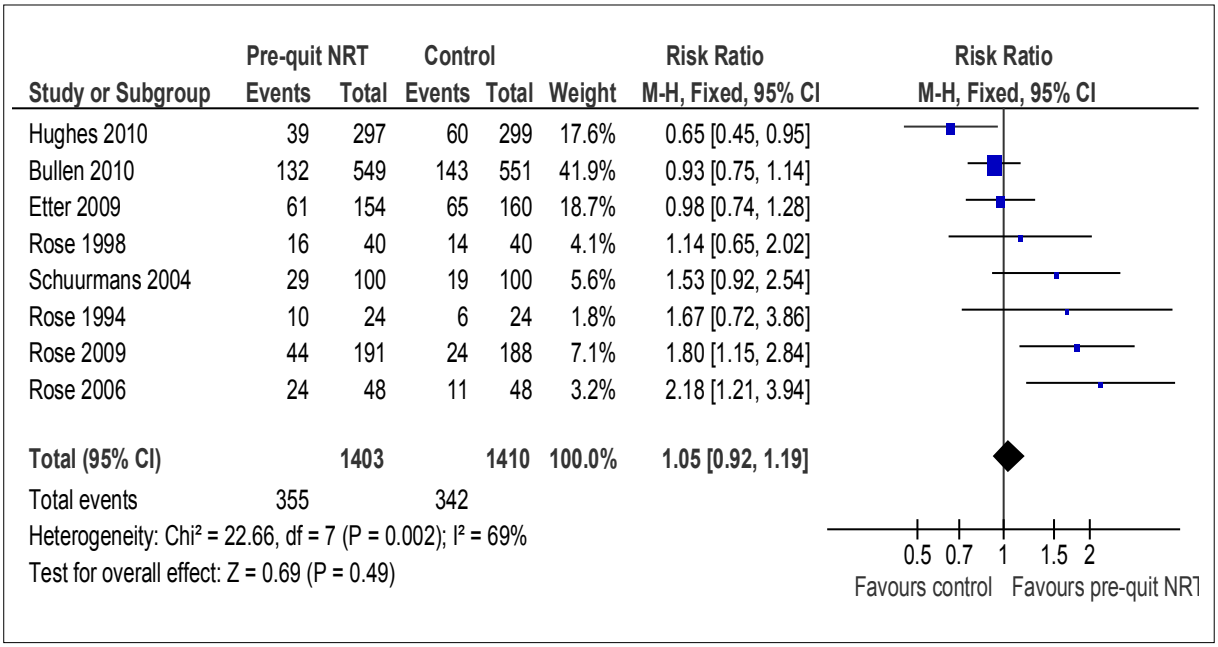

Figure 11: A forest plot illustrating the effect of NRT preloading on short-term abstinence

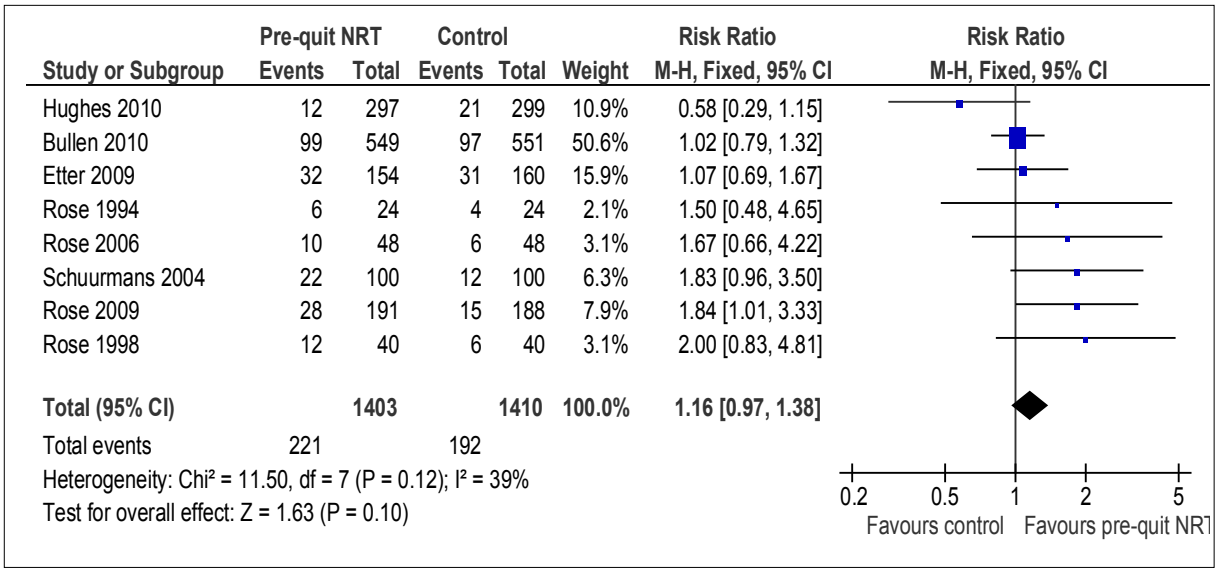

Figure 12: A forest plot illustrating the effect of NRT preloading on long-term abstinence

4.3.5.1 Hypothesis 1. Efficacy is mediated through reduced reward and hence reduced dependence

Two studies measured reward, satisfaction or enjoyment from smoking during preloading (Rose et al. 1994; Rose et al. 1998). Rose et al. (1994) reported that preloading significantly reduced smoking satisfaction, good taste of cigarettes, and the calming effect of smoking relative to control, but there was no main effect of preloading on enjoyment of respiratory tract sensations when smoking. It was not possible to calculate effect sizes from the report. Rose et al. (1998) reported that nicotine preloading did not affect the reward from cigarettes pre-quit, with almost identical reductions in reward in both active and placebo groups. Taken together, there is little evidence that preloading influences the positive reward from smoking.

Four studies reported data on the effect of preloading on variables relevant to negative reinforcement from smoking, during the pre-quit period (Rose et al. 1994; Rose et al. 1998; Schuurmans et al. 2004; Rose et al. 2006). Rose et al. (1994) reported some evidence that nicotine patch treatment reduced negative affect in smokers with high baseline ratings, but effect sizes were not calculable. Rose et al. (1998) reported that negative affect increased in nicotine treatment compared to placebo during the first week only of four weeks preloading, but again no effect size was calculable. Rose et al. (2006) measured negative affect pre-quitting but results presented do not enable the reader to determine whether there was an effect of nicotine preloading. Schuurmans et al. (2004) reported no effect of preloading on a composite (Wisconsin) scale of withdrawal symptoms. Overall we found no evidence that preloading influenced negative reinforcement.

Reduced positive or negative reinforcement from smoking should reduce cravings during the pre-quit period and four studies had data. Rose et al. (1994) and Rose et al. (1998) found no effect of preloading on craving. However, Rose et al. (2006) reported an approximate 20% reduction in craving during preloading, and Hughes et al. (2010) a 10% reduction, whereas very little difference was observed in the control groups of both studies. Therefore the effect on pre-quit cravings is small if it exists.

Our hypothesis was that reduced craving would be associated with reduced dependence scores and lower cigarette consumption (cpd, CO, and cotinine) during preloading. In five studies participants were advised to smoke as they chose (Rose et al. 1994; Rose et al. 1998; Rose et al. 2006; Rose et al. 2009; Bullen et al. 2010). Rose et al. (1994) found that participants reduced cigarette consumption by more than half in the nicotine preloading condition, whereas there was little change in the placebo group. Rose et al. (1998) showed an approximate one third reduction in cpd in the active patch condition compared with placebo, where there was little reduction pre-quit. There was no apparent reduction in CO but plasma nicotine derived from smoking fell by around 20% in the nicotine treated group and was steady in the placebo group. Rose et al. (2006) showed an approximate 20% reduction in daily cigarette consumption in the nicotine preloading group, versus 10% reduction without preloading. CO levels declined by about 10% in the active group and did not change in the non-nicotine group. Bullen et al. (2010) found the preloading group reduced daily cigarette consumption by 63% and the no preloading group reduced by 16%. Schuurmans et al. (2004) reported almost no reduction in cpd in both active and placebo groups, and CO declined little (12% versus 3%), but the investigators had asked participants not to change their smoking behaviour. Etter et al. (2009) and Hughes et al. (2010) both asked the preloading group to

reduce their smoking. Etter et al. (2009) reported a 48% reduction in consumption and 9% in the group who received no preloading. Hughes et al. (2010) found that cpd reduced by 54% (13 cpd), as well as CO levels by 21% (6 ppm), in the preloading condition, in comparison to a 1% (0.3 cpd) reduction in cpd and a 0% (0 ppm) reduction in CO in the control group. Only one study reported on cotinine concentration while smoking (Rose et al. 2006). Cotinine concentration rose by about 60% during preloading with patch, compared with almost no change using placebo. Taken together the data indicate that preloading reduces smoking consumption moderately and variably across studies, but this seems partly related to the instructions given on how to smoke. Reduction in smoke intake measured by CO is less affected than cpd.

Only two studies reported change in dependence over the pre-quit period (Rose et al. 2006; Hughes et al. 2010). Hughes et al. (2010) reported that participants in the preloading condition decreased their dependence, by increasing the time to first cigarette after waking from 15 to 28 minutes, whereas this measure of dependence did not change in the control group. They also reported that similar outcomes occurred when dependence was measured using self-rated addiction and the FTND; the change in scores is not specified, however the difference between the preloading condition and control was significant in both cases ($p< 0.0001$). Hughes et al. (2010) also reported that the regularity of smoking (stereotypy) decreased in the preloading condition by 10%, but stayed the same in the control condition during the pre-quit period. Rose et al. (2006) showed a decline of about two FTND points (20%) in the group receiving nicotine preloading and one point in the group on placebo. In both of these studies cigarette consumption declined on average and this contributes to FTND score, so in the case of FTND, it is not possible to know whether other indices of dependence declined, or whether

these changes were accounted for by reduction in consumption. However the decline in other measures of dependence (self-rated addiction and stereotypy), that do not depend on cigarette consumption, in Hughes et al. (2010) support the theory that dependence was reduced by preloading.

We hypothesised that reduced positive or negative reward from smoking would manifest as reduced pre-quit consumption, reduced dependence, and hence reduced intensity of withdrawal after quitting. Rose et al. (1994) showed similar levels of craving after cessation in nicotine preloading and placebo groups. Rose et al. (1998) showed an approximate 10% reduction in craving after cessation in both the active and placebo groups. Bullen et al. (2010) reported that craving was 0.24 units (3% of the whole scale) lower in the preloading group than the no preloading group. Etter et al. (2009) reported similar craving levels in smokers receiving preloading compared to those who did not. Overall withdrawal scores were measured by Schuurmans et al. (2004) and Etter et al. (2009), both showing almost no difference in active or comparator groups. Some studies (Rose et al. 1994; Rose et al. 1998; Rose et al. 2006; Etter et al. 2009) reported scores for individual withdrawal symptoms. These indicated no large differences and when these were compared statistically (Etter et al. 2009) the differences were not significant. Overall there appears to be reasonable evidence that nicotine preloading does not reduce post-quit smoking withdrawal.

A subsidiary hypothesis arising from this proposed mechanism is that patch, which leads to supra-normal nicotine blood concentrations when smoking, would be more effective than short-acting NRT, in which nicotine concentration is typical of smoking alone (Fagerstrom

and Hughes 2002). We tested this by carrying out a sub-group analysis, splitting the studies in terms of whether they used gum/lozenge (Etter et al. 2009; Hughes et al. 2010) or patch (Rose et al. 1994; Rose et al. 1998; Schuurmans et al. 2004; Rose et al. 2006; Rose et al. 2009; Bullen et al. 2010) pre-quit. Bullen et al.'s (2010) study included participants that used patch and participants that used gum only, but did not present results split this way for the continuous cessation outcome. As only 9% used nicotine gum, for the purposes of this analysis, we included all participants in the patch category. For short-term abstinence the RR for the patch group was 1.17 (95% CI= 1.00, 1.37) and for gum/lozenge was 0.82 (95% CI= 0.66, 1.02), p=0.009 for the difference in RRs (Figure 13). Splitting the studies in this way for short-term outcomes did not remove heterogeneity which was still 66% for the patch sub-group and 67% for the gum/lozenge sub-group. For long-term cessation, the nicotine patch also appeared somewhat more effective than gum with a RR of 1.26 (95% CI= 1.03, 1.55), compared to a RR of 0.87 (95% CI= 0.60, 1.26), although the difference between the sub-groups was not statistically significant (p=0.08). Heterogeneity was still present, with an I^2 of 28% in the patch group and 55% in the gum/lozenge group (Figure 14). This supports the hypothesis that preloading using nicotine patch is more successful than preloading with short-acting NRT only, and that there is no benefit to preloading using short-acting NRT, although these conclusions are clouded by unexplained heterogeneity.

A second subsidiary hypothesis is that longer preloading would lead to better cessation rates. Five studies that used patches had a preloading period of two weeks (Rose et al. 1994; Schuurmans et al. 2004; Rose et al. 2006; Rose et al. 2009; Bullen et al. 2010) and one of four weeks (Rose et al. 1998).

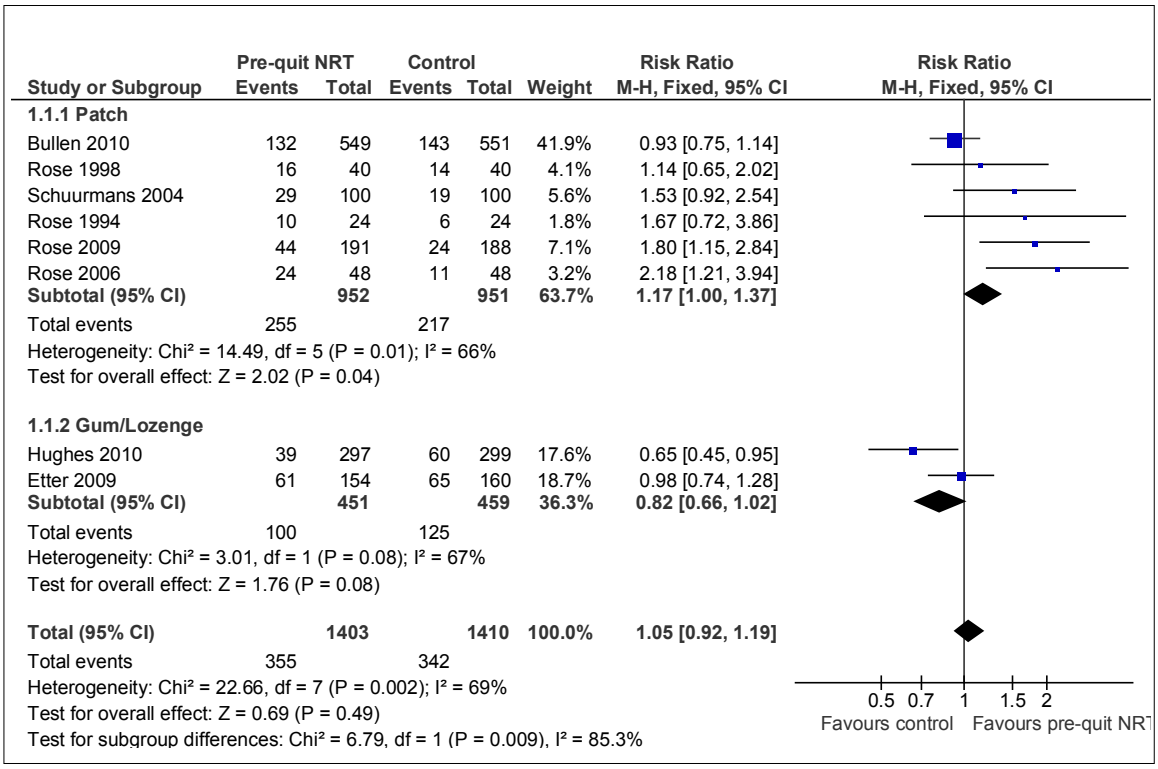

Figure 13: A forest plot illustrating the type of NRT sub-group analysis , for the preloading meta-analysis (short-term abstinence rates)

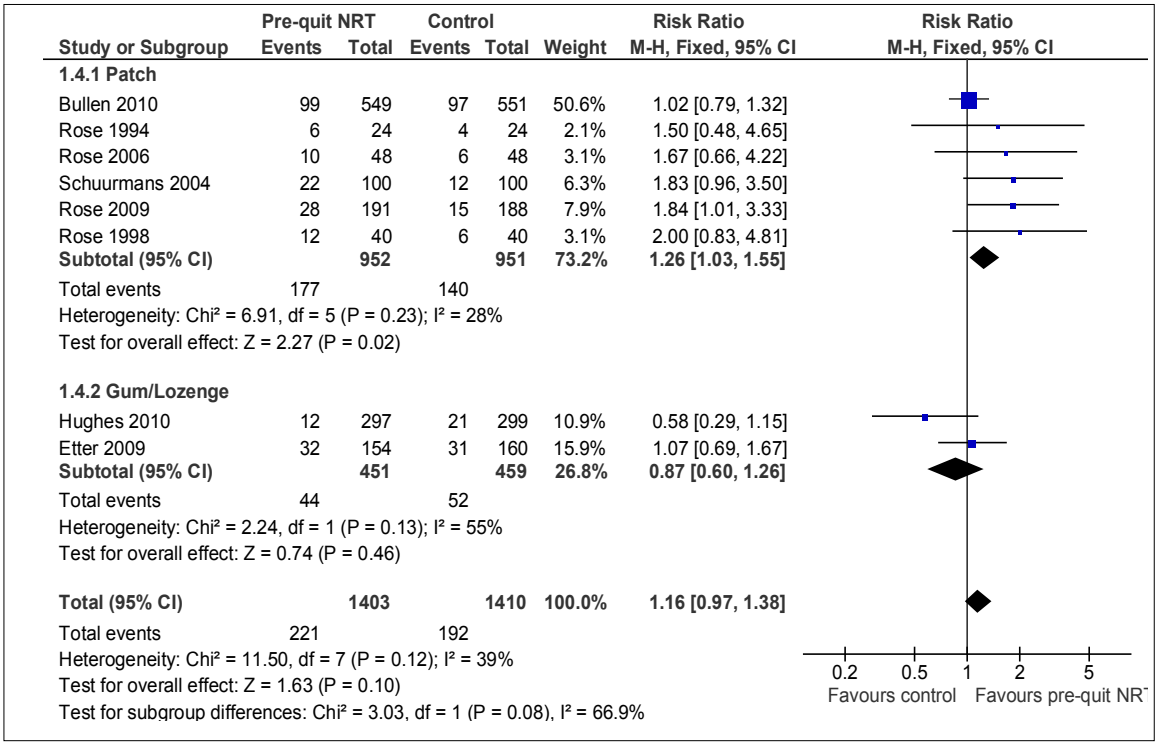

Figure 14: A forest plot illustrating the type of NRT sub-group analysis, for the preloading meta-analysis (long-term abstinence rates)

For short-term outcome (Figure 15) the RRs of the two groups were similar, with a two week RR of 1.18 (95% CI= 1.00, 1.39), and four week RR of 1.14 (95% CI= 0.65, 2.02). For long-term cessation (Figure 16) the RRs were 1.23 (95% CI= 1.00, 1.52) and 2.00 (95% CI= 0.83, 4.81), but in neither case was the test for difference in sub-groups significant (p=0.92 and p=0.29 respectively). The wide confidence intervals show the data are insufficient to examine the effect of length of preloading.

4.3.5.2 Hypothesis 2. Efficacy is mediated through increased post-quit adherence

In all included trials, participants were randomised to NRT or placebo/no NRT pre-quit, but all participants used active NRT after quit day. Our hypothesis was that preloading would enhance post-quit adherence to NRT relative to control. Adherence to NRT treatment was measured using a variety of measures in all eight of the studies, however only four of these studies made between-group, post-quit comparisons (Schuurmans et al. 2004; Etter et al. 2009; Rose et al. 2009; Hughes et al. 2010). Two studies used placebo patch pre-quit as a control (Schuurmans et al. 2004; Rose et al. 2009), therefore we would expect that adherence would be similar across the groups, which was the case. Rose et al. (2009) found that overall adherence was high post-quit and that there was no difference between groups. Schuurmans et al. (2004) found that at quit day, two, six and 10 weeks follow-up 95%, 79%, 58% and 38% of participants in the active patch group complied with nicotine treatment respectively, and in the placebo patch group 87%, 77%, 57% and 39%. In Etter et al. (2009) and Hughes et al. (2010)- the only studies to compare preloading with no preloading (without placebo) and report post-quit adherence between groups- there was no significant differences in adherence

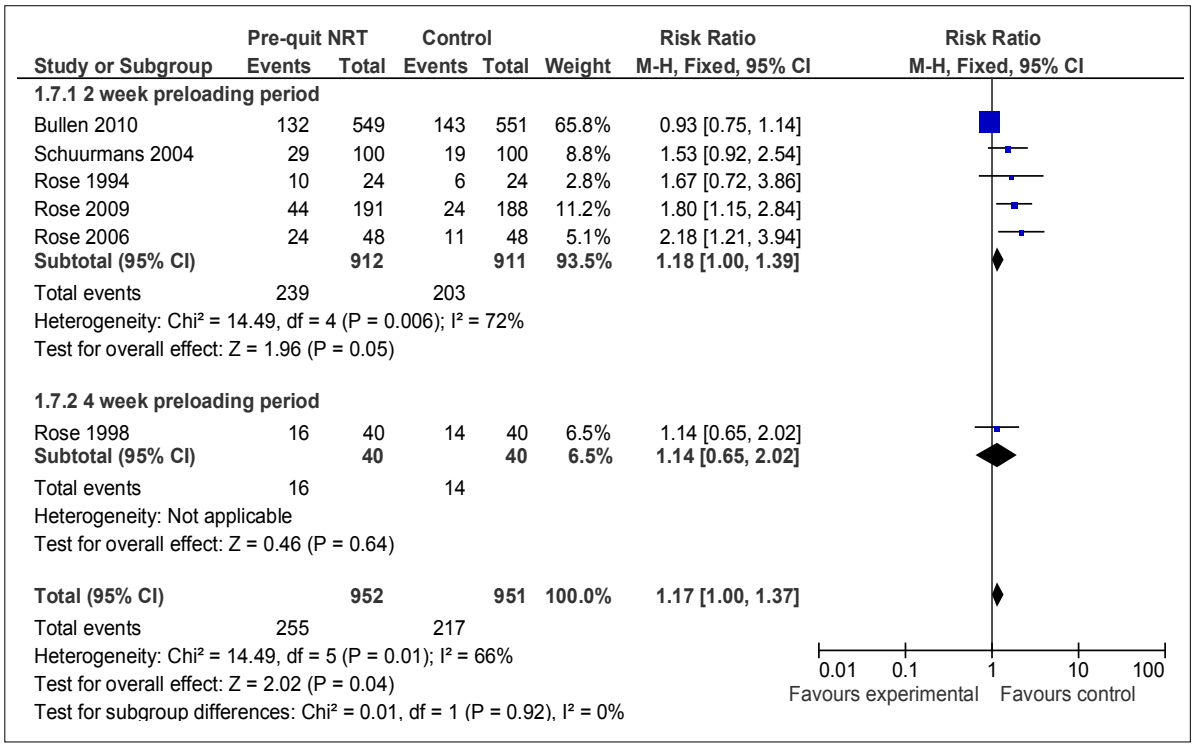

Figure 15: A forest plot illustrating the length of preloading sub-group analysis, for the preloading meta-analysis (short-term abstinence rates)

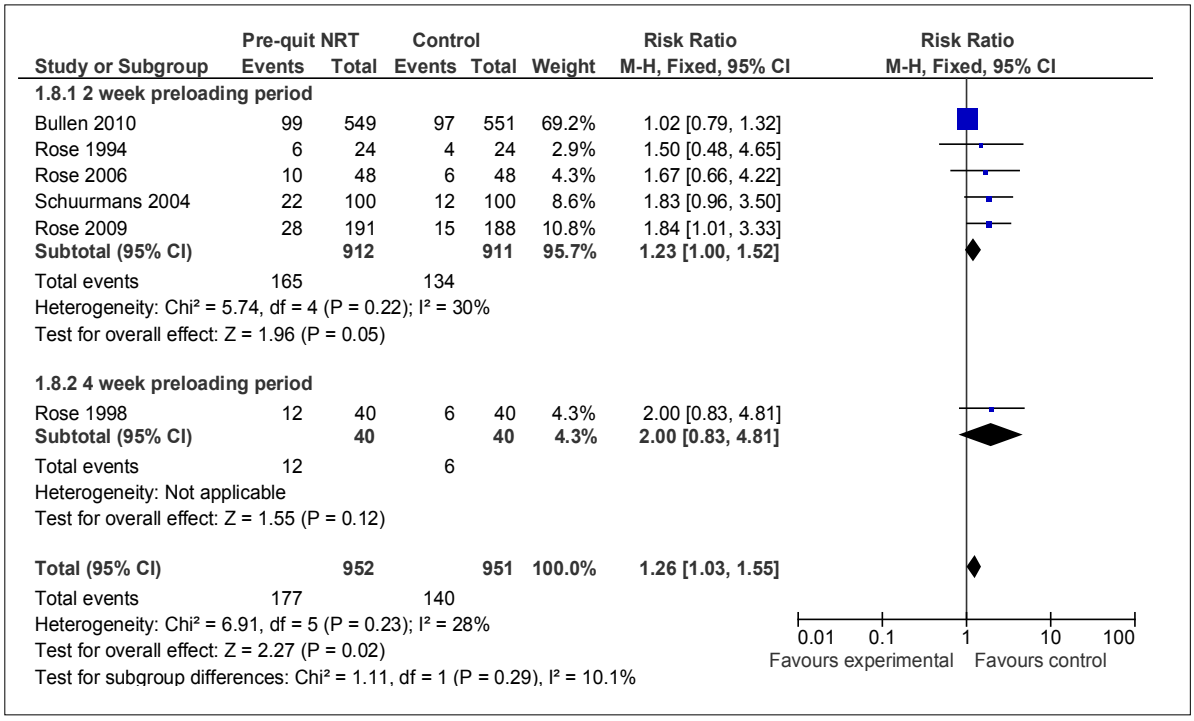

Figure 16: A forest plot illustrating the length of preloading sub-group analysis, for the preloading meta-analysis (long-term abstinence rates)

post-quit. Etter et al. (2009) found that at eight weeks follow-up preloading participants had used gum for 68%, and control participants for 67%, of the past 60 days (p=0.80), 41% of the preloading condition and 40% of the control condition (p=0.45) were still using nicotine gum daily, and preloading participants had used NRT for an average of 6.5 days of the week, and the control condition for 6.2 days of the week. The available evidence on adherence does not support the hypothesis that preloading achieves efficacy by enhancing adherence to post-quit NRT.

4.3.5.3 Hypothesis 3. Efficacy is mediated through increased confidence

We hypothesised that if preloading reduces cpd pre-quit then this will increase confidence in quitting. Only Etter et al. (2009) and Hughes et al. (2010) reported on confidence in quitting. Etter et al. (2009) showed that the preloading group reduced consumption by 48% compared with 9% in the group who received no preloading. However, confidence ratings were not affected, with scores measured on a 0–100 scale three days after quitting, reported as 73 in both groups (p=0.88). Hughes et al. (2010) found that the preloading group reduced cigarette consumption by 54% and the control group by 1%. This corresponded to an increase in self-efficacy (measured using the nine-item form of Velicer's scale) in the preloading group from 18 at baseline to 23 pre-quit, out of a possible 45 (an 11% increase), with minimal change in the control (data for the control condition alone were not provided). A similar effect occurred when confidence was measured using the five-point confidence in quitting scale, however data were not reported. Therefore there was contrasting and inconclusive evidence that reduced smoking enhanced confidence in ability to quit.

4.3.5.4 Hypothesis 4. Behavioural support modifies the effect of preloading

Our fourth hypothesis was that the intensity of behavioural support provided pre-quit moderates the effect of preloading, through increased pre-quit adherence. Providing support during preloading could increase adherence, and in turn the efficacy of preloading, because participants can raise any misunderstandings, worries and/or problems with the regimen. To investigate this we carried out a sub-group analysis to assess cessation outcomes, by splitting the studies into two sub-groups based on whether or not behavioural support was provided during the pre-quit period. All included studies provided participants with behavioural support, which varied from minimal with no in-person support to moderate intensity. The studies offering clinic visits (Rose et al. 1994; Rose et al. 1998; Schuurmans et al. 2004; Rose et al. 2006; Rose et al. 2009) all included support part-way through the preloading period bar one (Schuurmans et al. 2004), which provided support at baseline and one to two days before quit day. One trial provided telephone support (Bullen et al. 2010), but not during the pre-quit period (Bullen et al. 2008). Hughes et al. (2010) provided telephone support three times for 10 minutes each during the pre-quit period, in addition to a session at baseline. The remaining study was a self-help study (Etter et al. 2009) with support only by a booklet and/or website. The mid pre-quit support group therefore included five studies (Rose et al. 1994; Rose et al. 1998; Rose et al. 2006; Rose et al. 2009; Hughes et al. 2010) and the no mid pre-quit support group contained three studies (Schuurmans et al. 2004; Etter et al. 2009; Bullen et al. 2010) (Table 6). For short-term abstinence, splitting by the type of behavioural support (mid pre-quit support versus no mid pre-quit support) resulted in a RR of 1.15 (95% CI= 0.93, 1.44) for mid pre-quit support, and an RR of 0.99 (95% CI= 0.85, 1.16) for no mid pre-quit support; p=0.27 for sub-group difference **(**Figure 17). Heterogeneity was lowered to 38% in the no mid pre-quit support group, but was high in the other group at 78%. The result was similar using

Table 6: Details of support provided as part of studies included in the preloading meta-analyses

Study ID	Method of contact	Support facilitator	Pre-quit support contacts	Minutes per contact	Content of contact
Bullen et al. (2010)	Established telephone quit-line	Trained advisors	Control condition quit immediately. Preloading condition received pre-quit support at baseline only (Bullen et al. 2008)	Not specified	Not specified
Etter et al. (2009)	Mailed NRT & booklet. Smoking cessation website	No person contact	Could use booklet & website as required	Not applicable	Booklet included instructions to participants (no further details). Website: www.stop-tabac.ch
Hughes et al. (2010)	Telephone & US National Cancer Institute's 'Clearing the Air' booklet.	Counsellors with a bachelor's degree in psychology or counselling	Control condition: Baseline, 2 days pre-quit. Preloading condition: Baseline, 1 week after baseline, 2 weeks after baseline, 2 days pre-quit.	All participants received 70-90 minutes in total. Preloading received at least 1 hour pre-quit.	Manuals used by counsellors can be found at: http://www.uvm.edu/~hbpl/?Page=data.html
Rose et al. (1994)	Clinic visits & self-help booklet	Research assistant	Baseline, mid-way through pre-quit (wk 1), quit day	15	Participants interviewed about difficulties & offered encouragement & behaviour change strategies. Booklet advised on quitting strategies
Rose et al. (1998)	Clinic visits & self-help booklet	Research assistant	Baseline, wk 1, wk 2 & wk 3 pre-quit, quit day	10-15	Participants interviewed about difficulties & offered encouragement & behaviour change strategies. Booklet advised on quitting strategies
Rose et al. (2006)	Clinic visits	Not specified	Baseline, mid-way through pre-quit (wk 1), quit day	5-10	Brief supportive counselling. Booklet advised on quitting strategies & quitting benefits
Rose et al. (2009)	Clinic visits	Not specified	Baseline, mid-way through pre-quit (wk 1), day before quit day	Not specified	Not specified
Schuurmans et al. (2004)	Clinic visits	Experienced nurse	Baseline, 1-2 days before quit day	20	Counselling given. (No further details specified)

NRT- nicotine replacement therapy, wk- week

long-term abstinence rates, where the RR was 1.30 (95% CI= 0.93, 1.83) for the mid pre-quit support group and 1.10 (95% CI= 0.90, 1.36) for no mid pre-quit support; p=0.42 for sub-group difference (Figure 18). Again this analysis did not eliminate heterogeneity (49% mid pre-quit support, 26% no mid pre-quit support). Given the imprecision of these estimates, the data are insufficient to conclude whether pre-quit support enhances the effectiveness of preloading, though there is very modest support for this hypothesis.

The evidence that behavioural support enhances effectiveness would be supported by data showing that such support enhanced adherence to preloading. All studies that offered support part-way through the pre-quit period (Rose et al. 1994; Rose et al. 1998; Rose et al. 2006; Rose et al. 2009; Hughes et al. 2010) reported that pre-quit NRT use was high, ranging from 90–100% of patches applied in the Rose studies, and 93% of participants using lozenges on a median of 83% of days, and on average using four to five lozenges (18.6mg) per day in Hughes et al. (2010). The three studies providing no mid pre-quit support reported mixed adherence. Bullen et al. (2010) reported that 61% of participants used all of their NRT in the preloading arm pre-quit. However, both Etter et al. (2009) and Schuurmans et al. (2004) also reported adherence was high. In Etter et al. (2009) participants used 7.9 gums per day on average pre-quit. Schuurmans et al. (2004) reported 95% of participants were using preloading active or placebo patches at quit day. This suggests that participants generally adhered to treatment well in the preloading arms, and so the addition of support during preloading did not enhance adherence, and in turn the effectiveness of preloading.

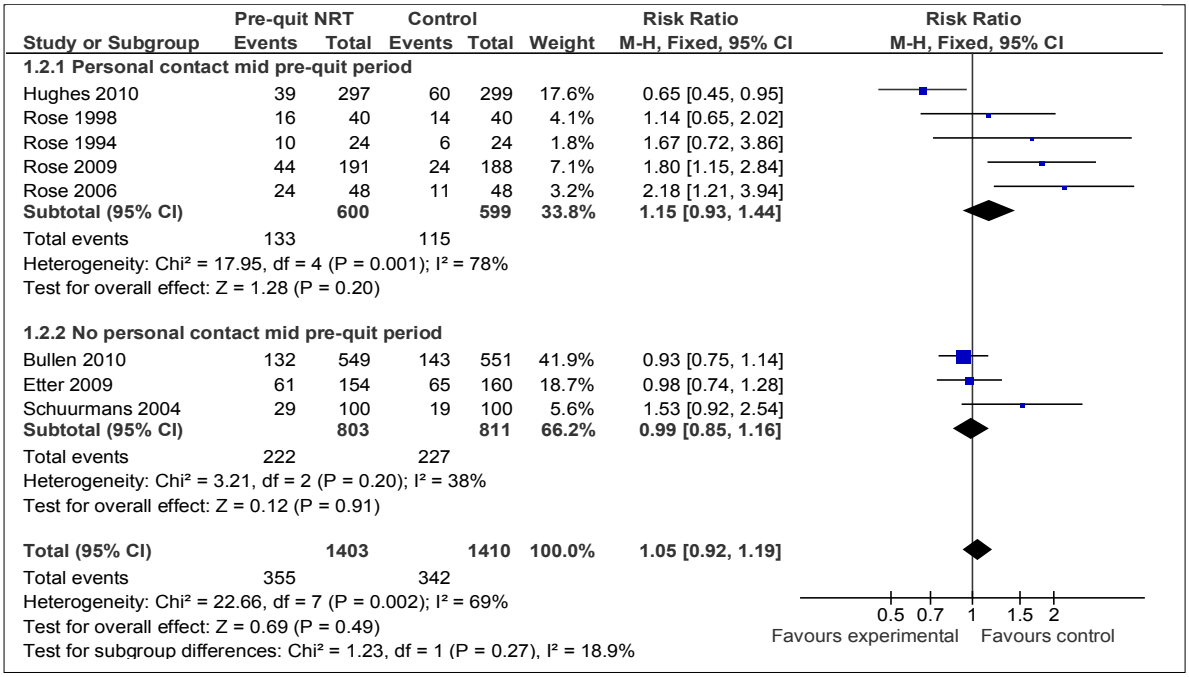

Figure 17: A forest plot illustrating the type of behavioural support sub-group analysis, for the preloading meta-analysis (short-term abstinence rates)

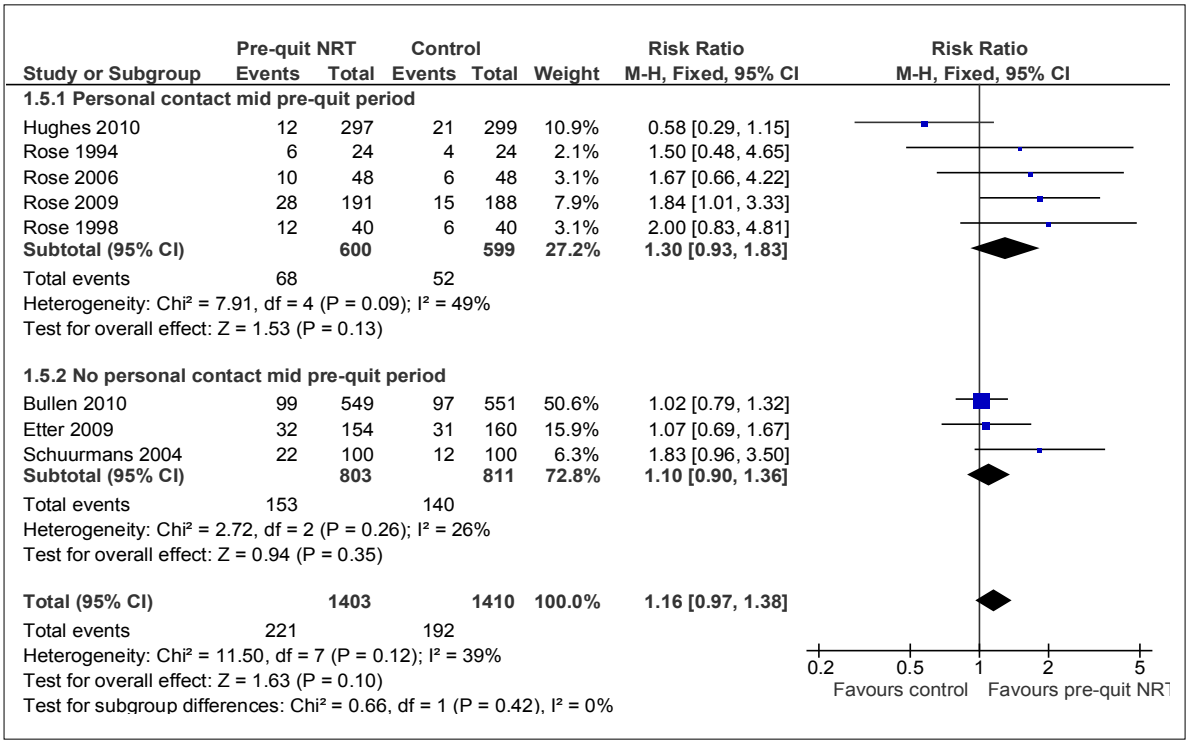

Figure 18: A forest plot illustrating the type of behavioural support sub-group analysis, for the preloading meta-analysis (long-term abstinence rates)

4.3.6 Additional moderators of the preloading effect

We also extracted any available results from the included studies, of analyses investigating whether differences in participants' characteristics at baseline were associated with differences in the effect of preloading on abstinence. Five included studies carried out this type of analysis. Bullen et al. (2010) conducted sub-group analyses splitting participants by ethnic group (Maori/non-Maori), age group (<40 years old/≥40 years old), sex (male/female), and social economic group (left school below year 12 or with no qualification/attained year 12 and above), and found that there was no significant differences in the effect of preloading on abstinence for any of these distinctions. Hughes et al. (2010) investigated the interaction of baseline age, sex, race, cpd, FTND, self-rated addiction, confidence in ability to quit, intention to quit, confidence could quit gradually/abruptly, quitting method preference, self-efficacy and regularity of smoking on abstinence, and found no interaction between any of the moderators and either point prevalence or prolonged abstinence. Rose et al. (2006) also found that age and FTND at baseline did not interact with the effect of preloading on abstinence. However, Rose et al. (2009) did find that baseline FTND interacted with 10-week continuous abstinence rates (p=0.03), with NRT preloading showing a greater effect for those with scores less than six, compared with those with six or higher. Thirty-four percent of smokers with lower FTND scores achieved abstinence in the preloading arm and 9% in the control arm, 14% of smokers with high FTND scores achieved abstinence with preloading, compared with 11% in the control arm. Rose et al. (2009) also specified that they would investigate an interaction for age, sex, withdrawal, smoking satisfaction, cigarettes per day, CO and cotinine levels at baseline, however the results of these analyses were not reported, which might imply none were significant. Finally, Schuurmans et al. (2004) reported that smokers of fewer than 16 cpd who received preloading had similar rates of abstinence whether or not they received

active or placebo patches. However, among heavier smokers, active patch users were significantly more successful (p=0.01) than placebo users. This cut-off was based on an exploratory technique and therefore no test for sub-group differences was appropriate or performed. The data from Schuurmans et al. (2004) and Rose et al. (2009) are somewhat contradictory and therefore there is no strong evidence that any characteristics discernable at the start of treatment identify participants who might benefit more than others from preloading.

4.3.7 Quality assessment

Each included study was rated on whether they might cause bias in terms of randomisation sequence generation, concealment of the allocation sequence, blinding to study arm allocation, and incomplete outcome data. For each criteria a study was rated as 'Yes' if unlikely to cause bias, 'No' if they may cause bias, and 'Unclear' if there was insufficient information to make a judgment (for more detail see Appendix 25). In terms of sequence generation all studies claimed to be randomised; three of these reported acceptable sequence generation methods (Etter et al. 2009; Bullen et al. 2010; Hughes et al. 2010). The remainder did not specify the method used to generate the randomisation sequence, so were rated 'Unclear' (Rose et al. 1994; Rose et al. 1998; Schuurmans et al. 2004; Rose et al. 2006; Rose et al. 2009). Although Schuurmans et al. (2004) did specify that randomisation was performed with a computer generated list, in order to have allocated exactly 100 participants to each arm it is likely that a special system would need to have been used, which was not described.

When rated in terms of concealment of participant allocation from researchers, the same four studies were rated as unlikely to cause bias, as they specified that allocation was concealed (Schuurmans et al. 2004; Bullen et al. 2010; Hughes et al. 2010) or they involved no therapist contact (Etter et al. 2009). The remaining four studies did not report on allocation concealment and thus were rated as 'Unclear' (Rose et al. 1994; Rose et al. 1998; Rose et al. 2006; Rose et al. 2009).

In the blinding category three studies were classified as unlikely to cause bias (Schuurmans et al. 2004; Rose et al. 2006; Rose et al. 2009). They were all double-blinded, using placebo nicotine patches in the control arm, so that participants and researchers were unaware of who was receiving active treatment. None of the remaining studies (Rose et al. 1994; Rose et al. 1998; Etter et al. 2009; Bullen et al. 2010; Hughes et al. 2010) used placebos, therefore it was impossible to conceal treatment arm after allocation had occurred. As a result these studies may have caused bias in this respect. To investigate this possibility we conducted a sub-group analysis on the main meta-analysis, comparing the effect of preloading in the double-blinded studies with the effect of preloading in the unblinded studies. For short-term outcome there was a significant sub-group difference ($p<0.001$) with an RR of 1.78 (95% CI= 1.33, 2.39) for the double-blind studies and an RR of 0.91 (95% CI= 0.79, 1.05) for the unblinded studies (Figure 19). The difference was smaller but still significant ($p=0.01$) for the long-term outcome with an RR of 1.80 (95% CI= 1.21, 2.68) in the blinded studies and an RR of 1.02 (95% CI= 0.84, 1.25) in the unblinded studies (Figure 20).

When rated in terms of incomplete outcome data five studies were classified as unlikely to cause bias for the meta-analysis (Rose et al. 1994; Schuurmans et al. 2004; Etter et al. 2009;

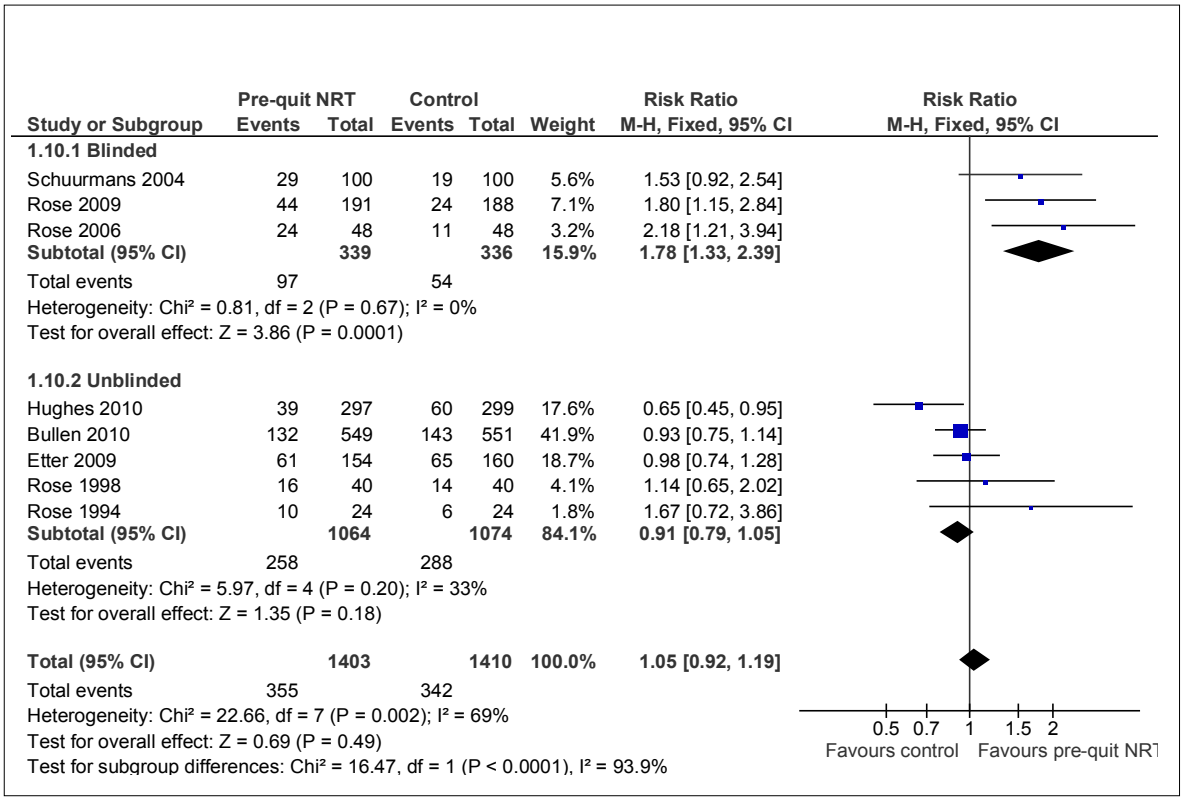

Figure 19: A forest plot illustrating the blinding sub-group analysis for the preloading meta-analysis (short-term abstinence rates)

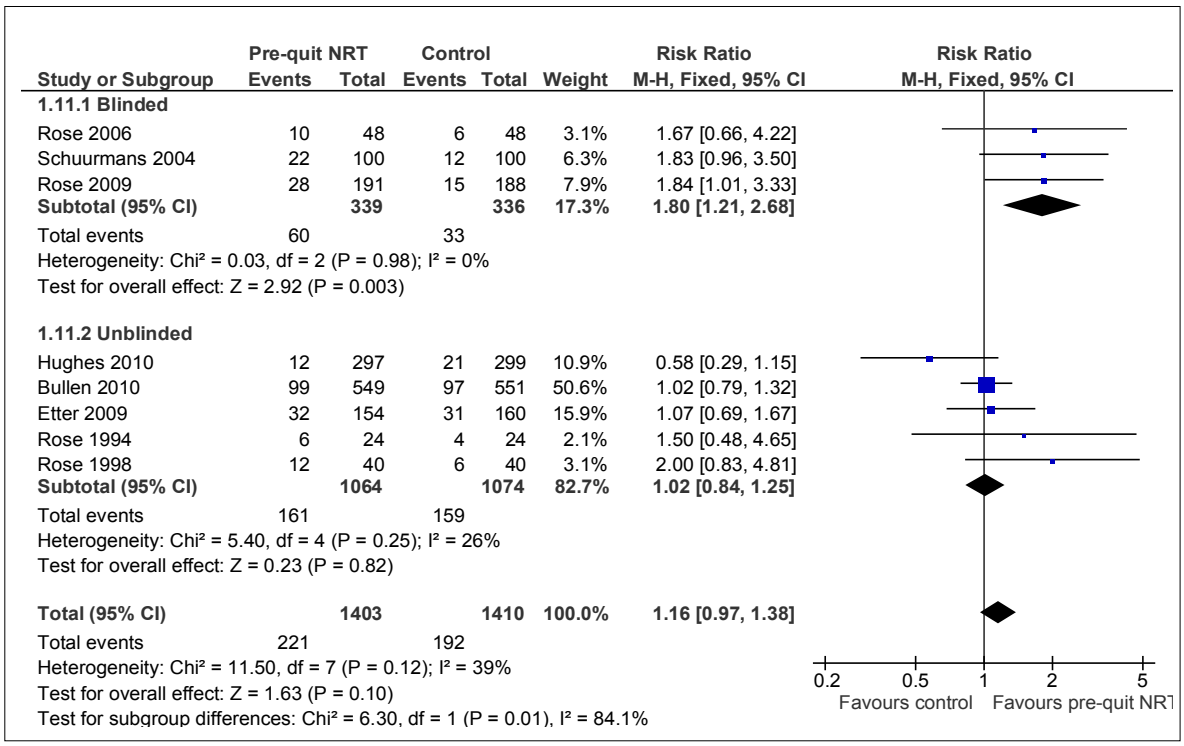

Figure 20: A forest plot illustrating the blinding sub-group analysis, for the preloading meta-analysis (long-term abstinence rates)

Bullen et al. 2010; Hughes et al. 2010), as they all had reasonable and similar attrition rates across conditions at follow-up points. Hughes et al. (2010) did have differential drop-out over the pre-quit period, reporting the rate of completion of baseline and pre-quit surveys as 57% in the preloading arm and 82% in control arm ($p< 0.0001$). Although data on abstinence are based on ITT, we had to use data on responders only for assessing the effect of the intervention on the mediators and this potential bias should be borne in mind. The remaining three studies (Rose et al. 1998; Rose et al. 2006; Rose et al. 2009) were rated as 'Unclear' for incomplete outcome data, either because they did not report drop-out past the quit day, or because they did not give drop-out for each group separately.

Another potential bias relates to biochemical validation of abstinence (Table 5). Studies that did not validate abstinence could potentially over-estimate it. Five studies (Rose et al. 1994, Rose et al. 1998; Schuurmans et al. 2004; Rose et al. 2006; Rose et al. 2009) validated abstinence at both short- and long-term follow-ups, and two studies validated at long-term follow-up only (Etter et al. 2009; Hughes et al. 2010). Bullen et al. (2010) was the only study that did not verify abstinence biochemically. Validation had occurred in a small subset of the participants and was then generalised to the whole population, however this was only for point prevalence not continuous abstinence. We chose not to use these rates over self-reported continuous abstinence rates, based on the assumption that we would not expect the proportion of participants claiming abstinence, but failing validation, to differ between arms, and the conclusion of the SRNT Subcommittee on Biochemical Verification (2002) that studies with limited face-to-face contact, and where data collection is by telephone are unlikely to benefit from biochemical verification because of higher refusal rates. In reality the extent that self-report inflates abstinence rates rarely differs across conditions. This is supported by the only

two included studies that allowed comparison of validated and non-validated quit rates in this analysis (Etter et al. 2009; Hughes et al. 2010). They both found that the proportion of biochemically non-validated participants who claimed to be abstinent did not vary significantly across conditions (p=0.86 and p=0.61 respectively).

Finally we generated and examined funnel plots to establish whether our results may be subject to publication bias. These plots were largely asymmetric with the smaller studies providing more positive results and the larger studies indicating less positive effects (Appendix 26).

4.4 Discussion

This updated meta-analysis reports modest evidence of a weak favourable effect of nicotine preloading on abstinence. However, this effect did not achieve significance for short- or long-term abstinence rates and is substantially weaker than the effects reported in previous meta-analyses (Shiffman and Ferguson 2008; Stead et al. 2008). Furthermore, results were clouded by heterogeneity, particularly for short-term outcomes.

The evidence also suggested little apparent effect on users' positive or negative reinforcements for smoking and minimal effect on reported cravings during preloading. Despite this, some studies (Etter et al. 2009; Rose et al. 1994, Rose et al. 1998; Rose et al. 2006; Bullen et al. 2010) reported reductions in smoking intensity, daily cigarette consumption and dependence, but this varied from study to study. It was hypothesised that a reduction in these variables would lead to a reduction in withdrawal intensity post-quit, thought to drive return to smoking, however there was no evidence of this, and there was

reasonable evidence that preloading did not enhance adherence to post-quit NRT. The two studies (Etter et al. 2009; Hughes et al. 2010) that reported reductions in cigarette consumption and measured change in self-efficacy showed contrasting results, therefore we are unable to conclude whether preloading increased self-efficacy, mediated by the decrease in cigarette consumption pre-quit. There was weak evidence that preloading with patch was more effective than with gum, reaching significance for short-term abstinence, but only approaching significance for long-term abstinence; and a very weak non-significant effect of intensity of pre-quit behavioural support on the effect of preloading. Overall, none of our mediational hypotheses received strong support, but many studies did not report on these mediators and none have conducted tests of mediation. Similarly there was very little evidence of any influence of moderators on the effect of preloading, and the only studies that did report an effect appeared to be contradictory. One study (Rose et al. 2009) reported that preloading was more effective than control in less dependent smokers, with no difference in effect in highly dependent smokers, whereas another (Schuurmans et al. 2004) reported that preloading was more effective than control in heavier smokers, with no difference in effect in lighter smokers.

This review and meta-analysis was originally carried out to update the existing meta-analyses of nicotine preloading to support an application for funding. Due to the time constraints this necessitated the review cannot be classified entirely as systematic, as study eligibility and data extraction was not carried out by two independent reviewers. Nevertheless the review was carried out with a clear structure, as recommended by the Cochrane Collaboration (including searches, study eligibility assessment, data extraction and quality assessment), and all stages of the review were overseen by a second reviewer. As a result, we believe this review to be of

a high quality. For the comparable time period, we identified the same literature as the previous Cochrane Review (Stead et al. 2008), which was carried out systematically, and since publication we have not been notified of any studies that we missed. Therefore, at the time of writing, we believe that this review incorporates all extant literature and represents an update on previously published reviews (Shiffman and Ferguson 2008; Stead et al. 2008).

The previous reviews both resulted in substantially more positive effect estimates of preloading with large confidence intervals, although in the case of Shiffman and Ferguson (2008) this may be partly caused by the fact that a random-effects model was used, rather than fixed-effects. However, Stead et al. (2008) carried out a fixed-effect analysis, as used in this study. Our more negative result appears to be due to including recent, large, more negative studies (Etter et al. 2009; Bullen et al. 2010; Hughes et al. 2010). There are several reasons why these studies could be more negative than the earlier studies. Two of the three studies (Etter et al. 2009; Hughes et al. 2010) provided short-acting NRT for preloading and the strongest evidence of sub-group differences was from dividing studies by whether or not they used a nicotine patch. These two studies also asked participants to use the (short-acting) NRT to reduce their smoking. This could undermine the efficacy of preloading because it is likely to retain the natural rise and fall of blood nicotine levels, and mean participants experience the positive and negative reinforcement that is thought to be related to the development and maintenance of tobacco addiction. However, the evidence that NRT preloading with patches did not have marked effects on positive or negative reinforcement casts some doubt on this. A further reason relates to the intensity of behavioural support, because two of the three studies provided very limited support pre-quit, or self-help only. There was very weak support for the hypothesis that support intensity matters and therefore that this explains the more negative

findings of later studies. A final issue is that the funnel plots were noticeably asymmetric, with large negative studies and small positive studies, raising the possibility of publication bias. However, as there were potentially important methodological differences between the studies, this does not itself prove publication bias. Overall, there were too few studies to simultaneously control for several key methodological differences in meta-regression, to investigate these issues further.

Another way that this analysis builds on previous investigations is the focus on potential mediators and moderators of the effect of preloading on abstinence. However, these data were sometimes incompletely reported. For example, data had to be extracted from graphs and/or they were reported insufficiently to allow meta-analysis, by not reporting the number of participants in the analysis, or standard deviations. In some studies, data on mediators and moderators were collected and we believe analysed, but not reported, fuelling concerns that only statistically significant results were presented. The extracted mediators and moderators, however, do not appear to be convincing explanations for the effect of preloading or differences between trials, and therefore this weakness is unlikely to be giving a false picture. This finding may highlight that this is an area where measurement and reporting could be improved and that the question of whether preloading is effective, how it might be effective, and in whom it might be most effective is still largely unanswered.

However, it is important to acknowledge that theories of dependence, such as those investigated in this review (i.e. self-efficacy) are social constructs, and so may differ based on the experiences of the participant (West 2006). As smokers find it hard to introspect and communicate about these concepts questionnaires are developed in an attempt to capture the

underlying structure of the concept. However a concept as defined by one person will not necessarily resonate with another, and may change over time relative to experience. These limitations need to be considered when carrying out analyses of the sort included here, and may to some extent explain the lack of conclusions we are able to draw.

Although the evidence is weak, we believe that the most plausible hypothesis is that preloading undermines the learning process that led to addiction and it is this that leads to enhanced cessation. Weak support was provided for this with our comparison of nicotine patches with short-acting NRT. However it is important to note that the type of NRT used was not the only substantial difference between the studies in each of the sub-groups of this analysis. As previously mentioned the studies that used short-acting NRT for preloading both also asked participants to reduce their cigarette consumption during the pre-quit period, whereas the control group were asked to quit abruptly (Etter et al. 2009; Hughes et al. 2010). Therefore there is no way of knowing whether the effect detected in these studies is a function of instructions of how to quit, type of NRT used, or both. To investigate this it would be useful to examine the effect of preloading using acute NRT in participants asked to smoke as normal.

If NRT preloading does work in the way outlined above then longer preloading could be more helpful. Evidence of this was too scanty to draw conclusions, because nearly all studies used the same length of preloading. Taking the evidence as a whole, we believe that future preloading RCTs might reasonably choose to use a patch and a longer period of preloading. A full mediation analysis of theoretically possible mediators, perhaps using the framework we propose, and appropriate moderators, would also be helpful.

The efficacy of preloading could depend on the intensity of behavioural support. Until recently, people were advised not to smoke and use NRT concurrently, and, as a result, they may feel reluctant to use nicotine preloading. Behavioural support during preloading could address these concerns increasing the likelihood of adherence to treatment, and thus increasing the likelihood of abstinence. However there was little evidence for this. Perhaps participants were not worried about smoking and using NRT at the same time, or this issue was addressed satisfactorily at the baseline behavioural support session. Regardless of this finding, it seems important to have a counselling protocol that encourages therapists to elicit patients' concerns and seeks to address these.

To assess whether issues in the design, conduct, or reporting of studies affected the apparent efficacy of preloading we carried out a quality assessment. In most cases judgements indicated that studies were either unlikely to cause bias or that the evidence was unclear. The only studies that were judged to be a potential cause of bias were those that were unblinded, where participants and therapists (where used) were aware of treatment allocation. We carried out a sub-group analysis to test whether this could influence the effect estimate, which showed a significant difference between those studies that blinded participants and those that did not. If a placebo effect had occurred then we would expect that the effect of preloading would be higher in the unblinded studies, however the opposite was the case, with preloading more effective than placebo in blinded studies, but only as effective as control in the unblinded studies. This suggests that failure to blind was not a bias in this review. However, there were differences between the blinded and the unblinded studies- for example two of the three largest unblinded studies used short-acting NRT (Etter et al. 2009; Hughes et al. 2010)-

which were associated with lower efficacy, and it could be this or other differences between studies that partly explain this unexpected finding.

Based on the previous apparently conclusive meta-analyses, some smoking cessation clinics have routinely recommended preloading treatment. This update gives no strong evidence of efficacy and suggests routine use is not supported by evidence. Nor does this review give any basis for selecting a sub-group of patients who might benefit more from preloading. If preloading is used, we would select the patch, over a short-acting form of NRT. Patients could be told to smoke freely, to try to smoke as normal, or to reduce their consumption, but there are no data to suggest which instruction would be most efficacious. Other data indicate that concurrent smoking and NRT use is safe and patients could be strongly reassured of this (Fagerstrom & Hughes 2002). However, further trials are required to improve the precision of the estimate of effect of preloading, to try and establish the cause or causes of the heterogeneity in the current trials, and to enhance understanding of the mechanisms and moderators of action. By improving understanding of these mechanisms clinicians may have a basis for deciding which patients would benefit from preloading, and therefore be able to offer targeted cost effective treatment.

4.5 Response to Rose (2011): Nicotine preloading: The importance of a pre-cessation reduction in smoking behaviour

After publication of the above review in Psychopharmacology (Lindson & Aveyard 2011[a]; Appendix 3), Jed Rose, the lead author of four of the included studies (Rose et al. 1994; Rose et al. 1998; Rose et al. 2006; Rose et al. 2009), submitted a corresponding Letter to the

Editors (Rose 2011). Our published response (Lindson & Aveyard 2011[b]; Appendix 4) was as follows.

Rose (2011) raises two discussion points. Firstly, that the effect of nicotine preloading may be correlated with the extent to which smokers reduce smoking during preloading, and secondly that the use of measures of non-continuous abstinence may underestimate the effect of preloading.

Rose (2011) cites within study data supporting the first point. For example Rose et al. (2010) found that participants who reduced cotinine concentration more than 50% were three times more likely to be abstinent than those who reduced less. This was also observed in a recent trial of four weeks of varenicline preloading (Hajek et al. 2011). We agree that these findings could offer insight into the mechanisms by which preloading has its effects. Therefore we investigated this further using data from our meta-analysis (Lindson & Aveyard 2011[a]) to make between study comparisons, using sub-group analysis. Four of the eight studies asked participants to smoke freely during the preloading period, and provided data on pre-quit reduction in smoking in the preloading arm. The only common marker of reduction reported was cpd. The two studies reporting reduction of less than 50% of baseline cpd gave a RR of 1.83 (95% CI= 0.97, 3.47), while those reporting a reduction of more than 50% gave a RR of 1.04 (95% CI= 0.81, 1.34) for long-term abstinence. However the difference between sub-groups was not significant (Figure 21). These data therefore do not suggest that the ability of preloading to suppress smoking is a good explanation for the between study heterogeneity we observed in our review.

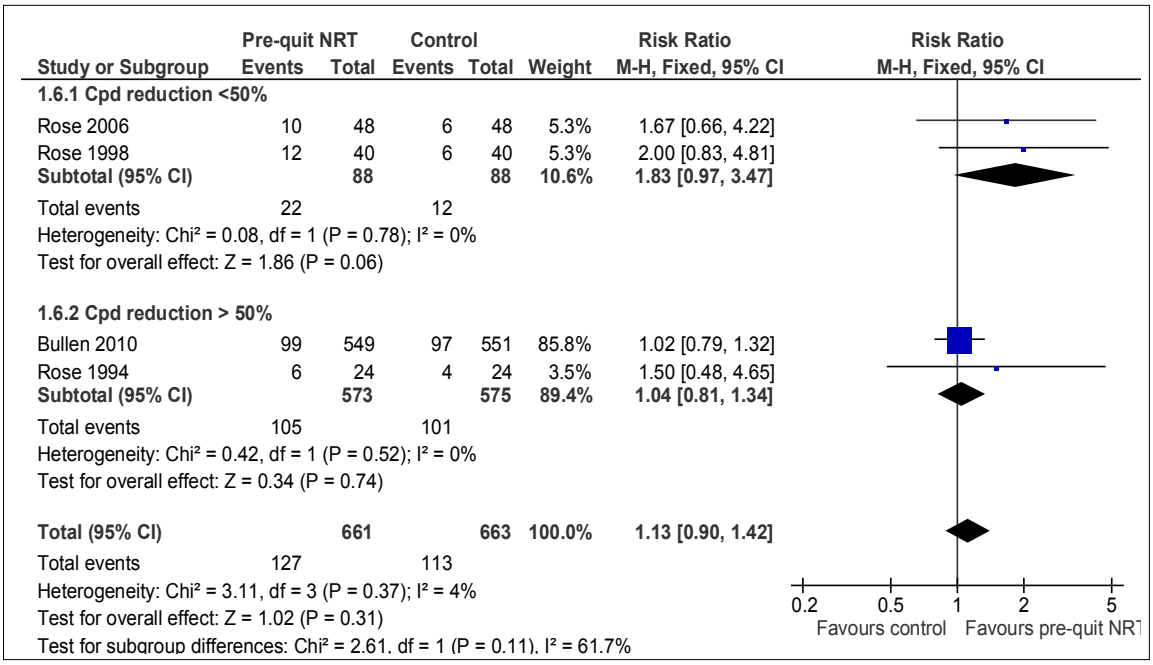

Figure 21: A sub-group analysis comparing the effect of NRT preloading on long-term abstinence in studies where participants reduced their cpd by less than 50%, and in studies where participants reduced by more than 50%

In response to Rose's (2011) second point we investigated the suggestion that *"studies finding the largest effects of nicotine preloading used as an outcome measure continuous and complete smoking abstinence assessed from the quit date on."*, again using sub-group analysis. When measuring long-term abstinence prolonged or point prevalence rates were used for three studies resulting in a pooled RR of 0.95 (95% CI= 0.68, 1.34), and a RR of 1.25 (95% CI= 1.01, 1.53) for the studies using continuous abstinence. However the test for sub-group differences was not significant (Figure 22).

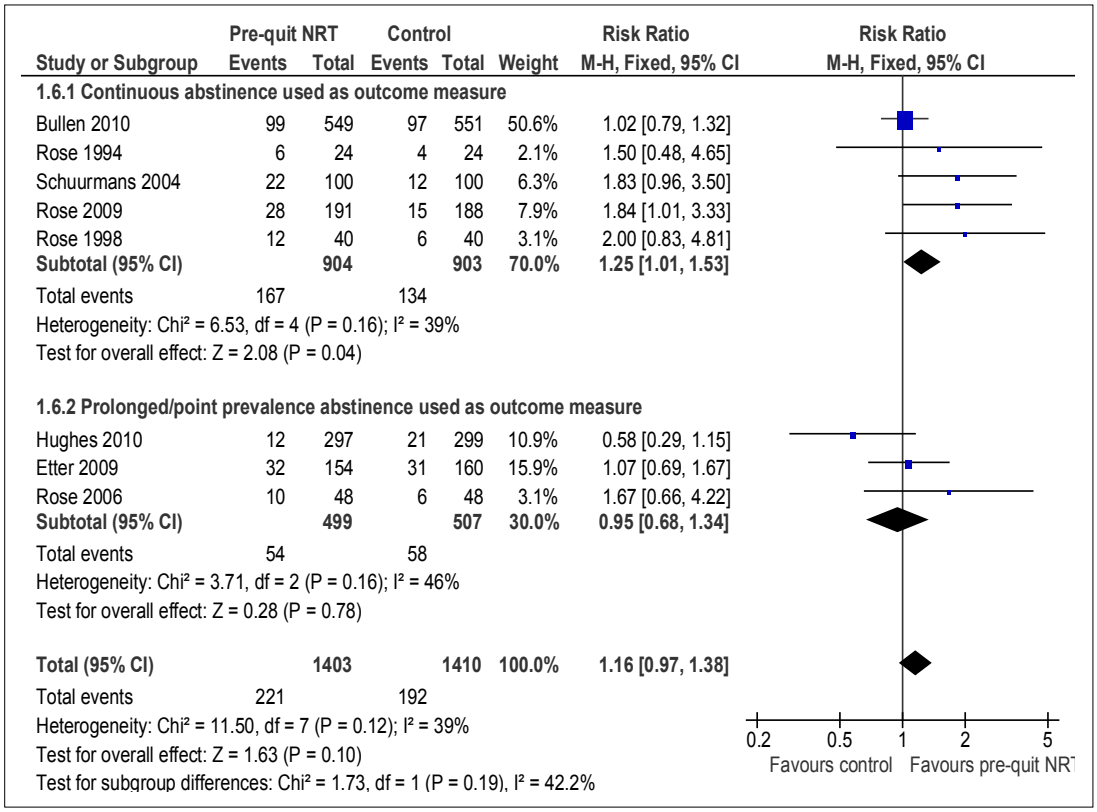

Figure 22: A sub-group analysis comparing the effect of NRT preloading on long-term abstinence in studies where continuous abstinence was used and studies where prolonged or point prevalence abstinence were used as the outcome measure

Rose et al. (2009) suggest that trials not reporting continuous abstinence underestimate the true benefit of preloading, because in a real-life setting participants will not be supported to continue NRT during lapses after quit day. This may be so, but it is also likely that adherence to preloading would be lower outside a trial than within it for the same reasons. Until recently, people were advised not to smoke and use NRT concurrently. The message to the contrary is not well-known, as we have witnessed in our own trial (Lindson et al. 2009[a]). Instructions to preload or to continue NRT during a lapse are party to the same discriminations by smokers. In fact preloading may present more of an issue due to the prolonged nature of the concomitant usage.

In conclusion we agree that both points raised by Rose (2011) are important, but they do not appear to explain heterogeneity between studies. Further within trial analyses are needed, in particular focusing on differences between active and placebo conditions, as in Rose's recent studies (Rose et al. 2009; Rose et al. 2010). It would be useful to understand why those people who reduce their smoking do so- the mediators of reduction. Given the uncertainty over the size of the benefit and mechanism(s) of action, we suggest a further trial of nicotine preloading is needed.

CHAPTER 5: A QUALITATIVE STUDY OF SMOKERS' EXPERIENCES OF DIFFERENT QUITTING METHODS: ABRUPT, REDUCTION AND NICOTINE PRELOADING

5.1 Background

As outlined in Chapter 1 smoking reduction prior to quitting and nicotine preloading are methods that could be used to increase smoking quit rates. Surveys have revealed that providing support for smoking reduction is likely to be a popular approach to cessation (Hughes et al. 2006; West 2008), which suggests that if it were adopted by the NHS SSS it may encourage more smokers to take-up this type of support. In addition the Cochrane Review reported in Chapter 3 suggests that if offered it would be unlikely to result in quit rates markedly different to those currently achieved through quitting abruptly. Therefore, the next stage should be to establish the best way to implement a smoking reduction approach in clinical practice. Stop smoking services do not provide supported reduction programmes, so the way these programmes might best operate is unclear. However a limited number of studies investigating reduction have looked at the feasibility of reduction methods, reducing smoking whilst using NRT versus placebo, and the relative efficacy of different reduction methods. In some cases the goal was cessation and in others simply reduction. These studies have used a range of methods to reduce smoking, which we have categorised into three broad types: unstructured, cigarettes per day (cpd) and smoke free periods (sfp) reduction. The following sections (5.1.1– 5.1.3) provide a narrative review of some of these methods, including some studies that have aimed to establish the best ways to carry out reduction. We conducted a search to find trials incorporating a reduction method or comparing two or more types of

reduction, using MEDLINE, Google Scholar, PsychINFO, SRNT abstract search, a citation search, and contact with key authors. We have not distinguished between studies that enrolled participants who were not ready to quit smoking and encouraged them to reduce, and studies that enrolled participants ready to quit. Motivation to quit is fluid in many smokers (Hughes et al. 2005) and evidence shows that most people who are not ready to quit, but want to reduce, are more willing to quit in the end (Hughes & Carpenter 2006; Asfar et al. 2011). A systematic review would have been time consuming and outside the scope of this thesis, nevertheless, although not exhaustive this review should provide further justification for the reduction methods used in RRT (Chapter 2), and provide the background knowledge needed to appreciate participants' responses to the interview study reported from Section 5.1.4 onwards.

5.1.1 Smoking reduction methods

5.1.1.1 Unstructured reduction

The first group of studies specify only that participants should reduce their smoking, and usually do not give either a specific goal or a specific method of how to do so. Cummings et al. (1988) provided participants with suggestions of how to reduce, for example by setting daily goals or changing habits, but ultimately the decision was left with participants. Other studies have told participants to reduce their smoking, using NRT as a substitute for cigarettes (Fagerstrom et al. 1997; Bolliger et al. 2000; Batra et al. 2005; Rennard et al. 2006). These studies, utilising unstructured reduction methods have found that reducing smoking whilst using NRT is safe and feasible, and more successful than simply reducing with no

pharmacotherapy (Wang et al. 2008; Moore et al. 2009). A majority (92%) of participants in one study thought this was a good method to give up smoking (Fagerstrom et al. 1997), and despite a number of the studies only enrolling participants who were either unwilling or unable to quit, a number of participants had successfully quit smoking at follow-up (Hughes & Carpenter 2006).

5.1.1.2 Cigarettes per day reduction

The second more specific method of reduction advises smokers to reduce by giving depleting target numbers of cpd, sometimes with advice on how to control smoking to achieve this target. A study by Gunther et al. (1992) asked participants to reduce by a set number of cigarettes per week until they reached abstinence. Depending on the amount they smoked at baseline this varied between five and ten cigarettes. The remaining cigarettes for each week could be smoked at any time. Shapiro et al.'s (1971) cpd approach was more structured and designed to divorce smoking from associated environmental cues, by providing participants with a new signal to smoke, which had no meaning to the individual. This signal was provided by either a paging device or watch timer, which was programmed to go off at fixed or random time intervals. In the first week of the study the timer/pager was set to go off at intervals that ensured smoking was at the individuals' baseline rate. For the remaining weeks the daily rate of smoking was reduced by four cigarettes at the beginning of the programme and by two at the end, so that the median number of weeks participants were in the programme was between seven and nine. Participants were asked to smoke only on timer/pager cues, not to refuse smoking on these cues, unless in a situation where smoking was illegal or impossible, and not to make-up for missed cigarettes. Participants were almost

uniformly enthusiastic about the intervention and the possibility it gave to reduce smoking. At follow-up, six weeks after the termination of the programme, participants reported that they had reduced their daily cigarette consumption, from baseline, by a median of 43%. Cinciripini et al.'s (1994) approach was a variation of this method. Participants reduced the number of cigarettes smoked by two to five per day (dependent on number of cigarettes smoked at baseline), by gradually increasing the time between each cigarette smoked (the ICI). Cigarettes were reduced over a three week period; after this participants were expected to quit abruptly on a specific day. The study aimed to produce an initial report of treatment efficacy and compared reduction to a control, minimal, self-help treatment where participants were given no specific instruction of how to quit, but were given guidance about possible aids to cessation. Seventy-eight percent of participants complied with the reduction schedule in the first week, 71% in the second and 68% in the third, and 24 hour abstinence rates superior to the control condition occurred at both week five (70.6% versus 24%), and week nine (68% versus 18%) of treatment. Abstinence rates in the reduction group remained high at six month and twelve month follow-up (53% and 41% respectively), which compare favourably with other cessation programmes (Section 2.1).

Hughes et al. (2010) conducted a study of gradual versus abrupt quitting, which used three methods of reducing cpd to reduce smoking to 75% of baseline in week one, 50% of baseline in week two and 25% in week three. Participants were able to choose between the reduction methods, and therefore were not randomised. The first method involved increasing ICIs in the same way as Cinciripini et al. (1994), whilst in the second and third, participants were asked to rank the cigarettes they smoked each day according to how difficult they thought they would be to give up. They then progressively gave up either the hardest cigarettes or the

easiest cigarettes first. The report states that the majority of participants chose the ICI method (60%); however researchers' observations suggested that many of the participants did not exclusively use their chosen method, or didn't use any of the suggested methods. As a result the outcomes of the use of the specific reduction methods were pooled into an overall reduction group.

5.1.1.3 Smoke-free periods

The third method of reduction reduces the number of time periods during the day when smoking is allowed. During the remaining time participants may smoke as much as they like. Interventions which aim to reduce consumption by reducing cpd could have adverse effects, by focusing the smokers' attention on what they are missing. By nominating periods in which smoking is prohibited, and at all other times is allowed, smokers are encouraged to focus on successful periods of abstinence, which could in turn raise self-efficacy. Findings from an experimental study by Dols et al. (2002) provide further support for this approach- participants allocated to a condition in which they expected to smoke but could not do so had significantly more cravings than participants allocated to a condition where smoking was prohibited. Marston & McFall (1971) reduced smoking periods by dividing the day into four time periods and asking participants to rank these in terms of how difficult they would find it to abstain from smoking during this time. Participants were then asked to first stop smoking in the period they had rated most difficult and proceed to eliminate each of the ordered time periods until they had stopped smoking entirely. Kyle & Shiffman (2005) and Shiffman et al. (2009) adopted a slightly different approach by asking participants to substitute their smoking with a piece of nicotine gum for the first hour after waking, and on each subsequent day to

increase this sfp by another hour, using an additional piece of gum. After a maximum of four weeks the sfp covered the entire day, and hence led to abstinence. Participants who used the gum to aid their reduction rather than placebo were significantly more likely to achieve initial cessation (2mg gum- OR = 1.42; 4mg gum- OR= 1.90), and six month continuous abstinence (2mg gum- OR= 1.80; 4mg gum- OR= 5.96) (Shiffman et al. 2009).

5.1.2 Studies of the relative effect of different reduction methods

5.1.2.1 Speed of reduction

Haustein (2002) compared reduction over four weeks, and over 12 months in smokers not ready to quit. Participants were given brief advice to reduce their smoking using unstructured reduction. The primary outcome measure was successful reduction, which was measured as sustained reduction of 50% of baseline. The use of short-term rather than long-term reduction was more successful at four, six, nine and twelve month follow-up (significant in all cases), and an RR of 4.57 (95% CI= 1.00, 20.93) was achieved for confirmed prolonged abstinence at 4 months post-quit. Blalock et al. (2003) provide further support for more rapid reduction by comparing cpd reduction in a slow reduction group and a fast reduction group in smokers wanting to quit. The slow group reduced their cigarettes by 66-99% over a two to three week period, and quit in week three or four. The fast group reduced by 50% during week one and quit in week two. Both groups used nicotine patches throughout the reduction period. Two week continuous abstinence rates were 39% in the fast group and 26% in the slow group. The findings therefore favour faster reduction over slower reduction, but the evidence is preliminary.

5.1.2.2 Structured versus unstructured reduction

Cinciripini et al. (1995) compared two types of cpd reduction in smokers wanting to quit. The first type was scheduled, where ICI was progressively lengthened to accommodate the planned reductions in cigarettes. The second was unscheduled, where participants were merely told how many cigarettes they were to smoke each day, and they could smoke them when they pleased. Both groups were given a cigarette allowance of two thirds of baseline in week two, one third of baseline in week three, and one third of week two allowances in week four. Both groups were required to quit abruptly in week five. At one year follow-up 44% of the scheduled group were abstainers compared to 18% of the non-scheduled group ($p<0.05$).

A similar study by Levinson et al. (1971) also found that participants assigned to the scheduled group were significantly more likely to be successful quitters at three month follow-up than participants assigned to the non-scheduled group.

5.1.2.3 One structured method versus another structured method of reduction

Riggs et al. (2001) took this one step further by comparing two different methods of scheduled cpd reduction in smokers not interested in quitting, but who wished to reduce. The study had a cross-over design so that each participant used each method for two weeks with a two week wash-out period in between. In the hierarchical reduction method, participants smoking normally were asked to record all cigarettes they smoked in one week and rate them in terms of how difficult it would be to give them up. They were advised to reduce by giving up the easiest first progressing to the harder ones. In the ICI method participants followed the regimen used by Cinciripini et al. (1994), progressively lengthening the interval between

cigarettes smoked on a fixed schedule. In both arms cpd were reduced by 25% in the first week of reduction and another 50% of the remaining cigarettes were eliminated in the second week. Participants were encouraged to replace each cigarette with a piece of nicotine gum. Both forms of reduction significantly reduced CO levels, with no significant difference between groups. Likert scale ratings of ease of reduction and likeability of treatment also showed no significant variation between groups. Therefore Riggs et al. (2001) conclude that the two methods are equivalent and future studies could give the choice of either method.

Two methods of increasing sfp were compared by Flaxman (1978). Both arms utilised a method similar to the hierarchical method used by Riggs et al. (2001), developed by Gutmann & Marston (1967), where situations leading to cigarette smoking are ranked according to perceived difficulty of refraining from smoking in that situation. Flaxman (1978) asked participants to give up smoking in the stimulus situation ranked as easiest first, progressing to the most difficult; by progressing to the next most difficult situation every three days. In one group participants were asked to do this until they were not smoking at all, and in another group until they were smoking half of their base rates, and then to stop abruptly. No difference in daily post-treatment smoking rates was found between the two groups at follow-ups (weeks one to eight, and six month).

5.1.3 Tentative conclusions

Conclusions that can be drawn from this evidence are limited by the quality of some studies, for example many had small sample sizes, and/or unclear reporting of abstinence rates or reduction success. Therefore the evidence on how reduction is best achieved is weak.

Preliminary evidence suggests that reduction is most successful when NRT is used as a concomitant aid, when it takes place over a limited time period (weeks rather than months), and when structured and/or carried out to a schedule. Additionally, cpd reduction appears to be equally successful and popular when carried out using a hierarchical method and when achieved by decreasing ICI; but this conclusion applies to reduction only, not reducing then stopping.

5.1.4 Study justification

The RRT, outlined in Chapter 2, was designed to investigate the abstinence rates achieved in smokers using behavioural reduction methods in comparison to smokers using an abrupt quitting method, similar to that already offered by the NHS SSS. In-line with current practice participants using either method are provided with NRT post-quit alongside their behavioural support. However, based on the tentative conclusions drawn from the aforementioned reduction studies, a number of further design decisions were made. NRT is provided pre-quit day as well as post-quit day in both arms, reduction takes place rapidly over two weeks, and participants are advised to follow a structured programme. Three variations of this core smoking reduction method are offered: 1) scheduled cpd (SR); 2) hierarchical cpd (HR); and 3) smoke-free periods reduction (SFP). With the HR method participants can then go on to choose to forgo either their easier (HR-E) or harder (HR-H) cigarettes first. As the main focus of the trial is to compare abstinence rates when quitting abruptly and reducing to quit the trial was designed with the power to do as such. An unfeasibly large number of participants would have had to be recruited to compare abstinence rates across the different

reduction methods, and so it was decided that participants randomised to the reduction arm would choose their method of reduction, rather than being randomised to it.

However another way to investigate the reduction methods further and to gain insight into the differences and similarities between abrupt and gradual quitting is to carry out qualitative analysis of participants' feelings about, and experiences of, the methods used. To our knowledge there has been no qualitative investigation of nicotine preloading, and as reported above there is almost no data on service users' opinions of reduction methods. That which exists appears to be based on a few closed questions on intervention acceptability (Shapiro et al. 1971; Fagerstrom et al. 1997; Riggs et al. 2001). There are several reasons why asking patients about their perceptions of a treatment could be useful. Firstly it establishes whether there is a desire for a treatment service. If this is not the case then even if the treatment were made available it may not be used, regardless of how successful it is. Surveys suggest that smoking reduction is a popular route to quitting (Hughes et al. 2006; West 2008), however this is in response to a question along the lines of 'How do you plan to quit?', and so may not reflect whether smokers would specifically wish to access a smoking reduction service. It may also be interesting to establish the desire for an abrupt quitting service, as up until now it has been the only treatment option available through the NHS SSS; therefore patients who want help to stop have been forced to use this method regardless of whether they thought this was suitable or not. As well as establishing overall satisfaction, questioning a patient about a service they have experienced also provides the opportunity to ask about things that they may have liked or disliked about the method they used, and ways that they feel it may be improved, opening up the possibility to tailor the methods more specifically to the needs of the user population. Finally asking participants how they think the methods did or did not

work for them may provide insight into the mechanisms through which the methods have their effects. Qualitative approaches generally offer the opportunity to delve further into a topic, and perhaps explore issues that were not anticipated by the researcher. In topics where research is limited, such as smoking reduction and nicotine preloading, this could be valuable; thus providing the motivation for this study.

We used qualitative interview methods to explore the opinions of RRT participants about the quitting methods used in the study, including the behavioural methods of abrupt quitting and reduction to quit, in the form of the SR, HR and SFP methods; as well as the use of NRT prior to the quit day (nicotine preloading). This allowed for comparison between smokers using the different methods, and who were and were not smoking at four weeks post-quit.

5.2 Method

5.2.1 Study design and participants

Participants were recruited from the RRT - a randomised, controlled, non-inferiority trial, comparing abrupt quitting with reduction to quit, and utilising nicotine preloading treatment in both arms. Participants in RRT are recruited through GP surgeries in the West Midlands, as described in Section 2.2.5. They are randomised to one of two trial arms (Section 2.2.6.1). Those participants randomised to abrupt quitting are asked to smoke as normal, whilst wearing a nicotine patch for two weeks of preloading, and then asked to quit on an agreed quit day. Participants in the reduction arm are asked to reduce their smoking over two weeks (to 50% of baseline cpd/smoking periods at the end of the first week, and to 25% of baseline cpd/smoking periods at the end of the second week), and then to quit completely on an agreed

quit day. Participants who reduce their smoking use both nicotine patch preloading pre-quit, and an acute form of NRT to replace those cigarettes missed. All participants use NRT in the form of patches and an acute form of their choice post-quit day, and use diaries to monitor their smoking and NRT use for three weeks following randomisation. Those participants in the smoking reduction arm are asked which of three behavioural methods of reduction (SR, HR, SFP) they would like to use (described in Section 2.2.6.3). They then plan their smoking reduction, with the help of their research nurse, using a smoking reduction schedule designed for the method of their choice (See Appendix 9, Appendix 10 and Appendix 11 for fictional examples of completed schedules).

All participants screened over the phone as eligible to take part in the trial, and booked in to have their first appointment between 15th March 2010 and the end of the interview study (when theoretical saturation was reached and the last participant had been interviewed- 15th December 2010), were sent a PIS for RRT, containing information about the interview study (Appendix 5). At their first visit participants attending during this time period were also told about the interview study by their research nurse and asked to complete a consent form for RRT, which included an opportunity to opt in or out of also consenting to take part in an interview (Appendix 6). We gave interview notes sheets (Appendix 14), providing information about the interviews, and topics and questions that may be asked, to those participants who consented to take part. Participants were encouraged to make notes on the sheet during the cessation programme to aid their recall during the interview, which took place at the end of the behavioural support programme.

5.2.2 Interviews

RRT participants, across all study arms, who attended their first trial visit between 15th March 2010 and November 12th 2010, consented to take part in RRT and the interview study, and provided a contact telephone number for the interviews were telephoned approximately five weeks post-quit day, from a private room, to see if they were still interested in taking part in the study. Five weeks post-quit was chosen as no other contact regarding the trial was made that week. Therefore it was hoped that participants would not feel the interview was burdensome, but their memories of the programme would still be fresh. Contact was attempted at least three times before the attempt to contact any participant was abandoned. All interviews were carried out by a researcher (NL), and took place over the phone, in an attempt to make participation as convenient as possible and to maximise the number of people taking part. A semi-structured interview schedule (Appendix 13) was used to conduct the interview, including topics such as first impressions of the quit method used, how easy it was to carry out, good and bad points, changes that should be made, feelings over the pre-quit period, the use of pre-quit NRT, and why the quitting method worked or didn't work for them; also allowing participants to expand on any issues that they raised independently of these. All interviews were recorded using a telephone adapter and digital recorder, and took between 10 – 40 minutes to carry out. Recruitment for the interview study ceased when no new themes began to emerge during the interviews; therefore when theoretical saturation occurred.

5.2.3 Data analysis

All interview sound files were transcribed verbatim by an independent transcription company, as the study progressed. This meant that transcripts could be read and findings taken into account when interviewing others; adding topics to the interview schedule where relevant. Transcripts were imported into NVivo 8 (QSR International Ltd, Melbourne, Australia) and read by two researchers (NL & RB). Initial themes were then identified and discussed. Using these NL began coding the transcripts in an ongoing and iterative process, and these were double-checked by RB. We discussed this analysis regularly as the interviews proceeded. This meant that themes and coding were malleable throughout the interviews and analysis. On completion of this coding, data was charted thematically (See Appendix 27 for example thematic chart) and by case (See Appendix 28 for example case chart), as per the Framework approach to qualitative data analysis (Ritchie & Spencer 1994). This allowed us to summarise themes, and compare these between different quitting methods, and between those participants abstinent and not abstinent at 4 weeks post-quit. Abstinence was measured according to the Russell Standard (West et al. 2005), allowing a grace period of two weeks for slips (Hughes et al. 2003), and validated by an exhaled CO reading of less than 10ppm. Two researchers (NL, AM) summarised and compared a sub-section of charts, to ensure inter-researcher consistency; the remaining charts were analysed by one researcher (NL) and checked by another (RB). Finally charts were used to identify extracts from the transcripts to illustrate findings in the Results (Section 5.3).

5.2.4 Ethical considerations

As stated in Section 2.2.15 RRT was reviewed and approved by the National Research Ethics Committee (08/H0408/213), the MHRA (2008-006433-28), and local NHS Research & Development offices. A substantial amendment for the interview study, was submitted and approved by the National Research Ethics Committee, and the authorities above were notified. Written informed consent was obtained from all participating in the interview study. Participants were informed that the interview element of RRT was optional, and would not affect their participation in the rest of the trial. When consenting participants were contacted by telephone they were also asked for their verbal consent and were given the opportunity to opt out of the study at that point. We also reminded participants before recording started that the interview would need to be recorded to allow for analysis, and asked for their verbal consent to do this. Participants enrolled in the interview study were provided with a new anonymised study number, independent of their RRT study number. One file was used to link this study number to participant details and this was password protected and kept on an encrypted computer. All interview sound and transcription files were stored with no identifying information on an encrypted computer, and were also password protected and encrypted when sent to or from the transcription company. All files sent to the transcription company were anonymised.

5.3 Results

5.3.1 Participant characteristics

During the course of the interview study 168 participants recruited into RRT also consented to take part in an interview, and five refused. Of the 168 consenting participants 54 were contactable at five weeks post-quit, still agreed to be interviewed, could be interviewed at a time convenient for interviewer and interviewee, and went on to complete their interview (Table 7). We were able to interview participants that had used all of the methods apart from HR-D. This was a reflection of the lack of participants choosing this method of quitting in RRT. Participants were recruited from 13 general practices across South Birmingham (six practices), Worcestershire (one practice) and Warwickshire (six practices) PCTs. The majority of participants were recruited from Warwickshire PCT, and the number of males and females in the study were roughly evenly matched. The average age of participants was 56 years and participants smoked on average 24 cpd at baseline, with an average FTND of six. Four weeks after quit day 22 of the 54 participants (41%) were abstinent, according to the criteria described in Section 5.2.3. In the following sections we will outline the opinions of these participants about the quitting methods used in RRT; taking into account themes that were present across methods, differences between perceptions of the abrupt and reduction methods, and the different methods of reduction, feelings about nicotine preloading, and finally whether there were any differences in participants' feelings dependent on whether they had successfully quit or not at four weeks post-quit.

Table 7: Characteristics of RRT interview study participants

Characteristic	Study arm				
	Abrupt quit (N=20)	Reduction to quit			Total (N=54)
		SR (N=10)	HR-E (N=8)	SFP (N=16)	
Recruited from South Birmingham PCT (N)	6	3	3	5	17
Recruited from Worcestershire PCT (N)	4	0	0	5	9
Recruited from Warwickshire PCT (N)	10	7	5	6	28
Female (N)	10	5	3	11	29
Age in years (mean, sd)	54.6, 10	58.5, 8.4	55.1, 12.6	55.9, 9.1	55.8, 9.7
Baseline CO in ppm (median, IQR)	25, 12	26, 17	24, 7	27.5, 16	26, 12
Baseline number of cpd (median, IQR)	20, 14	25, 10	22.5, 5	25, 14	24, 10
Baseline FTND score (median, IQR)	5.5, 1	5.5, 4	6, 3	7, 3	6, 2
Abstinent at four weeks post-quit day (N)	9	5	1	7	22

N- number of participants; SR- scheduled reduction method; HR-E- Hierarchical- easy reduction method; SFP- smoke-free periods reduction method; PCT- Primary Care Trust; sd- standard deviation; ppm- parts per million; IQR- inter-quartile range; cpd- cigarettes per day, FTND- Fagerstrom Test for Nicotine Dependence

5.3.2 Commonalities across methods

5.3.2.1 Preference for a particular method

Most participants said that when they had been asked by their nurse on entering the study whether they would prefer the abrupt or reduction method, they did have a preference, which

they backed up with reasons (see Section 5.3.3.1). However, neither method seemed more popular than the other overall. In practice, all of the methods used were described by almost all participants as easy to understand, to fit in with their lifestyle, and in most cases easy to carry out (Box 1, Quotes 1 and 2).

5.3.2.2 Pre-quit preparation period

Participants generally felt positively towards the period of treatment and preparation for quitting. The opportunity to continue smoking (even if reducing) prior to quitting appears to have been judged as an important time of mental preparation, by giving an opportunity to think about the quit attempt with the reassurance that cigarettes were still there (Box 1, Quotes 3 and 4). Despite this, a few participants had some suggestions to improve the utility of this period. A couple of participants thought that the pre-quit period should be lengthened to four weeks to allow for longer reduction when using the reduction method, as they had found reduction over two weeks too sudden. Whereas another participant had found it hard to give the research nurse information about their usual smoking habits on entering the study, and so felt they would have benefited from a baseline period to record these for use when planning their reduction schedule. In contrast, two abrupt participants suggested that the pre-quit period should be shortened. One participant felt they had already lost the will to smoke after one week of the study, and the other would have liked to quit immediately on entering the study, as they had felt ready to do so then.

Box 1. Commonalities across methods

Quote 1-Abrupt
I: When you were given instructions on what you would have to do, did you find them easy to understand or did you have any difficulties with them?
P: No, no absolutely fine
I: Okay and how did you actually find the method to carry out
P: It wasn't hard, it was when it got to the third, fourth week that I was struggling with it. The first few weeks were absolutely fine
I: Do you think it fit in quite well with your lifestyle or did anything get in the way
P: No, I mean the only thing that's got in the way is the fact that I live with my husband who's still smoking.

Quote 2- Reduction (SFP)
I: When you were given the original instructions- actually what to do- did you find them easy to follow and understand?
P: Yes it was brilliant yep
I: Right so there was no problems at all understanding?
P: No
I: So then did you find the method easy to carry out? So did you find it easy to abstain from smoking when you were asked to?
P: Yes it's very good, it helped you to space yourself as well which was very good
I: Did you find it easy to stick to your pre-quit instructions? Did you find that you were able to keep to the schedule that you worked out with the nurse?
P: Yes I did, yes
I: That's great. Would you say that the method fit in well with your personal lifestyle, and you as an individual?
P: Yes very much so.

Quote 3- Abrupt
P: It does give you time to think about it, if nothing else...I thought the thinking about it for two weeks prior to it, and then actually using those inhalers, I think they're a great idea.

Quote 4- Reduction (SR)
P: With this way I've found that you had something to look forward to each day, even if your cigarettes were two hours apart or three hours apart, it was something to look forward to every day. And then by the time you'd got to the quit day it wasn't so much of a shock to the system- your body. You were already going four hours without a cigarette by then anyway.

Quote 5- Abrupt
P: The diaries did help, cos it just makes you think, and because you've got it all week- you have to fill it in by the end of the week- you flick through it yourself and you think to yourself ooo that's terrible that is smoking that much, and just that number, yeah it does help.

Quote 6- Abrupt
P: With the cutting down, each time you know you've cut down on another cigarette, and that made it feel- you'd write it down- and it made you feel 10 times better because you knew you'd cut down on one more.

Quote 7- Reduction (SR)
I: Do you think it was useful to be able to record how much you were smoking each day?
P: Oh yes, because it brings you up short if you've gone one over. And it makes you realise it's written down. Yes I did like that.

Quote 8- Abrupt
I: Was there anything particularly about that you found helpful, any aspect of it in particular?
P: The nurse support?
I: Yeah.
P: Yeah, I think just having her there, she was very non-judgmental and very approachable, and I think just having that person there that you knew you were going to see every week. Even if we had have smoked I wouldn't have felt uncomfortable with her, but she made me want to quit, she definitely helped me without her realising quite honestly.

Quote 9- Abrupt
I: Do you think that there's anything about this method that could stand in the way of people being successful?
P: No, I think if you've made up your mind you definitely want to quit, I think it's all about will power isn't it? I don't think it's anything to do with the method.

5.3.2.3 Monitoring

Another element of all methods consistently regarded positively was monitoring of cigarette consumption and feelings about quitting. This was in the form of expired CO level measurements, recording cigarettes smoked in diaries and responding to questions about levels of craving and confidence. Monitoring was perceived as helpful in three ways: 1) it made participants aware of the amount they were usually smoking, which was more than they had anticipated (Box 1, Quote 5); 2) participants could see improvement either in the amount of cigarettes smoked, their CO levels or their responses to questions, which spurred them on (Box 1, Quote 6); and 3) it made them aware when they had not progressed as they would have liked (Box 1, Quote 7).

5.3.2.4 Support, NRT & mindset

As well as the behavioural methods and nicotine preloading treatment used in RRT, several other issues appeared pertinent to all participants concerning their RRT quit attempt. Almost all participants found the nurse support helpful. They felt that they were given a great deal of encouragement and found it useful to be able to talk through their quitting experiences weekly. Seemingly due to this relationship with the nurse a number of participants felt spurred on to succeed, so as not to let her down (Box 1, Quote 8). It also appeared that a number of participants had not used NRT to aid their quit attempt before and that they found the use of NRT in general (rather than for preloading in particular), as well as the use of a combination of patches and an acute form of NRT (which has only recently been implemented in some NHS SSS) useful. However, the issue that came across most strongly, irrespective of the methods being investigated, was one of personal mindset. When

participants were asked whether they felt the method they used could hamper a quit attempt, or when non-abstinent participants were asked whether they thought there was anything about the method that had prevented them from quitting, the answer was most commonly *"No"*. Regardless of the method used participants believed that the most important predictor of success was a smoker's personal circumstances and mindset, and therefore if a person is not ready to quit then they won't succeed (Box 1, Quote 9).

Taken together these findings appear to suggest that all of the quitting methods used in RRT are feasible to use in clinical practice. Despite the fact that generally participants prefer abrupt quitting or reduction to quit, neither is more popular, which perhaps suggests that smokers should be given a choice. The importance of tailoring is further supported by the fact that although participants were generally in favour of a pre-quit period, some participants felt this could be altered to better fit their individual needs. Despite the interviews being focused on the behavioural methods of quitting used and nicotine preloading, participants also highlighted the importance of the intensive behavioural nurse support, the use of NRT in general and the quitters' personal circumstances and mindset to the success of the quit attempt.

5.3.3 Comparison between the abrupt and reduction to quit methods

5.3.3.1 Gradual adaptation versus getting it over with

The only dislike given of the abrupt quitting method was that it was too sudden and extreme an approach, likely to invoke panic (Box 2, Quotes 1 and 2). This was raised by a number of

Box 2. Comparison between the abrupt and reduction to quit methods 1

Quote 1- Abrupt
P: The abrupt one- the horrible one, the cruel nasty mean one.

Quote 2- Reduction (SFP)
P: I think the abrupt one kind of frightens people at first, thinking ahhh, I get to this day and that's it and I think in some smokers you panic.

Quote 3- Reduction (HR-E)
I: How do you think this method could help people to quit?
P: It's a lot easier because it's not just sudden, you're gradually doing it, so it's like, oh how can I put it? It just seems a lot easier, that your mind and your body get so used to not having so much nicotine and not smoking so much. By the time it comes to completely stopping, you've already wanted to stop anyway.

Quote 4- Abrupt
P: I think if you've got no will power to actually cut down, then I think that was the best way to do it, just to stop abruptly. To make up my mind, and the fact is I was given a date and there was no sort of choice about it, it was a case of like well that's it do it.

Quote 5- Reduction (SR)
P: I just found it difficult cos there was a lot going on in my life, it was quite stressful and I thought oh I can't do it all.
I: So was it that you found it clashed with anything particularly in your lifestyle, or that it was just an extra thing to worry about?
P: It was just an extra thing, and things were happening, and oh there was all sorts going on. I thought this is ridiculous.
I: Was there anything actually that you thought was a good point to the method or that you liked about it?
P: I did like it, but there's just so much going on.

Quote 6- Reduction (SR)
P: Cos it was abrupt [previous quit attempt] I just stopped. I hid everything, whereas with cutting down gradually it was still there in front of me waiting for the next one. Whereas to hide it was great; I hid everything.

Quote 7- Abrupt
P: Sometimes I didn't smoke as many as on a normal day without patches. You're obviously going to the routine knowing, I was sort of on this course now for me to stop smoking. I think knowing that- whether that was at the back of my brain- but I felt I didn't get the cravings so much. So it naturally cut itself down to be honest. Not like, 15, 14 and then cut down to six or seven. I found that one packet lasted a couple of days, or just under two days. I found it was lasting much longer and that's how I could tell, not that I was counting you see.

Quote 8- Abrupt
P: I reduced
I: How were you doing that?
P: Just cutting down each day, having one less cigarette each day, every day I was just cutting down on one cigarette. I mean, now I'm not having none at all...even me husband said to me, instead of when you get up in the morning and light one up, leave it for about half an hour and then leave it a bit longer, which I did and that works better. That helped a lot, doing it like that.

participants who also thought they wouldn't be able to quit abruptly, and that the method would be particularly difficult for heavy and/or long-term smokers, such as themselves. In comparison participants seemed to think that reducing before quitting would suit this type of smoker, as it would not result in the *"shock to the system"* that abrupt quitting would. One participant took this a step further by suggesting that the length of the reduction period should be tailored based on the length of time the individual had been a smoker.

The primary reason given for why participants thought reduction worked was that it gave time to adapt and prepare the body and mind (Box 2, Quote 3), by becoming used to smoking deprivation, and seeing the progress that had already been made through the use of monitoring. It therefore seems reasonable to assume that more adaptation may be required in those who have been smoking for a longer period of time. However some of those in favour of abrupt quitting thought the reason that it worked was that *"it gets it over with"*, eliminating cues to smoke, such as smoking paraphernalia, so that it is simpler and easier; whereas reduction provides the opportunity to back out. As a result one participant thought it would take more will power to stop via reduction than to quit abruptly (Box 2, Quote 4). Some support was provided for this by the fact that a number of the non-abstinent reduction group claimed that they were smoking a reduced amount, but felt they were stuck on the tricky, more rewarding cigarettes, which they had left until last during the reduction period. Relapsed participants in the abrupt group did not suggest that they felt stuck on particular cigarettes; however this could be because they had analysed their smoking less during the course of the pre-quit period, and were less conscious of the importance placed on particular cigarettes. A small number of participants also found that the reduction approach was too cumbersome and

provided something else to worry about alongside outside stressors (Box 2, Quote 5). One participant described the programme as a *"nuisance"* as he often found he was supposed to be smoking when he was doing something else, such as gardening. Whereas another found the reduction programme difficult because the fact that she was reducing meant that she had cigarettes with her, which provided the temptation to smoke as she usually would (Box 2, Quote 6).

5.3.3.2 Compliance

In all methods participants reported some deviation from the instructions they were given, however the nature of this non-adherence varied across methods. Most notably it was not just the participants in the reduction to quit arm that reduced their cpd pre-quit. In fact the majority of the participants in the abrupt arm claimed that they did so too. In most of these cases the reduction could be interpreted as unintentional, as participants reported that they felt that they just could not smoke as much, sometimes as a result of nausea, but were made aware of their reduction only through looking back at their diaries (Box 2, Quote 7). However a smaller number of these reducers chose to reduce their smoking despite instructions not to. For example, one participant admitted to aiming to reduce their smoking by one cigarette each day (Box 2, Quote 8), whereas others stopped smoking in particular places or situations, such as the car.

Only a small number of people in the reduction arm reported not reducing their smoking over the two weeks prior to their quit day, with one participant quitting abruptly after two days.

The reason given was that his work got in the way of scheduled smoking times, meaning that he was missing cigarettes he could have smoked, and was hardly smoking anyway. The participant felt that after not smoking for a period of 24 hours it would seem *"daft"* to smoke another cigarette. In the main, the remainder of participants in the reduction group reported trying to keep roughly to the quota of cigarettes they were asked to smoke, but allowed for flexibility in scheduling, by not always smoking at the times specified (Box 3, Quotes 1 and 2). Some of the reasons given for this were the desire to save cigarettes to smoke at times when they would be most rewarding, activities got in the way when smoking should have taken place, such as shopping or meetings at work, not feeling the need to smoke at the specified time, and a lack of motivation to check their schedule to see when they should be smoking. One of the justifications for the reduction methods is that if smokers smoke only at specified times this will break the association with their usual conditioned environmental cues (Section 1.2.2). Therefore a failure to do this may undermine the efficacy of the method. However, although participants acknowledged that what they were doing was outside of the guidelines, they did not seem to appreciate the impact this may have (Box 3, Quote 2). This could suggest that the potential mechanism of the method was not explained fully to participants (as supported by Box 3, Quote 2), or that this explanation was not understood.

5.3.3.3 Pre-quit confidence

Some participants in both the abrupt and reduction arms reported that their confidence increased during the pre-quit period, whereas others reported no change or a decrease. However increases in confidence were more common in the reduction arm. In both arms,

Box 3. Comparison between the abrupt and reduction to quit methods 2

Quote 1- Reduction (HR-E)
P: I could've followed it [the reduction schedule] a bit more closely, but it wasn't your fault it was my fault. No, actually I took the thing on board seriously and we looked through the ones that- the cigarettes- that we could dispense with, the peak demand times, and I tried to keep fairly close to that but switched them around a bit. I found that some days the early morning craving wasn't there. I didn't say well okay I didn't have one at first in the morning so I'm going to have two later on.

Quote 2- Reduction (HR-E)
P: Sometimes when it was to cut out one at midday, I sort of couldn't keep to that like a rigid rule, that midday you couldn't have a cigarette....sometimes I'd go from first thing in the morning when I had one until about early evening before I had another one...and she [the nurse] said it doesn't matter really, she said it'll work out so it sort of still worked out, I'd kept that I was allowed, say to smoke 15 cigarettes a day, I'd sort of worked out that I only did have the 15 cigarettes a day.
I: Do you think doing it that way fit in alright with your lifestyle or was there any times when it clashed with anything that you'd usually do?
P: No because like I say it wasn't a rigid thing that you had to have one at this time and then you couldn't have one at that time.

Quote 3- Reduction (HR-E)
I: After you'd gone over your two weeks reducing and you reached your quit day, how did you feel then about quitting?
P: Good, because I'd cut right down, so like I say I wasn't buying cigarettes
I: And over the two weeks where you were reducing, do you think your feelings about quitting changed at all? So do you think you got any more confident or any less confident as time went on?
P: I got more confident. I knew that by the time it came, that was it, I'd be finished.

Quote 4- Reduction (SFP)
I: Do you think you got any more confident or maybe less confident as you went along?
P: I think I got a little bit more confident, because you know the puffer thing that counts [CO monitor]. Yeah, I'd like to have one of those in the house, because it was 34 on the first one and then it went down to nine, then it went down to five.

Quote 5- Reduction (HR-E)
P: I knew I wouldn't be able to [quit] on the day when it came. I mean, it's still my target. I will quit and I've come down from about, on a bad day 30 to six or seven a day. People say, well you haven't packed in but to me to come down to that low at this stage is quite good.

Quote 6- Reduction (SR)
I: How do you think this method could help people to quit?
P: They can plan their day around their smoking to begin with, and it helps them through up to your quit date, because you are actually in control of that, it's your choice and you know when you want to smoke and when you can't smoke, which I think is brilliant.

Quote 7- Abrupt
I: Do you think there's any changes that you'd make to the method?
P: Only maybe that if you do go for a trial like this, you are given the option as to which method you're going to use...between the reduction and the sudden stopping.

Quote 8- Abrupt
I: Do you think there were any problems or bad points or things you didn't like about it?
P: I think it would have been nice if we'd had a choice of which way we wanted to do the stopping...you know where we did the abrupt or the gradual

people whose confidence increased reported that this was due to evidence of their progress so far, in the form of a drop in cigarette consumption and/or CO levels, and the reflection of this in diary and questionnaire responses (Box 3, Quotes 3 and 4). This may suggest that although all participants liked the monitoring element of their programme, it may have had a greater impact in the reduction group.

5.3.3.4 Reaction to post-quit reduction

The majority of both abrupt and reduction arm participants, who weren't abstinent at the time of their interview, claimed to be smoking less than the amount they had at baseline. Based on method instructions this is perhaps surprising, as it could be assumed that smoking levels would be easier to control for smokers who already had some experience in reducing their smoking, and that there would be greater likelihood of returning to previous smoking behaviour if these hadn't been altered at all prior to quit day. However, in reality, participants in both arms reduced pre-quit. Abrupt participants provided little opinion of post-quit reduction, whereas participants in the reduction arm saw it as a positive. As a result it could be feared that participants happy with their reduction would be less likely to attempt to quit in the future. However many of the smokers who claimed to be pleased also said that their ultimate goal was still to quit (Box 3, Quote 5).

5.3.3.5 Decision making

When asked what they liked about the method they used a popular element of reduction was that it allowed participants to make decisions, which helped them feel in control (Box 3,

Quote 6). When randomised to this arm participants were provided with a choice of one of the three reduction methods on offer, and within the HR and SFP methods they also had a say about which cigarettes or time periods they cut-out on each day of the programme. In the abrupt quitting arm participants were not given these options, and this was reflected in the fact that a number of participants suggested that choice between methods should be made available (Box 3, Quotes 7 and 8).

In summary of Section 5.3.3 the abrupt method was perceived as both *"scary"* and an opportunity to get quitting over with, whereas reduction was seen as both an opportunity to gradually adapt and to back out of the quit attempt, suggesting that personal perceptions of the methods varied considerably. However the process of quitting in practice appeared not to differ greatly across arms with many abrupt participants reducing pre-quit- albeit without a schedule- whilst many reduction participants exercised flexibility when using their schedules. This may explain why non-abstinent participants in both groups were smoking fewer cigarettes post-quit; although reducers were more likely to see this as a positive. Participants regarded the monitoring positively; however it may have had more impact in the reduction group, as the perceived decline in cigarette consumption was thought to be the cause of increased feelings of confidence pre-quit. Finally the availability of choice emerged as a poignant issue, as its presence in the reduction method was seen as a good point, whereas the lack of it in the abrupt method was seen as a deficiency.

5.3.4 Comparison between reduction methods

5.3.4.1 Reason for reduction method choice

Participants commonly reported that they had selected their reduction method to fit with the demands of their job, particularly for the SFP method; perhaps as this is most easily tailored (Box 4, Quote 1). Participants chose sfp with the nurse and these were reduced on a day to day basis, whereas smoking in the SR method was determined by the length of the regular ICI, and for the HR method specifying particular cigarettes may have been difficult for people whose timetable changed over the week. Participants also reported choosing both the SFP and SR methods because they seemed simplest when the nurse explained the three methods. It seems likely that participants were using the term simple to encompass the simplicity of incorporating the method into their lives.

The HR and SFP methods provided the opportunity to choose whether easier or harder cigarettes were foregone first. Most commonly, participants chose to lose easiest cigarettes first, illustrated by the fact that no one who used the HR-D method was available for interview; mainly due to the lack of participants who chose this method. This approach meant that the harder cigarettes were left until last, but most people did not report that reduction became harder over time. The reason for this could be, as one participant suggested, that eliminating the easier cigarettes first got the *"mind and body working to get rid of the harder ones"*. The thought of cutting out the harder ones first seemed daunting to some participants (Box 4, Quotes 2 and 3), in the same way that abrupt quitting did. A small number of SFP participants started by cutting out the harder cigarettes first. They said that this was to test

Box 4. Comparison between reduction methods

Quote 1- Reduction (SFP)
P: From the time I got up, and when I went to work, and just all the different things I did in the day, like cooking tea and just the certain times when I didn't smoke, so I did the choosing really, I did all the choosing of sort of when, but she made sure that it was reducing down quite a lot.

Quote 2-Reduction (HR-E)
I: Were you given a choice of whether you eliminated the ones that you found easier first or the ones that you found harder first?
P: I think probably, but had I been given that choice I can't imagine why anybody would choose to give up the harder ones, and so it didn't take me long to reject it.

Quote 3- Reduction (HR-E)
I: Why was it that you chose to eliminate the easier ones first, rather than the harder ones?
P: It's the thought of getting up in the mornings and not having a cigarette with a cup of coffee; that was the most important one.
I: Do you think leaving the harder ones until last made it harder for you towards the end or do you think..?
P: No I actually got down to smoking three a day.

Quote 4- Reduction (HR-E)
P: I did two things right away, one of which is I decided not to smoke in the car...that was much easier than deciding only to have one cigarette in the car or y'know I need to have one on the way to work and not on the way back, so there were kind of categories, some of which were very simple

Quote 5- Reduction (SR)
P: As it got bigger spaces, it did make me clockwatch a bit and I didn't think- at that stage- I stood much chance of packing in.

Quote 6- Reduction (SFP)
P: If they [other quitters] read it like I read it, you think oh well this is good and then you get into it for a couple days, and it's like wait a minute, I can still smoke 40, 60, 80 cigarettes a day, I just have a specified time that I can smoke.

Quote 7- Reduction (SFP)
P: I found that in the times when I could smoke, although I wasn't smoking as many cos obviously it was impossible to smoke as many, I found that I was probably smoking more in the times that I could smoke, that's what it felt like anyway. Cos I knew like for three or four hours, I wouldn't be able to have one, so I just thought I can't see how this is going to work.

Quote 8- Reduction (SFP)
P: When we initially went on the reduction plan we did tend to try and cram as many in as possible, at the onset, but we soon got out of that habit.

themselves and whether they would be able to do it. However, they tended to report the method as harder to carry out than those who started with the easier cigarettes first.

5.3.4.2 Scenarios not cigarettes

The flexibility that participants exercised in their scheduling, contrary to programme guidelines (Section 5.3.3.2), was arguably most marked in the HR method. Using this method participants were asked to identify each individual cigarette they would usually smoke during a day and then reduce by individual cigarettes. However a number of participants claimed to have reduced by categories of cigarettes. They did this by stopping smoking in particular places or situations, for example when at work or in the house. One participant claimed that this seemed easier than reducing by individual cigarettes (Box 4, Quote 4). As mentioned in the previous section (5.3.4.1), it is understandable that this may be the case if a person's daily timetable, and therefore smoking times, change over the course of the week, meaning that they smoke at different times/situations on different days. This is likely to be the case for people who work during the week and have the weekend off.

5.3.4.3 Clockwatching

Some participants reported difficulty clockwatching using both SR and SFP methods. As the time lengthened between cigarettes some participants said that they were anxiously waiting for the time to come to smoke, and one said that this reduced their confidence (Box 4, Quote 5). However another participant said that although they did find themselves constantly checking their watch initially, this lessened as time went on.

5.3.4.4 Is smoke-free periods a reduction method?

Although most participants using SFP were pleased with the method, some interviewees felt that it wasn't a reduction method. As participants were required to reduce the times in the day when they were smoking rather than the cpd, they felt that it would still be possible to smoke a considerable amount in the available smoking periods. One participant, who said she was a very heavy smoker, felt that even as the periods decreased she could still have smoked her usual amount of cpd (Box 4, Quote 6), whereas another two participants said although they thought it would be impossible to smoke their baseline cpd they did find themselves smoking more than they usually would in the remaining smoking periods (Box 4, Quotes 7 and 8). However, during the course of the pre-quit period participants recognised this issue and all three decided to ensure that they did reduce their cpd. In particular one participant set herself cigarette quotas, as in the cpd methods. After this issue was raised I fed this back to interviewees, by asking sfp participants if they thought they were reducing their cpd, despite not being given a quota to work toward. All of those asked confirmed that they did reduce and this was usually estimated to be at a level similar to that specified in the cpd methods (reduce to 50% of baseline in the first week, and to 75% in the second week).

A small number of issues arose which were specific to one reduction method or another. Participants who reduced using the HR method appeared to find it more intuitive to reduce by categories of cigarettes rather than individual cigarettes; whereas in the SR and SFP methods clockwatching was raised as an issue, which reduced confidence in a minority. However participants chose the SFP and SR methods because they seemed easiest to them. This suggests that the choice of reduction methods is likely to be based on personal perceptions and circumstances, as the preference for abrupt quitting and reduction to quit appeared to be

(Section 5.3.2.1). The majority of participants appeared to prefer and find it simpler to forgo easier cigarettes rather than harder cigarettes first, and finally a small number of participants quitting using the SFP method found it a challenge without a quota of cigarettes to work toward.

5.3.5 Nicotine preloading

5.3.5.1 Effects of preloading

The general feeling across both the abrupt and reduction arms was that preloading was helpful. This is despite the fact that many participants in the abrupt arm experienced nausea during the pre-quit period, which was likely to be due to the use of nicotine patches whilst smoking. Nausea has been reported previously in cases such as this (Fagerstrom & Hughes 2002; Rose et al 2009). However it may also be of note that it is listed as a side-effect of nicotine overdose on nicotine patch labels, and so there is a possibility that this was a psychological effect manifested through expectation.

Participants who experienced nausea felt that this was a useful part of the method and aided their quit attempt. Accordingly a number of the abrupt participants stated that the reason they thought preloading was used in the trial was as aversion therapy, to put participants off smoking (Box 5, Quote 1). Support for this mechanism came from two sources:

Box 5. Nicotine preloading 1

Quote 1- Abrupt
P: I think it was to make you so sick of nicotine that you wouldn't want a cigarette, I don't know.

Quote 2- Abrupt
P: I just didn't like the, it give me leg ache and nausea and stuff, smoking with the patches on...I did enjoy when you first go on the course, they tell you to smoke as normal, and the first week I did. I said to the lady I really, really don't enjoy smoking no more, but I didn't get to the quit date then I had another week to go, to carry on smoking. I really didn't want to do it; I said I'll try and she said to me I really do want you to smoke as normal, but if you can't you can't, and I really couldn't. I was smoking but it was one or two a day, and I was thinking to myself, what's the point? I would have liked it to be a shorter period of time from when I first seen her to the quit date.

Quote 3- Abrupt
P: I sometimes found it harder because I actually wanted to smoke less for some reason, but not an awful amount less. But sometimes, getting towards the evening I would think oh, I haven't had as many as what I would normally have.

Quote 4- Abrupt
P: Actually the last few days I didn't quite, I think we worked out that I needed, my normal smoking was about twenty-five a day and I was really struggling to hit the twenty-five, but it was just feeling you know a bit nauseous all the time.

Quote 5- Reduction (HR-E)
I: Did you get on alright with using the patches and smoking at the same time?
P: At the very start they did make you feel sick actually and you didn't really wanna smoke. Because you had your set times to smoke you did smoke and sometimes you felt a bit queasy. But the less you smoked you know the better it got so.
I: So did you find that you were sometimes even reducing more than you had to?
P: The first week when I had the patches, and when I had set times when I had to smoke, and some of them cigarettes I missed out, to be honest; because it did make you feel a bit queasy.

Quote 6- Reduction (HR-E)
P: Initially I had the patches and the micro tabs I think. I did give the micro tabs up, I don't know why, I suddenly began to feel quite sort of ill, and I was fine when I cut those out.

Quote 7- Reduction (SR)
P: I do think the patches didn't do much for me, but the gum itself has been great. I stick a piece of gum in me mouth whenever I felt like a cigarette and that gets rid of the urges, but the patches I was a bit disappointed in them. Didn't seem like they did much for me, but the gum has been great, yeah.

Quote 8- Reduction (SFP)
P: The patches, they didn't seem to do a lot for me and then I did ask if I could use the inhalator. I found that a bit more helpful.

Quote 9- Reduction (SR)
P: The actual false cigarette thing [nicotine inhalator] was really good it really felt like you were having a cigarette.

1) Participants who felt positive about stopping smoking on their quit day because smoking had become intolerable, and who claimed that it was a relief to be able to stop (Box 5, Quote 2); and
2) As previously mentioned in Section 5.3.3.2, the many participants in the abrupt quitting arm of the study that reported a reduction in their smoking pre-quit, despite being advised to smoke as normal. In most cases, participants did not appear to strive to reduce, it seemed to occur because they did not feel the need to smoke (Box 5, Quote 3) or because they felt nauseous (Box 5, Quote 4).

Only two participants in the reduction arm reported nausea; one of whom managed this by reducing smoking further (Box 5, Quote 5), and the other by using less of their acute NRT (Box 5, Quote 6). This suggests that reduction participants were more able to regulate the effects of preloading, and this was perhaps what abrupt participants were also doing through their reduction (Section 5.3.3.2). It is interesting that this occurred despite participants' assumptions that the purpose of the treatment was as aversion therapy, as this would be expected to undermine efficacy. However, as previously reported reduction in the abrupt arm appeared to be largely unintentional, suggesting that the unconscious desire to reduce nausea over rode behaviour motivated by an awareness of potential treatment mechanisms.

Craving reduction was also thought to be a mechanism of preloading, however participants in the abrupt arm were more likely to advance this theory, again suggesting that the effect of preloading may have been greater in these participants. In the abrupt group, nausea, a loss of enjoyment when smoking, and lack of craving often went hand in hand; however, despite the fact that nausea was rarely experienced in the reduction group participants did lose some of

the will to smoke. This was mainly attributed to the use of the acute NRT pre-quit, and interviewees often reported that they had not felt any effect of the patch (Box 5, Quotes 7 and 8). In general reduction participants reported that they used their acute NRT as instructed- whenever they had the urge to smoke, outside of scheduled smoking times, instead of a cigarette- and that this had reduced their need to smoke (Box 5, Quote 7). One participant explicitly said that they felt that their inhalator was a good substitute for their cigarettes (Box 5, Quote 9).

5.3.5.2 Lack of effect

Despite what appeared to be strong effects of preloading in some participants a few interviewees reported that they had felt no effect of using NRT and smoking at the same time. These participants often reported that they believed that preloading would reduce their need to smoke, but were disappointed when this was not the case (Box 6, Quote 1). In fact one participant claimed that her smoking actually increased during the pre-quit period. When asked why this was she said that she had been under a lot of stress at the time, however she also thought she had built up an association between the patch and smoking. The fact that she had been told that she could preload enhanced this, giving her no incentive to control her smoking with the patch on (Box 6, Quote 2).

Box 6. Nicotine preloading 2

Quote 1- Abrupt
P: I thought the patches would be stronger and have more of an effect. I mean, they were supposed to have a bit of a knock-on effect where you feel like you didn't want to smoke but I didn't feel that at all...I really wanted it to help, I really wanted it to cure me.

Quote 2- Abrupt
I: Were you still smoking the same amount [pre-quit], would you say than before you started the study?
P: Yes, I did, I smoked more as well, which is quite odd.
I: Do you think there's any reason why you..?
P: Oh yes, it was a stressful situation that arose, so yes....The first couple of days I thought I wouldn't have tried to smoke as many as I usually did, but sort of the second half of the day, I did any way, which shocked me because I thought, right, I've got a patch on, I shouldn't want to smoke so many but as time went on I did and I smoked more. And even I think I put a patch on and lit a cigarette at the same time. It was almost like they went together; it was a bit strange...I hoped that it would work this way, but it didn't, it just enhanced the fact that you could smoke and wear patches, and still be a smoker to me.

Quote 3- Abrupt
P: The irritation they [nicotine patches] caused to me where they were stuck on my arms and so on, was such that it started off that I couldn't sleep with them on ...So by this time I was into the sort of second week of this, and really I hadn't been able to take advantage of the patch. The diary I filled in said have you used the nicotine patches this week and if not can you explain. So I put a no, i.e. complete inability to sleep after being in bed for about five hours.

Quote 4- Reduction (SR)
P: I've stopped using the patches completely because of the way they affect my skin...quite severely.

Quote 5- Abrupt
P: When they told me- look here's the patches, the highest one, but carry on smoking the same amount, I was absolutely shocked with that. I was shocked.

Quote 6- Abrupt
I: What did you think about the instructions to smoke and be on the patch at the same time?
P: Well I was obviously a bit wary from years ago, they used to say doing such a thing was a real taboo thing to do, but, I kind of placed my faith in, people having better knowledge of the situation than I had.

Quote 7- Reduction (HR-E)
P: When I was told that the advice you shouldn't do them [smoking and using NRT] together was wrong I was very happy to believe it, and I formed my evidence myself that it wasn't right.

Quote 8- Reduction (SFP)
I: How did you feel about the nicotine replacement therapy that you used, and using the patches as you were smoking?
P: No problems at all. I have tried that in the past, a few years ago. I have tried quite a few times, when people were saying well you shouldn't be doing that because of the nicotine in your body, and it's like well what is nicotine? And in the past I found it helped.

5.3.5.3 NRT issues

Another potential problem with preloading, reported commonly across both study arms, were issues with the NRT used, such as skin irritation, sleep disturbance and trouble getting the patches to stay on. Some participants discontinued their NRT as a result of these (Box 6, Quotes 3 and 4), but most people who experienced these problems did not. Even though participants experienced side-effects, they still believed that NRT was helpful. However, it is important to keep in mind that not all non-compliance is intentional. The fact that a number of participants struggled to keep the patches on, exacerbated by a period of warm weather during the study, may mean that the levels of nicotine entering the blood stream were not as high as expected, or higher in some people than others.

5.3.5.4 Previous opinion and past experience

Overall few people intentionally did not adhere to preloading, even though, until recently quitters were warned against smoking and using nicotine patches concurrently. Many participants were aware of the warnings and reported surprise at being asked to preload (Box 6, Quote 5); however they trusted the expertise of the research team (Box 6, Quotes 6 and 7). Nevertheless, there were a few participants who still did not accept the *"logic"* of preloading and were worried that they were putting too much nicotine in their body, based on previous advice. One participant thought that the combination of the two could be fatal.

Only one participant reported that they had used nicotine preloading treatment in the past. She had decided to do so based on her perception of nicotine as a non-harmful component of

cigarette smoking. This participant was happy to preload for a second time and found it useful on both occasions (Box 6, Quote 8).

In summary of the issues raised regarding preloading, the unintentional pre-quit reduction reported in the abrupt group was most likely due (at least in part) to the effects of this treatment; such as nausea and loss of the will to smoke. Participants from the reduction group were less likely to report that they had lost the will to smoke or experienced nausea, and preferred their acute forms of NRT to patches. This may point to two different routes to the efficacy of preloading: 1) when used to quit abruptly- as aversion therapy; and 2) when used to reduce and then quit- to facilitate reduction through substitution. However some participants in both arms reported that they felt no effect of preloading at all. There were also problems reported with the NRT, although this didn't seem to greatly affect intentional adherence rates, and people tended to report finding preloading helpful regardless of this and the nausea experienced. Based on past experience many participants were surprised that they were asked to preload, but were willing to do so, and only one participant had used the technique before.

5.3.6 Comparison between quitters and non-quitters

5.3.6.1 The importance of preloading

In the abrupt group, most participants who achieved abstinence also experienced nausea or loss of desire to smoke, and felt that preloading had been useful to them. Some of these participants had also felt ready to quit on their quit day (Box 7, Quote 1). Non-quitters however, felt no such effects, with only one person disconfirming the general rule. Therefore,

Box 7. Comparison between quitters and non-quitters

Quote 1- Abrupt- quitter
P: I was praying for the quit day to tell you the truth, because I didn't enjoy smoking with the patches on.

Quote 2- Reduction (SR)- quitter
P: I liked the way you prepared yourself for it, because you was given a cut-off date, this was two weeks ahead, from when you first started. So you could slowly prepare yourself for that date, which I found better for me personally. I'd made my mind up that that date was the last date and I think the last day I only smoked about three cigarettes anyway.

Quote 3- Reduction (SFP)- non-quitter
P: I think that on the courses, it's like changing a thought process, not just having the nicotine therapy. It could help with a bit more time spent on thought therapy, as to why we smoke and what makes us pick the cigarettes up in the first place. I've just started reading this book- that's what makes me think now, well why do you need that cigarette. I just think anything that can be put there to help a smoker, rather than just giving them the therapy, like the nicotine replacement thing. Maybe a lot more talking could be done about cigarettes. I mean we all know what they do to us, but it's like changing a thought process in your mind really. I think that could benefit.

Quote 4- Abrupt- non-quitter
P: I didn't want to do it that way [abrupt], it was the other way [reduction] I wanted to do.
I: Was there any particular reason why you would have preferred to do it that way?
P: Because I knew I wouldn't be able to.
I: And you still think the same do you? That it's not changed, or has it changed at all during the course of the study?
P: No, not really.

Quote 5- Reduction (SR)- quitter
I: When you were first told that you were going to be reducing before quitting what were your first impressions of doing it that way?
P: I wasn't very happy.
I: So would you have preferred the abrupt quitting?
P: Then I would. But I wouldn't if I was doing it again.

Quote 6- Reduction (HR-E)- non-quitter
I: You said that before the study if you'd been given the choice you would have quit abruptly, so do you think your opinion has changed at all over the course of the study, or do you think it has stayed the same?
P: No, it has changed, because I do honestly believe that if I'd have quit abruptly when I had that bad weekend and I just smoked, I actually do believe I would have gone back to smoking like 20 a day and not just 5.

Quote 7- Reduction (HR-E)- non-quitter
P: I knew I wasn't going to be able to quit on that quit day, but I was quite chuffed that I'd managed to slice it down, and the nurses seemed to agree with me on that. I mean they didn't encourage me to say oh, well you didn't quit, carry on, but they sympathised with the fact that I had drastically reduced and was making a solid effort to try.

that fewer non-quitters claimed to reduce their smoking pre-quit than quitters, provides further support for the theory that preloading was responsible for the pre-quit reduction in the abrupt group.

Comparison between quitters and non-quitters in the HR group was hard as only one of the eight participants had quit. However it also appeared that preloading had a larger impact on quitters than non-quitters in the scheduled reduction group. As in Section 5.3.5.1 the emphasis was more on the effect of the acute NRT, than the patch.

5.3.6.2 Side-effects of NRT

Another potential impact of NRT on quitting in the abrupt group was highlighted by the fact that quitters didn't mention any of the problems with NRT highlighted in Section 5.3.5.3, such as skin irritation and sleep problems, whereas non-quitters commonly did. The most intuitive explanation is that adherence to NRT treatment (when preloading and/or post-quit) was affected by these issues. However this conflicts with the finding that preloading non-adherence seemed low in contrast to reports of NRT problems. It may be that quitters also experienced NRT issues, but these didn't seem significant enough to mention, as they were more focused on the positives of the quit attempt.

5.3.6.3 Preparation and monitoring

Quitters were more likely to stress the value of the preparation and monitoring (Sections 5.3.2.2 and 5.3.2.3) than were non-quitters (Box 7, Quote 2). In fact one of the non-quitters in the SFP group specifically pointed out that they would have liked the programme to offer more intensive behavioural support, with the opportunity to talk about individual cigarettes and the reasons for smoking them (Box 7, Quote 3). The discrepancy between the experience of this participant and others who highlighted the preparation and monitoring as a good point could suggest that some nurses focused on this more than others, that some participants didn't focus as much on this type of preparation independently, or that some quitters have a greater need for psychological therapy than others.

5.3.6.4 Post-quit opinions of quitting methods

Finally there was variation between the abrupt and reduction groups in terms of the association between smoking status and the opinions of participants about the quitting method they had used. Those participants in the abrupt group who had managed to quit and stay abstinent reported that they were happy with the abrupt method and would use it again; however those who were smoking said that they wished that they'd been in the reduction group and would try the reduction to quit method in future (Box 7, Quote 4). In contrast both quitters (Box 7, Quote 5) and non-quitters (Box 7, Quote 6) in the reduction arm were satisfied with their method and would use it again. This may be because reduction had been encouraged in the reduction group and so was seen as a favourable outcome (Box 7, Quote 7). Therefore despite not quitting these participants felt that they had achieved something. This is supported by the finding that many reduction to quit, non-quitters, smoking a reduced rate at

the time of interview were pleased with this outcome, whereas those in the abrupt group did not seem to find it significant (Section 5.3.3.4).

To summarise Section 5.3.6, participants in both the abrupt and reduction to quit arms of the study, who were abstinent at the time of interview, reported a larger effect of preloading than the non-quitters, as well as a greater importance of monitoring variables such as cpd, CO, and confidence as part of their quit attempt. As well as this more importance was put on preparing for the quit attempt psychologically by quitters in the reduction arm, whereas in the abrupt group NRT issues were more commonly reported in non-quitters. Interestingly, although non-abstainers in the abrupt group were likely to prefer the reduction to quit method at the time of interview, non-quitters who had used the reduction to quit method did not report that they would also use the alternative method (abrupt) if they tried to quit again. This may be due to the normalisation and encouragement of reduction throughout the reduction programme, meaning that post-quit reduction was seen as a success rather than a failure to quit.

5.4 Discussion

5.4.1 Exploration of findings

Little qualitative research has been carried out examining the attitudes and beliefs of smokers about the method that they use to quit; in particular exploring nicotine preloading, abrupt quitting and smoking reduction approaches. This interview study aimed to do this, in order to gain insight into the methods that would be most popular and therefore useful in practice, and how these may work.

Although people generally approved of the method that they were allocated at random, and judged it feasible and comprehensible, findings demonstrate that smokers preferred a particular method of quitting prior to allocation; although these preferences varied. This was true when specifying a desire to quit abruptly or by reducing, and when choosing between the SR, HR and SFP methods. Some participants viewed abrupt quitting as intimidating, whereas others thought that it was best to get the discomfort over with quickly. Reduction was thought to provide the opportunity to back out of the attempt, but also to adapt the body and mind to quitting. This suggests that there is a potential demand for both methods of quitting used in RRT. However despite these preferences many participants stressed throughout their interview the importance of personal mindset to the success of the quit attempt, which appeared to be classed as more important than the method of quitting used. This suggests that although smokers think the method of quitting is important, ensuring that they are ready to quit before embarking on this method should be the priority. This focus on personal mindset and willpower has been commonly found across qualitative smoking cessation research (for example Rollins & Lennox Terrion 2010; Ashford et al. 2011; Beck 2011).

After the quit attempt people's preference for the method of quitting they would use in future was related to the method they had used to try to quit, and its success on this occasion. Those smokers who had quit were more likely to say they preferred whichever method they had used. Whereas in the abrupt group non-quitters were more likely to say that they wouldn't quit that way in the future, and would reduce first. However non-quitters in the reduction to quit group would be happy to stick with the reduction method for future quit attempts. This is

perhaps surprising, as in terms of quitting the attempt would be deemed unsuccessful. However reduction targets were set throughout the pre-quit period, and therefore achievement of these had been reinforced and praised. This may have led to participants seeing reduced smoking as an achievement in itself. Although many of the abrupt quitters had also reduced their smoking pre-quit they didn't seem to acknowledge this as a positive. One of the fears associated with the use of the reduction to quit method is that it will undermine the quit attempt, as reduction may be seen as a favourable alternative (Hatsukami et al. 2004). However little support was offered for this, as those participants in the reduction arm who had successfully reduced their smoking post-quit still expressed a wish to quit altogether. This tentatively supports the findings of Hughes & Carpenter (2006) and Asfar et al. (2011), who found an association between smoking reduction and future quitting. A follow-up of RRT participants would be beneficial to establish whether this desire was fulfilled, and therefore whether there was an association between reduced post-quit smoking and future abstinence, as well as to compare associations between the abrupt and reduction to quit arms.

Monitoring and mentally preparing for the quit attempt over the pre-quit period, were seen as positives of all the methods. The significance of these components may be further supported by the fact that they were highlighted more by quitters than non-quitters. This could explain why structured reduction methods have been found to be more successful than unstructured ones (Levinson et al. 1971; Cinciripini et al. 1995). With a structured approach there is perhaps a greater likelihood of more uniform stepped-down reduction, leading to more visible, regular achievements when monitoring, which could result in increased confidence, as reported in Section 5.3.3.3.

The fact that the pre-quit period lasted for two weeks was generally liked. This is encouraging as past evidence suggests that a shorter smoking reduction period is favourable to a longer one (Haustein 2002; Blalock et al. 2003). However a very small number of participants suggested slight alterations to the length, which may suggest that tailoring to individual preference would be worth consideration. Allowing for this element of choice would probably be popular with service users, as the opportunity to make decisions about treatment programmes was generally highlighted as a good point in the reduction arm, where this was most prominent.

Other issues relevant to the reduction arm were, firstly, participants preferred to drop the cigarettes that they deemed easiest first, leaving the harder cigarettes to forgo last. People who favour reduction are likely to shy away from abrupt cessation, which means that immediately cutting out their most rewarding cigarettes is likely to be unpopular. Secondly some participants reported that they were clockwatching when carrying out the SR and SFP methods, which some thought reduced their confidence; however despite this no difference in reported clockwatching was found between quitters and non-quitters, suggesting that it was not detrimental to the quit attempt. Thirdly, a small number of participants questioned whether the SFP method was a reduction method, because it did not specify the number of cigarettes to smoke each day; however participants that used the method did smoke fewer cigarettes over time. Despite the feelings of the minority, and the suggestion by one that a quota of cpd should be provided to work toward, the method was generally popular. Therefore turning this method into another cpd method may be a mistake, as it would remove some of the variation and therefore choice available between methods. Also, as discussed in Section

5.1.1.3 a potential positive of SFP methods is the focus on what is being achieved (sfp) rather than what is being missed (cigarettes). However this highlights that this method may not suit all quitters, and that it may be necessary to emphasise that target quotas of cigarettes will not be used when presenting this as a quitting option.

Finally, the smokers in the reduction arm exercised a good deal of flexibility when working through their reduction schedules. This occurred perhaps most notably in the HR group, where some participants reduced by categories of cigarettes rather than individual cigarettes. As a result it may be beneficial, in future, to slightly tweak the method so that categories of cigarettes rather than individual cigarettes are eliminated, as in Flaxman (1978) (Section 5.1.2.3). However depending on the categories chosen this may lead to reductions that are too big or small to be sustained over the reduction period, and each individual and their proposed schedule would need to be assessed for suitability. There was some evidence that flexibility across reduction methods was because participants didn't appreciate methods' possible mechanisms of action, and that nurses perhaps did not stress these enough. Therefore in future it may also be possible to combat some non-adherence through detailed lay explanations, reiterated throughout the programme, of why the methods may work, and why it is important to stick to instructions.

There was also significant non-adherence to the instruction not to reduce cigarette consumption in the abrupt quitting group, where most people did reduce. Although a number of smokers did this deliberately, most appeared to do so as a result of nausea and the lack of a desire to smoke. It seems most likely that these feelings were due to the nicotine preloading

that took place in both the abrupt and reduction to quit study arms, and that reduction was an attempt to regulate these effects. Spontaneous reduction such as this has been observed in previous studies of nicotine preloading (Bolliger et al. 2000; Fagerstrom et al. 2000). Using the quantitative findings of RRT we should be able to tell the exact amount of participants in the abrupt quitting arm who reduced their smoking pre-quit, whether this was correlated with saliva cotinine levels, and therefore whether it was a result of preloading. Preloading appeared to be a more poignant issue in the abrupt group in comparison to the reduction group, and in quitters in comparison to non-quitters; perhaps suggesting that those who felt less or no effect of preloading were less likely to quit in both arms. In the abrupt group the negative experiences of nausea may have built up an association with smoking, which over shadowed its usual positive associations, in turn discouraging smoking after the quit day. If this is the case then effects such as nausea could be used as a marker of treatment success, and guide treatment during an abrupt quitting programme. This is something that would need to be tested further- perhaps by experimentally testing emotional responses to smoking paraphernalia after nicotine preloading- and again RRT data could be used to investigate an association between reports of nausea and abstinence. Claims by smokers in the reduction arm that they felt less of the effects of preloading suggest that even though the abrupt quitters claimed to reduce, this was unlikely to be to the extent achieved in the reduction group. It is also supported by the modest finding, in Chapter 4, that there was less of an effect of preloading in smokers reducing and using acute NRT, than smokers who quit abruptly using patches (Section 4.3.5.1). However, the majority of the reduction group still felt preloading was helpful to them; although the effect of the patch appeared to be non-significant when compared to that of acute NRT.

The difference in emphasis and reported effects of preloading could suggest that the mechanisms of treatment differ when a person is reducing their smoking to quit compared to when they are quitting abruptly. Participants in the abrupt group hypothesised that preloading was used as a form of aversion therapy; this was not the case in the reduction group where emphasis was put on the use of acute NRT as a substitute for cigarettes. This is in keeping with the biological mechanisms of addiction outlined in Section 1.2.3, which suggest that the doses of nicotine delivered in acute NRT, such as gum or inhalator are likely to mirror some of the effects of the nicotine inhaled in cigarettes, by activating AChRs in the brain, leading to a release of DA in the NA (Balfour 1994). This therefore, at least partially, satisfies the urge to smoke without smoking a cigarette. If this is the primary mechanism of action when reducing, then use of patches in these circumstances may be questionable. However these reflections by participants are only based on their own conscious awareness; there may have been unconscious benefits of the patch in both the abrupt and reduction arms. Also, participants in the abrupt quitting arm did not use acute NRT pre-quit, and it is possible that if they had this would have been viewed similarly to how it was in the reduction arm. If either, or both, of these possibilities are true then preloading mechanisms of action across trial arms may be more similar than participant responses suggest.

Side-effects of NRT were a commonly reported problem across study arms. These are issues that are known to commonly occur (through research studies and anecdotal evidence) when using NRT, such as skin irritation, sleep disturbance and trouble getting the patches to stay on, whether use is before or after the quit attempt (Campbell 2003; Schneider et al. 2004; Ebbert et al. 2007). Although these findings are nothing new they could affect adherence to

preloading. However despite this and participants' experiences of nausea, levels of adherence to the preloading treatment were still reported to be high and it was judged as helpful to the quit attempt. Therefore the reason why quitters cited NRT problems less frequently than non-quitters is not immediately obvious. It may be that quitters merely down played their own problems with the NRT, or that there was a lack of effect in some participants due to difficulty in keeping the patch stuck to the skin. Although until recently there were warnings against using NRT whilst smoking, and only one participant had previously used the approach, the majority of participants reported that they were happy to accept the advice of their research nurse, and partake in the preloading treatment. RRT should allow for the quantitative comparison of NRT side-effects with adherence rates, in an attempt to ascertain why NRT issues may have been noted more frequently in non-quitters than quitters.

5.4.2 Study strengths

A major benefit of studies such as this is it gives the opportunity to explore a subject where little information is already available, without constraining data analysis within the boundaries of what is already 'known'. During the interviews participants were given opportunities to raise any issues that they felt poignant and were encouraged to expand on these. As the study was run alongside RRT it also gave the opportunity to ask about the wide variety of methods that were used in the study, and allowed for comparison across arms, as well as comparison between quitters and non-quitters. The ability to compare, through the use of charting, is one of the strengths of the Framework approach (Ritchie & Spencer 1994).

5.4.3 Potential weaknesses

A potential weakness of the study was that interviews were carried out 5 weeks post-quit, so that some responses were based on retrospective recall. This could mean that accounts were clouded by memory loss or subsequent experiences of quitting. For example, quitters appeared to find preloading, monitoring and post-quit preparation a more significant part of their attempt than non-quitters. As stated above this could suggest that these factors influenced efficacy, but could also simply be that non-quitters were less likely to highlight any positives of the method. This is not supported by the finding that non-quitters in the reduction arm were still happy with the method that they used, however it needs to be given consideration when interpreting these results. Also, participants were asked which method they would have chosen pre-quit and which method they would use if they were to quit again. Again we could expect the first response to be clouded by the latter; however the results suggest that this wasn't the case, as many participants' responses differed across questions. As a way to eliminate this potential bias it would perhaps have been beneficial to interview participants at different stages of their quit attempt. This would however have lead to more intensive input from participants into the existing schedule of weekly appointments and daily diary completion, and would most likely have reduced recruitment rates into the interview study considerably.

Unfortunately we were unable to interview a participant who had used the HR-D method, as only a small number of people chose this approach, and those who did were not contactable. However due to the design of RRT there was bound to be variation in the number of participants choosing each reduction method. The lack of HR-D participants merely reflects

that this method was unpopular, as discussed in Section 5.3.4.1. The sample is also limited by the fact that the majority of participants were recruited from Warwickshire PCT, which is ranked as an area of 'very low' deprivation (Health Protection Agency 2011[a]), whereas South Birmingham is ranked as 'high', with 100% of the population living in urban areas (Health Protection Agency 2011[b]). Again this is a reflection on the relative ease of recruiting practices and patients from Warwickshire PCT to take part in RRT, and needs to be considered when generalising the results to other quitting smokers. Similarly the characterisitics of those RRT participants who agreed to be interviewed and took part in the interview study may differ from those who did not take part. However, caution needs to be exercised when generalising from the findings of any qualitative research, as samples are rarely indicative of the larger population; instead the emphasis should be on gaining insights into behaviour, with a focus on individual differences. If desired these can then go on to be tested before generalisation occurs.

5.4.4 Implications for research

As briefly touched upon above, something that should be taken into account regarding participants' responses to our interviews, as in any research that relies on participant response, is that they are reflections on what participants believe to be true, but may not be mirrored by objective measures. These reflections are useful as they give insights into what may be the case when measured more objectively, but also what is of importance to the service user, and so could affect things such as service uptake and adherence rates. Further investigation would be beneficial to test the insights that emerged through these interviews, some of which were proposed throughout Section 5.4.1. Other examples are that secondary outcomes of RRT

could be used to ascertain whether confidence levels changed over the pre-quit period and whether this differed between arms, thereby testing the assertion that smokers in the reduction to quit arm felt more confident as they reduced. Secondly, participants' explanations suggest that the mechanisms of preloading may differ when carried out alongside reduction and abrupt quitting. It may be possible to test this to some extent using RRT, as we shall be able to compare saliva cotinine levels and reports of nausea across the abrupt and reduction arms. It will be difficult to tease apart the mechanisms using measures of cravings as both routes would be likely to lead to a reduction in these, but in different ways. Preloading's mechanisms of action are likely to influence the type of NRT best used to preload, and so the relative efficacy of different types of NRT could help to indicate the mechanisms at work. The best way to objectively test the optimum use of NRT when preloading, during smoking reduction, would be to conduct a randomised controlled trial comparing the use of patch alone, patch plus acute NRT, and acute NRT alone.

5.4.5 Implications for practice

Differences in the perceptions of all the methods across individuals, suggest that an approach which may be helpful to one participant may not be helpful to another, and therefore choice could be beneficial. This choice would also be likely to appeal to service users, and therefore may mean that more people choose to quit through the NHS SSS. The finding that participants who unsuccessfully quit abruptly were keen to try another method next time, rather than doing the same thing again, also suggests that if reduction were offered service users may increase. The popularity of reduction even in those who failed to quit using the method suggests that this popularity may be more enduring than that of the abrupt approach.

Again, this would make service users who fail to quit more likely to go on to use the service again.

However the approach that a reduction method should take is still not entirely clear. The interview findings suggest that the SR, HR-E and SFP methods are all helpful and feasible approaches, but research still needs to be carried out to see whether these methods result in comparable quit rates. If that were the case then we would recommend that service users be given a choice of the three methods. However, it could put some quitters at a considerable disadvantage if any of the methods were significantly less successful than the others.

Many participants (particularly quitters) in both the abrupt and reduction to quit groups stated that they found some element of monitoring useful, whether this was in the form of regular measurement and recording of CO, cpd and/or attitudes toward quitting. As there is little reason to think that a focus on this component of a quitting method would be damaging we would recommend that this is taken into consideration when designing any method of quitting. Although findings suggest that participants found preloading helpful, and those that quit felt more effects, limitations of the method mean that these need to be taken into account alongside more objective measures of treatment efficacy before any recommendations can be made for use in clinical practice.

CHAPTER 6: CONCLUSIONS

6.1 A Summary of the thesis

Chapters 2 to 5 of this thesis each document a piece of research, and as such incorporate their own discussion points and conclusions. These conclusions are summarised in Table 8. The aim of this final Chapter is to revisit these conclusions, consider them in light of one another, and to relate them back to the original research objectives. These objectives were originally set out in Section 1.6 and were as follows:

1) To assess the relative efficacy of reduction to quit compared with abrupt cessation;
2) To assess whether nicotine preloading enhances abstinence rates relative to the use of NRT post-quit day only, and the means by which preloading enhances efficacy;
3) To explore the experiences of smokers who use reduction to quit, abrupt quitting and nicotine preloading, to ascertain the popularity of these approaches, and to gain insight into the best method(s) of implementation, and potential mechanisms of action.

Chapter 2 detailed a literature review, which supplied the justification for a new RCT comparing the efficacy of abrupt quitting and smoking reduction to quit. The protocol for the proposed trial, which will contribute to the fulfilment of objectives of 1) and 3), followed.

Table 8: Conclusions from Chapters 2 to 5

Chapter	Conclusions
Chapter 2	• A preliminary review of existing trials showed evidence that neither abrupt quitting nor reduction to quit provide superior quit rates. However, they had small sample sizes, were not reported according to recently accepted standards (Moher et al. 2001; West et al. 2005), and do not report on mechanisms of action. We therefore concluded a new trial was required. • Based on preliminary reviews, we concluded that smoking reduction is most likely to succeed and lead to cessation if supported by pre-quit NRT, and that using NRT prior to quitting abruptly may promote abstinence. Therefore, we determined that the control group- following an abrupt quitting protocol- should also use nicotine preloading to balance any effect of preloading across conditions. • Preliminary trial evidence suggests that reduction to quit is most effective when reduction takes place over weeks rather than months, and so the trial protocol proposes rapid two week reduction.
Chapter 3	• A meta-analysis of RCTs comparing abrupt quitting with reduction to quit suggests that the quit rates from either approach are similar. • There was no evidence that either reduction or abrupt cessation was more effective when examined in sub-group analyses of trials that provided self-help versus more intensive behavioural support, or pre-quit NRT versus no pre-quit NRT in the reduction arms. • There was insufficient evidence that reduction, typically supported by NRT, led to more adverse events than abrupt cessation. Trials reported adverse events differently, which made drawing conclusions difficult. A meta-analysis of trials of NRT versus placebo for smoking reduction shows strong evidence that NRT assisted cessation is safe (Moore et al. 2009). • Findings are not consonant with data from observational studies (Cheong et al. 2007; West & Fidler 2011), which show that people who reduce to quit, rather than quit abruptly, are much less successful. One explanation might be that efficacy depends on the method used to reduce.
Chapter 4	• The updated meta-analysis of eight RCTs, comparing nicotine preloading to controls, found a very weak non-significant effect of preloading on abstinence, in contrast with previous meta-analyses. However, although this provides no support for routine use, it is not possible to conclude that the preloading is ineffective due to high heterogeneity. • Sub-group analysis, by type of NRT, showed evidence of a larger effect of patch than acute NRT at short-term follow-up. However there was no strong evidence that patch was more effective than acute NRT at long-term follow-up. • We examined evidence that the effect of preloading was mediated through reducing the reward of smoking, increasing confidence in quitting, or increasing adherence to medication. The evidence suggested that preloading did not increase confidence and lead to increased post-cessation adherence. There was slight evidence that preloading reduced reward from smoking. The evidence was clouded by lack of reporting of mediators. • No substantial evidence of moderators of the effect of preloading were found. There was little evidence that intensity of behavioural support influenced treatment success. Adherence to preloading treatment appeared high, perhaps suggesting that smokers are happy to smoke and use NRT at the same time, despite previous warnings not to do so.
Chapter 5	• Quitting methods used in RRT (abrupt, reduction- SR, HR and SFP) appear to be feasible, understandable, and perceived as useful. However preference for a method and reasons for this varied, suggesting that there is a demand for a variety of quitting options. When a choice was given to reduce by easier or harder cigarettes first, choosing harder was largely unpopular, suggesting that this approach may not improve uptake to services if offered. • When asked to choose a method to quit should they relapse, successful quitters said they would use the same method again. However people randomised to abrupt and reduction, who failed to achieve abstinence, said they would try reduction to quit. Perhaps because people see achieving reduced smoking as a success. If reduction were offered as part of the NHS SSS this approach could encourage more people to re-use the SSS if not successful, and might be most enduring. • Smoking reduction necessarily involves self-monitoring of smoking behaviour, whereas abrupt quitting does not. However in RRT, even those following the abrupt programme self-monitored. In both arms participants reported that self-monitoring and consequent mental preparation for quitting was useful. Regardless of the method used, including a period of self-monitoring could enhance the efficacy of behavioural support programmes. • Participants advanced two explanations for the efficacy of preloading. Firstly that it reduced cravings and secondly that it was aversive, making smoking unpleasant. No studies in the preloading review (Chapter 4) reported the degree to which participants found smoking aversive and so future studies should examine this. However aversion was reported mainly in the abrupt arm. If this is the mechanism, it suggests that only non-reducing preloading is likely to result in a benefit, and there was weak support for this in Chapter 4.

Chapter 3 is a systematic review and meta-analysis of existing trials comparing abrupt quitting and reduction, and so the results also contributed to objective 1). Chapter 4 reported a similar literature review and meta-analysis, however the aim of this was to fulfil objective 2), by using existing trials to compare nicotine preloading treatment to placebo, or no pre-quit nicotine treatment. Finally Chapter 5 explored the results of the interview study outlined as part of the trial protocol in Chapter 2, in order to fulfil objective 3). As a result my overarching conclusions are as follows.

6.2 Both abrupt quitting and reduction to quit should be offered as quitting options by smoking cessation services

In the past trials comparing smoking reduction to quit and abrupt quitting have had small sample sizes. By conducting the meta-analysis reported in Chapter 3 we combined these studies to come up with a summary effect estimate, with an N of 3760. This effect estimate suggests that neither approach is superior to the other. This provides support for the use of either or both approaches by smoking cessation services, both inside and outside the NHS; although a comparison of the cost-effectiveness of these approaches would also be beneficial. The main aim of the NHS SSS in offering a reduction to quit approach would be to draw in people who would only use reduction, and therefore increase the reach of behavioural support. However because people who would have used abrupt cessation might choose reduction to quit instead, this necessitates trials to test the relative effectiveness. The participants included in our meta-analysis were randomised to either reduction to quit or abrupt quitting and therefore provide no information about whether smokers would actually choose either approach if both were on offer. Surveys of smokers have previously found that a number of

smokers quitting without support plan to, or have chosen to take a reduction approach (Hughes et al. 2006; West 2008). Findings from the RRT interview study, reported in Chapter 5, add to this, as questioning took place within the context of a supported quit attempt. We found that different people favoured different approaches, with a demand for both abrupt quitting and reduction to quit methods. Not only this, but the methods used in RRT were judged to be both feasible and understandable. This suggests that if offered smokers would take up a reduction approach to quitting, and that this wouldn't then overshadow the popularity and uptake of the abrupt method. It should be taken into account that, although the participants specified preferences, they had all agreed to take part in the trial, which necessitated agreement to be randomised to either approach. However, some participants specified that they would have preferred to have a choice of methods, so by offering this, services such as the NHS SSS are likely to appeal to more smokers, and attract smokers who would not otherwise have used behavioural support and perhaps medication. At present a feasibility pilot is being carried out in the NHS SSS, on behalf of the Department of Health, of a menu of quitting options available to smokers (Routes to Quit), including the following approaches:

- Abrupt quitting (as currently provided);
- Rapid reduction (for up to 4 weeks before quitting);
- Medication only (without a behavioural support programme);
- Gradual reduction (for up to 36 weeks);
- Self care (verbal and written advice and an open door policy for future support).

Service users are offered the abrupt approach first but if it is refused are offered the next method in the list, and so on, as above (Robinson 2010). The findings of the pilot will be a valuable means to assess the opinions of both service users and providers of the combination of approaches, within a pragmatic setting.

Our interview study also uncovered another potential mechanism by which offering a reduction option could increase use of the NHS SSS. Although quitters who quit abruptly said they would not wish to use the same method to quit next time, those who used the reduction method said they would use it to quit again. If this is mirrored outside this study then at present smokers who unsuccessfully quit abruptly through the NHS SSS have no alternative to turn to for their next attempt, and so may be unlikely to revisit the SSS (although, as previously mentioned in Section 1.4 this is contrary to surveys which have found that satisfaction with the NHS SSS is generally high (May et al. 2009; May & McEwen 2011). However, if reduction were offered as an alternative then unsuccessful quitters using either the reduction or abrupt approaches may still feel inclined to use the services again, and opt for the reduction method, giving the services a more enduring popularity with individuals. As the NHS SSS has been found to achieve quitting success rates of almost four times as high as when smokers seek no support to quit (West 2010), any action which could potentially encourage more people to use services, and keep using these services in the wake of an unsuccessful quit attempt, would be beneficial.

However there are two caveats to these conclusions. Firstly that none of the trials included in the meta-analysis in Chapter 3 were non-inferiority trials. Therefore the strength of the

conclusion we can draw is limited to the fact that neither reduction to quit nor abrupt quitting had superior quit rates. Only a dedicated non-inferiority trial will be able to tell us whether reduction is non-inferior to abrupt quitting (within a pre-specified margin of non-inferiority). Thus we designed RRT (protocol reported in Chapter 2) which- as well as following recognised trial and smoking research guidelines (for example Moher et al. 2001; West et al. 2005) to ensure high quality- is powered to detect non-inferiority, and therefore will provide a valuable addition to the existing literature. It needs to be taken into consideration however that to ensure feasibility of the trial the non-inferiority margin is fairly large, so that the trial will only be powered to detect non-inferiority of up to 9.5%. In some cases if a method was found to be 9.5% less effective than another this may be deemed as a significant difference, however in this case we believe that a difference this large would not deter the NHS SSS from utilising reducing smoking to quit as well as abrupt quitting. Nevertheless, non-inferiority need not be essential to the provision of a gradual approach to quitting, as the extra people that it may bring into services could outweigh a reduced success rate, leading to an increase in those quitting smoking overall. However if non-inferiority is not achieved it is only fair to make those quitters who do not have a firm preference for either method aware that one approach is more successful than the other, so that they are fully informed before making a decision about which way to quit.

Secondly, all the studies included in the meta-analysis (Chapter 3), were RCTs and provided participants with either self-help therapy or behavioural support. As previously mentioned (Section 1.4.2) observational studies have found that reducing to quit without support, does not give the same success rates as abrupt quitting (Cheong et al. 2007; West & Fidler 2011).

Therefore although the evidence presented in this thesis provides support for the use of both methods through smoking cessation services, at present there is little support for the use of reduction to quit by those who do not seek support, and so we should be specific about the way that reduction to quit is recommended to the general public. It seems likely that one of the key issues is that reduction should lead to a quit day. It is notable that this was a feature of all the trials reviewed in Chapter 3.

6.3 More research is needed into how people should be advised to reduce their smoking

As described above, this thesis provides evidence that reducing smoking to quit is a method worthy of consideration, for use by the NHS SSS. However the literature reviews carried out in Chapters 3 and 5 show that there are many possible ways that this reduction could be carried out, and that these different methods may have varying rates of success. The difference in the conclusions of RCTs and observational studies, comparing reduction to quit to abrupt quitting, supports this. Section 5.1.2 documents the very limited research that has been carried out comparing different approaches. More needs to be done to ensure that if reduction to quit services are adopted by smoking cessation services they are designed in a way that optimises success. The findings reported in Chapter 5 suggest that overall the SR, HR and SFP methods were all generally liked and feasible, however there may be some elements that are more favourable to a user than others, for example, cutting out harder cigarettes first was considerably less popular than cutting out easier ones first. Although user opinion such as this is important when designing an intervention it needs to go hand in hand with accurate effect estimates. It is possible that it is advisable to tackle difficult cigarettes

first, and with strong encouragement and support patients could be encouraged to reduce using this unpopular method.

Further research comparing the efficacy of different reduction to quit approaches is necessary; in particular we are unaware of any study that has compared the efficacy of a cpd and sfp approach to reduction. Although participants in RRT are carrying out variants of both methods, they were not randomised to these, and the trial is not sufficiently powered to make this comparison. On the other hand there could be barriers to carrying out an RCT of this sort. A recruitment criterion for all RCTs is that participants are happy and suitable to be randomised to any study arm. However different reduction methods are likely to suit different types of people; for example the SR method might be hard for someone who has a job to carry out, as they may find it hard to smoke on each ICI due to inference with job tasks or smoke-free laws. This may limit the number of people who could be recruited into the study, making it hard to reach recruitment targets, and limiting the generalisability of the findings.

Another way to gain insight into ways that an intervention could be manipulated to achieve optimal success is by investigating possible mediators and moderators of the effect. The mediators and moderators of the effects reported in Chapter 3 were not investigated, as this is beyond the scope of a Cochrane Review. However, although data concerning this, in the reports of included studies, appears sparse we do plan to formally extract the relevant data to see whether these can be combined and analysed, and if any conclusions can be drawn. A mediation analysis is also planned as part of the analysis plan for RRT. This should help to establish, whether reduction works by manipulating the neuropsychological pathways of

addiction, as proposed in Section 1.2.2, or whether it works by increasing self-efficacy pre-quit, which some participants suggested was the case in Chapter 5 (Section 5.3.3.3). It could also be used to strengthen the observational efficacy data, from the SR, HR and SFP study arms. If abstinence outcomes provide evidence that one of the reduction methods is more successful than the others, and this is supported by complementary changes in mediators, this provides stronger evidence that enhanced efficacy is due to features of the method, rather than differences in participants across methods.

If analyses of the sort proposed here were carried out we may gain an indication of whether one reduction method is considerably more successful than any other, and if so should be used singularly alongside abrupt quitting, or whether a number of approaches result in similar quit rates, and so a menu of options would be more appropriate. We found from our interviews (Chapter 5), that being able to make choices about the method used to quit was valued greatly by participants, and so offering this may present another opportunity to encourage more people to use SSS.

6.4 Further research is needed before nicotine preloading is recommended and used in practice

We also propose that more research is needed investigating nicotine preloading, before it is recommended to the general population and offered as part of SSS, for the following reasons.

6.4.1 Efficacy of preloading is still uncertain

Our Cochrane Review (Chapter 3) suggested that neither abrupt quitting nor reduction to quit was more successful whether participants used acute NRT pre-quit or not, and previous research suggests that concurrent smoking and NRT use is safe (Fagerstrom & Hughes 2002; Stead et al. 2008; Moore et al. 2009). However this cannot tell us the efficacy of NRT preloading relative to standard use of NRT. Whilst previous meta-analyses (Shiffman & Ferguson 2008; Stead et al. 2008) found a significant benefit of using NRT pre-quit, our updated meta-analysis (Chapter 4) found no such effect; although a sub-group analysis showed some evidence of a small but significant effect of nicotine patch preloading, at short-term follow-up only.

However, it would be wrong to dismiss preloading, because the summary estimate might be misleading. The meta-analyses in Chapter 4 showed considerable heterogeneity, which was not eliminated by splitting trials into the patch/acute NRT sub-groups. Despite investigations of mediators and moderators, and suggestions by Rose (2011), described in Section 4.5, we were unable to identify a likely source of this heterogeneity. Additionally many participants from the RRT interview study (Chapter 5) reported that they experienced effects of preloading, such as nausea and loss of the will to smoke, and despite the fact that some of these were unpleasant they judged preloading as helpful to their quit attempt, and reported high adherence (high adherence was also found in studies included in the meta-analysis in Chapter 4). Taken together we believe that the previous favourable meta-analyses, the heterogeneity in our more recent meta-analysis, and the encouraging response from treatment users provide justification for a further trial of nicotine preloading. This has been planned and

recently approved by the National Institute for Health Research (NIHR), and will have almost two thirds of the participants (N=1786) included in the most up-to-date meta-analysis (N=2813).

6.4.2 The cause of the heterogeneity in preloading trials (Chapter 4) needs to be established

As raised above we were unable to establish the cause of the heterogeneity present in the preloading meta-analysis (Chapter 4), however as mentioned in Section 4.1 and Section 6.3 in the context of reduction to quit methods, knowing the cause of this heterogeneity and therefore potential moderators of the effect, could inform the best ways to offer or manipulate treatment to secure the best quit rates. Mediators could also be used to do this; however there was also insufficient evidence to support any mediational pathways. The lack of good evidence for any of the mediators and moderators investigated in Chapter 4 may be because these factors did not influence the effect, but may also, at least partly, have been due to the standards of reporting, and that these differed across studies. For example, only a small effect, if any, was seen of preloading on pre- and post-quit cravings. This could suggest that preloading does not influence the neuropsychological mechanisms of addiction, described in Section 1.2.3; however based on the low quality of evidence we think that it is premature to draw this conclusion.

One potential mediator of the effect of preloading, which was not investigated in Chapter 4, was nausea, and this leads to the hypothesis that nicotine preloading may act as a form of

aversion therapy. This hypothesis was put forward by the participants of the RRT interview study (Chapter 5), who quit smoking abruptly. Loss of craving was also observed as a result of treatment by participants in both the abrupt and reduction arms. This would suggest that mechanisms such as these afford further study. For example, it may be possible to measure whether aversive conditioning has taken place under experimental conditions, by exposing smokers undergoing preloading and control treatment to smoking paraphernalia and/or cues pre- and post-quit, and measuring whether these invoke negative emotional and commensurate biological responses (such as sympathetic activation). The hypothesis that preloading works as aversion therapy was supported by RRT abrupt participants' claims that they reduced their cpd pre-quit, despite instructions to maintain their smoking rate. However, participants in the abrupt cessation arms of three trials included in the analysis in Chapter 3 also reduced their cigarette consumption, despite not using NRT (Flaxman 1978; Cummings et al. 1988; Cinciripini et al. 1995). This suggests that reduction is behaviour common to smokers about to quit regardless of the aversiveness of smoking. In the two studies (Flaxman 1978; Cinciripini et al. 1995) where it could be measured, the reduced consumption was not as great as was witnessed in the reduction arms of the study, but its presence, in spite of the lack of preloading, may point to another reason for this reduction. By looking at quantitative reports of cpd reductions in RRT we should be able to compare the extent of reduction in the abrupt arm with that in the reduction arm, and also to that in the Cochrane studies. If the reduction is greater than in the Cochrane studies it may suggest that this was at least partially mediated by nausea. However a comparison across studies, such as this, would only be able to provide very weak evidence.

The evidence that participants reduced in both reduction and abrupt quitting arms of studies (Chapters 3 and 5), and that neither approach had superior quit rates (Chapter 3) suggest that the abrupt quitting and reduction to quit methods may not differ as much in practice and effect as they do in their instructions. Along with the limited conclusions that can be drawn about the success of nicotine preloading, at present we are unable to present interventions that will provide quit rates greater than those already available. However providing smoking reduction methods in the NHS SSS may still increase overall population quit rates. If, as Michie (2009) proposed, reduction provides a goal which is in the first instance more in-line with current behaviour, then it could, if offered, both encourage more people to quit in the first place, and encourage those people who would like to reduce, or merely want to be offered a choice, to use behavioural support. This could in turn increase the likelihood that they would use medication to aid their attempt. There is evidence that both of these enhance success (Lancaster & Stead 2005; Stead et al. 2008). Anything, such as this, which can improve the rate of decline in smoking prevalence, will improve our chances of meeting the DoH's target (presented in Section 1.1) to reduce smoking prevalence to 10% by 2020.

APPENDIX 1: PUBLISHED RRT PROTOCOL (LINDSON ET AL. 2009[a])

Trials

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Study protocol

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Rapid reduction versus abrupt quitting for smokers who want to stop soon: a randomised controlled non-inferiority trial

Nicola Lindson*[1], Paul Aveyard[1], Jackie T Ingram[1], Jennie Inglis[1], Jane Beach[2], Robert West[3] and Susan Michie[4]

Address: [1]Primary Care Clinical Sciences, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK, [2]Public Health Nurse Specialist, South Birmingham Primary Care Trust, 6th Floor Triplex House, Eckersall Road, Kings Norton, Birmingham, B38 8SS, UK, [3]Health Behaviour Research Centre, Department of Epidemiology and Public Health, University College London, 2–16 Torrington Place, London WC1E 6BT, UK and [4]Centre for Outcomes Research and Effectiveness, Department of Psychology, University College London, 1–19 Torrington Place, London WC1E 7HB, UK

Email: Nicola Lindson* - nll839@bham.ac.uk; Paul Aveyard - p.n.aveyard@bham.ac.uk; Jackie T Ingram - j.t.ingram@bham.ac.uk; Jennie Inglis - j.inglis@bham.ac.uk; Jane Beach - jane.beach@sbpct.nhs.uk; Robert West - robert.west@ucl.ac.uk; Susan Michie - s.michie@ucl.ac.uk

* Corresponding author

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Abstract

Background: The standard way to stop smoking is to stop abruptly on a quit day with no prior reduction in consumption of cigarettes. Many smokers feel that reduction is natural and if reduction programmes were offered, many more might take up treatment. Few trials of reduction versus abrupt cessation have been completed. Most are small, do not use pharmacotherapy, and do not meet the standards necessary to obtain a marketing authorisation for a pharmacotherapy.

Design/Methods: We will conduct a non-inferiority randomised trial of rapid reduction versus standard abrupt cessation among smokers who want to stop smoking. In the reduction arm, participants will be advised to reduce smoking consumption by half in the first week and to 25% of baseline in the second, leading up to a quit day at which participants will stop smoking completely. This will be assisted by nicotine patches and an acute form of nicotine replacement therapy. In the abrupt arm participants will use nicotine patches only, whilst smoking as normal, for two weeks prior to a quit day, at which they will also stop smoking completely. Smokers in either arm will have standard withdrawal orientated behavioural support programme with a combination of nicotine patches and acute nicotine replacement therapy post-cessation.

Outcomes/Follow-up: The primary outcome of interest will be prolonged abstinence from smoking, with secondary trial outcomes of point prevalence, urges to smoke and withdrawal symptoms. Follow up will take place at 4 weeks, 8 weeks and 6 months post-quit day.

Trial Registration: Current Controlled Trials ISRCTN22526020

Background

Without help, most smokers who try to stop smoking relapse within one week and only 4% of quit attempts sustain abstinence for one year[1]. The best treatment results in about 22% one year prolonged abstinence[2], and the UK National Health Service (NHS) specialist stop smoking services achieve around 15% one year abstinence[3]. NHS support in primary care achieves around 7% one

year prolonged abstinence[4]. Thus, while treatment improves substantially the number who achieve abstinence, whatever method of stopping is used, return to smoking is the norm for the majority and, even with treatment, the majority of relapsers resume smoking during active treatment. Thus we have a cadre of patients who have been through treatment services many times. Currently, the NHS gives the same treatment on repeated attempts to stop as on the first attempt. Patients often choose different pharmacotherapies, but in other respects, the treatment is the same every time. A common sense view is that offering repeated courses of identical treatment that failed previously might be less effective than trying different treatment. Rapid reduction might offer a new way to quit to those who have failed previously.

The standard assumption of all smoking cessation treatment is that cessation begins on a quit day and cutting down prior to quitting is not advised. This is because of the belief that with reduction each remaining cigarette will become more rewarding and harder to give up and in the meantime the smoker will suffer a loss of motivation before reaching the point where total abstinence is attained.

Smokers, however, feel that cutting down is an appropriate way to stop smoking. In the English Smoking Toolkit Study, 57% of current smokers reported they were cutting down, of whom 26% were using nicotine replacement therapy (NRT) to assist in this[5]. 40% of quit attempts were made by cutting down first. A review of epidemiological studies suggests that cutting down does not deter people from cessation, but is associated with an increase probability of trying to quit[6]. A survey of respondents to an advertisement of people interested in cessation found that 66% planned to stop by cutting down gradually, while 13% planned to stop abruptly. In a second survey of people who responded to an advertisement for those planning to reduce smoking, 57% planned to reduce then stop[7]. A survey of American daily smokers showed that 35% tried to stop gradually while 65% tried abruptly on their last attempt[8]. Those who chose gradual cessation were as motivated to stop and as confident of success as those who used abrupt cessation. They had the same level of dependence. A recently published random sample of American smokers showed that nearly half of smokers planning to quit would choose reduction over abrupt cessation and two thirds of these were interested in using medication to assist this[9]. In these smokers, there was little interest in reduction as an end in itself, only as a means to stop. Even among reducers not planning to stop soon, cessation was the goal of half. People who want to use gradual cessation to stop smoking soon have no NHS treatment programmes to assist with their attempt. Thus reduction as a means of stopping is likely to be popular, as well as providing another option for smokers who have tried and failed to stop previously.

Literature Review

Observational studies have reported that those using gradual cessation were less likely to succeed than those using abrupt methods[10,11]. One reason may be, that those who chose gradual cessation as a means of quitting were less motivated to stop[12]. We therefore sought to find randomised trials. Based on Medline, Google Scholar, Psych Abstract, Society for Research on Nicotine and Tobacco abstract search, and a citation search plus contact with key authors, we identified the following trials as the only trials of abrupt and rapid reduction.

Marston & Mcfall randomised 65 students to one of four behavioural treatments, of which two were gradual reduction and abrupt cessation, but did not report smoking cessation rates[13]. In Gunther's trial, 55 smokers were randomised to reduction over five weeks and 55 to abrupt cessation after five weeks of behavioural support, followed by a further seven weeks of support[14]. The trial reports only relapse rates, but it is possible to calculate the relative risk (RR), 95% confidence intervals (CI) for unconfirmed undefined point prevalence abstinence at 12 months, which is 0.86 (0.44–1.68). Cinciripini randomised 128 people into four groups, scheduled reduction, non-scheduled reduction, scheduled smoking prior to quitting but no reduction, and normal smoking[15]. Baseline smoking rate was reduced by a third each week over three weeks. All groups received identical post-cessation cognitive behavioural therapy. The confirmed prolonged abstinence rates at 12 months were 44%, 18%, 32%, and 22% respectively. The Mantel-Haenszel (M-H) RR (95% CI) for reduction versus abrupt cessation is 1.14 (0.66–1.97). Flaxman randomised 64 participants to a 4 × 2 factorial trial[16]. Of relevance, two of the arms were gradual reduction and two abrupt cessation methods (crossed with aversive smoking, no aversive smoking). Post-cessation behavioural support was provided in each arm. The M-H RR (95%CI) for reduction versus abrupt cessation is 1.00 (0.47–2.13) for undefined unconfirmed point prevalence at six months. Cummings randomised 1895 smokers to a 2 × 2 factorial trial of daily versus unstructured self-help crossed with gradual versus abrupt quitting plan[17]. For unvalidated prolonged abstinence at six months, the M-H RR (95%CI) is 1.45 (0.87–2.42) for gradual cessation, based on exclusion of the 19% lost to follow up. The rates of loss were reported as 'fairly similar' in each arm. Cinciripini has recently completed a 3-arm study with participants randomised to cutting down with scheduled smoking and nicotine patch, nicotine patch pre-cessation treatment without reduction, or usual post-cessation patch only[18]. The results are unpublished, but preliminary data show improved cessation for

the reduction arm at four weeks but no evidence of difference between the arms in abstinence at six months. The reduction arm had lower craving, fewer lapses, and less negative affect (personal communication). Hughes is also conducting a trial of reduction versus abrupt cessation with no results as yet.

A second group of studies have led to a new use of NRT for gradual cessation in a programme called Cut Down Then Stop (CDTS). Critically, the CDTS trials enrolled smokers who wanted to reduce their smoking but did not intend to stop it in the next one or six months. They were randomised to either NRT or placebo. The treatment programme gives NRT over 6–9 months for reduction and for a further three months post-cessation. The CDTS NRT programme led to improvements in six month prolonged abstinence over placebo (7% versus 3%), an RR (95%CI) of 2.06 (1.34–3.15)[19]. Six months prolonged abstinence is a standard accepted for evidence of effectiveness in smoking cessation[20]. Half of those who sustain abstinence for six months remain abstinent for their whole lives[21]. These cessation rates are lower than those achieved by the NHS smoking cessation services[22]. The key point is that these were rates achieved in smokers who said that they did not intend or want to stop imminently (and who were on average highly addicted). It is possible that the different intentions of smokers enrolled in CDTS trials and those that use the abrupt quitting method offered by the NHS explains the difference in prolonged abstinence rates (7% versus 18% six months prolonged abstinence). The CDTS studies demonstrate that reduction with NRT is more effective than without, but cannot show whether reduction or abrupt cessation is more effective.

The positive effect of pre-quit NRT has also been discovered in trials utilising the abrupt method of cessation, as outlined in the recent Cochrane review, which summarised trials that gave NRT patches for two weeks prior to quit day in addition to after cessation. The RR (95% CI) was 1.79 (1.17–2.72) compared with usual post-cessation use only[23]. In all these pre-cessation trials, NRT patch was used. Two studies used nicotine gum, with less effect[24,25]. Shiffman and Ferguson conducted a meta-analysis of four studies (three in the Cochrane review and one other) that all used pre-cessation patch treatments (1 of the studies used pre-quit nicotine patch (PQNP) for 4 weeks and the remainder used PQNP for 2 weeks). PQNP significantly increased the odds of abstinence both 6 weeks after quit date (Odds ratio (OR) = 1.96), and at 6 months (OR= 2.17)[26]. Participants were twice as likely to quit if they used PQNP, when compared to participants who started nicotine patch treatment on their quit day. Additionally post hoc observations found that in 3 of the 4 studies (relevant data were not available for the fourth study) participants treated with PQNP spontaneously reduced the amount of cigarettes they smoked, and those who reduced more of their own accord were more likely to quit. This may be because these participants were more responsive to treatment or could be further evidence that reduction can increase the chances of success in smoking cessation.

There are psychological principles that suggest that reduction might be more effective than abrupt cessation. One is shaping, obtaining a target behaviour (not smoking for the rest of one's life) by making successive approximations of the target behaviour (gradual cessation produces progressively longer periods of abstinence). The second is the cognitive psychology principle that completing a step toward a goal (reducing cigarettes per day) increases self-efficacy that increases the likelihood of completing the goal (abstinence). The third is classical and operant conditioning principles that decreasing the association of environmental cues (conditioned or discriminative stimuli) and a behaviour weakens the behaviour (smoking reduction typically uncouples cues from smoking). The fourth is the psychopathology principle that lowering drug intake reduces drug dependence increasing ability to abstain completely.

There is evidence that gradual reduction should be much more rapid than used in the CDTS trials. In one CDTS trial, Haustein (currently unpublished) participants were randomised in a 2 × 2 factorial design of NRT versus placebo and rapid versus slow reduction[27]. Despite enrolling people who said they did not intend to stop smoking in the next month, rapid reduction outperformed slow reduction at the end of trial (12 months from baseline). For confirmed 7-day point prevalence reduction, the M-H RR (95%CI) is 1.01 (0.55–1.84), confirmed prolonged abstinence it is 4.57 (1.00–20.93), and for confirmed prolonged reduction it is 2.69 (1.08–6.68). A pilot study randomised 31 smokers ready to stop to reduce over two weeks or three[28]. The quit rates were slightly higher in the two week group and qualitative data indicated that rapid reduction helped demarcate the boundary between reducing and quitting.

Trial Objectives

Aim

To confirm or refute equivalence of two different behavioural instructions in stopping smoking, namely reduction or abrupt cessation.

Objectives

1) To measure smoking abstinence at 4 week, 8 week and 6 month follow-up in both the abrupt and reduction treatment arms.

2) To investigate possible mechanisms by which the behavioural advice to reduce prior to quit day achieves its effects.

Method

All methods outlined below are in compliance with the Declaration of Helsinki as approved by the National Research Ethics Service (08/H0408/213)

Why a non-inferiority trial?

Given reduction is so intuitive and appealing; it is likely to attract smokers who would have used abrupt quitting had reduction not been available. It is imperative to show that such smokers would not be worse off if they opted for a reduction programme and we propose to test this with a non-inferiority trial. Non-inferiority trials can show superiority but conventional superiority trials cannot show non-inferiority[29]. We propose an unblinded pragmatic trial large enough to show equivalence of the methods.

Inclusion criteria

Participants must meet all of the following inclusion criteria to be eligible for enrolment into the trial:

1. males and females 18 years or older,

2. smokes at least 15 cigarettes or 12.5 grams of loose tobacco daily as roll your own cigarettes, or blows 15 parts per million or above on exhaled carbon monoxide (CO) reading.

3. willing to stop smoking completely in two weeks

4. evidence of a personally signed and dated informed consent document indicating that the subject has been informed of all pertinent aspects of the study and consents to participate and be randomised to either arm

5. be willing and able to comply with all study procedures.

Exclusion criteria

Subjects presenting any of the following exclusion criteria will not be included in the trial:

1. currently using other NRT, bupropion, nortriptyline, mecamylamine, reserpine, or varenicline, or undergoing any treatment for tobacco dependence (e.g. acupuncture),

2. unstable angina pectoris, myocardial infarction, or cerebrovascular accident during the last 3 weeks,

3. severe cardiac arrhythmia

4. currently uncontrolled hyperthyroidism

5. active phaeocromocytoma

6. pregnancy, lactation or intended pregnancy

7. suspected alcohol or drug abuse

8. participation in other medicinal trials within the last three months and during study participation,

9. previously had severe skin reactions to nicotine patches or severe eczema or other skin diseases that make patch use hazardous or undesirable.

10. a severe acute or chronic medical or psychiatric condition or previously diagnosed clinically important renal or hepatic disease, that may increase the risk associated with study participation or may interfere with the interpretation of study results and, in the judgment of the investigator, would make the subject inappropriate for entry into this study.

Withdrawal criteria

Trial Withdrawal: It is standard practice in smoking cessation trials to regard those who fail to attend for support and treatment as having relapsed, which is based on some evidence[20]. Therefore, failure to attend will not count as withdrawal from the trial and the only withdrawals will be those where a patient asks to be withdrawn. Such patients will not be replaced and, unless s/he refuses permission, data available up to that point will be used. Such withdrawals are expected in fewer than 5% of participants. This is standard procedure in smoking cessation studies.

Treatment withdrawal: One of our exclusion criteria is previous adverse reactions to NRT; so given that most smokers have used NRT recently, the established safety profile of NRT and the evidence from trials of combination NRT, we do not expect any serious adverse events due to the medication. Nevertheless, there will be a detailed work instruction for the trial that will detail the weekly assessment of side-effects, and the procedure for serious adverse events (SAE) and suspected unexpected serious adverse reactions (SUSARs). In the event of an SAE or SUSAR that is judged either possibly, probably, or definitely related to NRT, the prescription for NRT will be withdrawn and not re-instituted in that person.

Participant Recruitment

We will recruit participants through South Birmingham, Solihull, Heart of Birmingham and Warwickshire and Worcestershire Primary Care Trusts in several ways. We will request that general practitioner's practices write to patients on their practice lists recorded as smokers and

offer them treatment. We will also request that the stop smoking services write to people on their databases who have tried to stop and failed. The letters sent out will ask those patients who wish to take part in the trial to respond to the research team. In our experience, 5–10% will respond. Finally the trial treatment will also be offered to people booking for treatment with stop smoking services. Following telephone screening for preliminary eligibility, potential participants will be booked in for an assessment visit. Written informed consent will be obtained from participants at the first assessment session before they have been randomised to a treatment arm.

Participants in both treatment arms will be seen weekly for 2 weeks prior to quit day, on quit day, and weekly for 4 weeks post-quit. A further follow-up visit will take place 8 weeks post quit-day and a final follow-up phone call at 6 months. Therefore all participants will be enrolled in the trial for 6 months and 2 weeks.

It is not unusual for people to delay their quit day, once committed, for a variety of reasons, e.g. death of a close family member or friend. In this situation we will allow participants to delay their quit attempt for a maximum of 2 weeks. They will be advised to carry on with their pre quit NRT regime as prescribed and their actual quit date appointment will be recorded as their visit 3 appointment. Extra visits in between week 2 and week 3 will be recorded in the case record form and extra diaries and NRT will be issued to the participants to cover their delay period. Extra visit questionnaires will also be given to the participant for completion. Participants wishing to delay their quit day by >2 weeks will be classified as abandoning this quit attempt, NRT will be ceased and the participant will be advised to contact their local stop smoking service when they are ready to set a new quit date. They will be provided with the name and number of their local stop smoking service.

Allocation to trial arms and treatments

Randomisation

Participants will be seen at an assessment session, similar to that used by stop smoking services, where participants will be randomised 1:1 to reduction or abrupt cessation in the assessment session. We will use Stata to accomplish stratified randomisation by therapist with blocking within each stratum to ensure balance. The blocks will be randomly ordered blocks of 2, 4, and 6. Each therapist will open sealed numbered envelopes in turn after consent and initial procedures to determine allocation to abrupt cessation or rapid reduction.

Participants in the reduction arm will be offered a choice of ways to reduce and asked to choose the method they feel is right for them. Those without strong preferences will be randomised to one of the three reduction methods. We will use Stata to accomplish stratified randomisation by therapist with blocking within each stratum to ensure balance. The blocks will be randomly ordered blocks of 3 and 6. Each therapist will open sealed numbered envelopes in turn after consent and initial procedures to determine allocation to abrupt cessation or rapid reduction.

It is quite likely that we will see couples, friends, or relatives who want to quit together and attend clinic as a group. In this situation they will be randomised together so they go into the same arm and given the same study number but made identifiable by adding an A or B to the end of their number.

Behavioural intervention in the abrupt cessation (control) arm

Participants randomised to abrupt cessation will have a brief discussion about smoking and about the nicotine patch treatment. Participants will be informed that the rationale of wearing the patch is to divorce the cigarette smoking behaviour from its reward (the delivery of nicotine). The relatively high constant level of nicotine is thought to blunt both the pharmacological cue to smoke and the reward from smoking when it occurs. The instruction will therefore encourage the smoker not to reduce consumption at all, even if they feel like smoking fewer cigarettes, because this will work against the stated rationale (not smoking will allow nicotine levels to fall to subnormal (for the participant) levels and create an urge to smoke that will be rewarded by smoking). Patches will be provided for use until the next visit and homework given to identify critical cigarettes, which is the basis for the pre-quit session discussion the next week, used in standard behavioural support. This will be followed by five weekly sessions on quit day and weekly thereafter, following the typical 7-session UK withdrawal orientated therapy programme[30]. Should a participant resume smoking during this treatment, participants will be allowed to renew their quit day following the new NHS standards. From quit day onwards participants in this arm will get combination NRT, meaning patch plus top-up acute product of their choice and be advised to use generous doses of NRT because dose is related to outcome[31] and combination treatment is more effective than patch alone[23]. Combination NRT is standard in our clinics and advised by the National Institute for Health and Clinical Excellence for dependent smokers[32]. Participants will be allowed to choose the type of acute NRT they prefer. Participants will be provided with a diary in weeks 1 and 2 to record the number of cigarettes smoked per day, and whether patches are being used, in week 3 this will be extended to include the amount of acute NRT product used per day.

Behavioural intervention in the rapid reduction (intervention) arm

The rapid reduction arm differs from the control arm only in the advice given in the pre-quit period two weeks before quit day. We will offer one of three reduction methods and the participants who do not have a strong preference for one or other method will be allocated at random to one of the three methods. The therapist will have a second set of sealed envelopes to accomplish this prepared as for the main randomisation. The two methods that focus on cigarettes per day will aim to reduce consumption to <50% of baseline at the end of the first pre-quit week and <25% by quit day.

The three methods are as follows:

a) Scheduled reduction (SR) method. In this method, a median inter-cigarette interval is calculated and then this altered so as to achieve the gradual reduction of cigarettes per day. For example, if a person is typically awake for 16 hours per day and smokes 16 cigarettes per day, then the median inter-cigarette interval is 1 hour. To achieve a 50% reduction, the inter-cigarette interval needs to increase to two hours. In this method, a person must smoke every two hours whether or not they want to do so. If they cannot smoke, that cigarette is missed and the next opportunity takes place two hours later. This method is potentially difficult in a country with smoke-free laws and for people with some types of jobs.

b) Hierarchical reduction. There are two variants: hierarchical reduction- difficult (HR-D) and hierarchical reduction- easy (HR-E). In this method, participants classify their usual cigarettes as either habitual cigarettes or particularly rewarding cigarettes. The HR-D method aims to get participants to reduce smoking by removing the difficult cigarettes first. The rationale is that getting rid of the hardest ones is the most difficult and if this can be accomplished well before total abstinence, this will enhance confidence and reduce the chance of a slip. HR-E is similar to HR-D except that participants seek to avoid smoking less rewarding or easier cigarettes to forgo. The rationale is that this gives participants early initial success and allows them confidence to tackle more difficult cigarettes later. If allocated to hierarchical reduction participants will be able to choose whether they will forgo easier of more difficult cigarettes first.

c) Smoke free periods (SFP). This method is different to all other methods in that it does not focus on cigarettes per day as the marker of reduction. In this method, participants map out their typical day, marking the smoking periods of the day. In a country with smoke free laws, smoking behaviour is concentrated into smoking breaks, except perhaps when at home. The SFP procedure will concentrate on reducing the number of smoking periods over the reduction time. In a smoking period, participants will be allowed to smoke as much as they want, but they will not be allowed to smoke outside the smoking period. The rationale is that smokers typically report few urges to smoke in places where smoking is forbidden, but find that not smoking when it is allowed more difficult. This method provides clear boundaries about when smoking is and is not allowed, unlike all other methods that depend on reducing cigarettes per day except perhaps scheduled reduction. It also focuses participants on what is being achieved- smoke free periods- and not on what is being forgone- cigarettes not smoked.

Each participant will complete a diary recording both the target for that day and a report on whether the participant met that target. In methods that focus on cigarettes per day, participants will be asked to put aside the next day's cigarettes into a separate pack to encourage adherence to the target. Participants will be instructed to replace cigarettes missed with a type of acute NRT (for example nicotine gum) and encouraged to use this sufficiently to avoid smoking more cigarettes than quota or smoking in a smoke-free period. Every evening, participants will record cigarettes smoked, acute NRT used (and the remainder in the packet), and note issues in a free text field. In a current trial, we find most participants complete the diary reliably.

Trial Medication

The trial takes place within the context of NHS smoking cessation clinics, which provide behavioural support and medication to assist smoking cessation. Around 70% of smokers in these clinics use nicotine replacement therapy (NRT) as their medication to assist quitting and this is the only pharmacotherapy that will be available to participants in this trial. Current best practice is to use NRT in combination, which has been endorsed by the Medicines and Healthcare Regulatory Authority as good practice and recommended by the National Institute for Health and Clinical Excellence[32].

In this study, we propose using both nicotine patch and an acute form of NRT in combination (See Table 1). We will use Niquitin, Nicotinell, Wockhardt, and Nicorette NRT products, including 24 hour patches, which are licensed for 16 hour use also (there is no evidence that the effectiveness of 16 hour patches or 24 hour patches is different[33]). These patches provide about 1 milligram (mg) per hour of nicotine. Participants will be advised to wear the patch 24 hours per day, but will be advised to wear it only during day time should they experience sleep

Table 1: Daily medication regimes

	Rapid reduction	Abrupt cessation
Pre-quit period -2 weeks to quit day	21 mg/24 hour patch, 1 mg of absorbed nicotine per cigarette forgone as a minimum from acute NRT.	21 mg/24 hour patch, No acute NRT.
Quit day onward	21 mg/24 hour patch, Minimum of 6 mg of absorbed nicotine from acute NRT. As much as needed to feel comfortable.	21 mg/24 hour patch, Minimum of 6 mg of absorbed nicotine from acute NRT. As much as needed to feel comfortable.

disturbance or vivid dreams. Although the medications provide the same amount of nicotine delivery with similar pharmacokinetics, the license dosing advice differs. Niquitin CQ recommend the 21 mg patch for smokers who smoke 10 or more cigarettes per day, while Nicotinell recommend the 30 cm^2 (= 21 mg) patch for smokers of 20 or more cigarettes per day. The evidence is that most smokers who smoke 10 or more cigarettes per day get less nicotine from their patch than they did from their cigarettes[34,35]. We have therefore chosen a cut-off of 15 cigarettes per day. In addition, all participants will be offered additional intra-nasal or oral nicotine replacement (gum, microtabs, lozenges, or inhalator) with the choice of delivery system left to personal preference. The dose of these products used will vary, but participants will be advised to take at least 1 mg of absorbed nicotine for each cigarette forgone in the reduction phase because each cigarette delivers about 1.2 mg on average, though this is highly variable[36]. A 2 mg oral product, for example gum, delivers about 1 mg available systemically, and a 10 mg inhalator cartridge yields about 3 mg of nicotine that is systemically available. In the cessation phase, participants in both arms will be given identical dosing instructions and advised to use at least 6 mg of absorbed nicotine daily, which is the minimum dose associated with improved outcomes[33].

Rationale of the pre-quit NRT in the abrupt and rapid reduction arms

By utilising pre-quit NRT in both arms we will ensure that any effect is caused by the difference in reduction rather than differences in nicotine intake. Smoking and using a patch gives higher concentrations of nicotine than just smoking, whereas smoking and using an acute form of NRT does not[37]. It is thought that high levels of nicotine dissociate the cigarette from its reward and this is responsible for the effectiveness of nicotine pre-treatment, which is not apparent when acute forms of NRT only are used. Consequently, we have chosen a nicotine patch for both arms. However, gradual reduction could undermine the nicotine pre-treatment effect so we aim to keep nicotine levels high using a patch during reduction and replacing cigarettes with acute NRT.

Duration of medication use and discontinuation

The license for NRT allows continued use for up to 9 months, but patch use will be phased out using the step down doses between 2 and 3 months after quit day. For participants who are still lapsing but showing determination to stop smoking, the patch will be phased out more slowly, providing no signs of overdose are evident. The dose reduction regimes vary in the summary of product characteristics and in any case the dose reduction is individual, based upon confidence in reducing the patch dose and occurrence of urges to smoke. Oral NRT is commonly continued for several months in abstinent smokers [38-41] and there are reasons to assume this is beneficial, and again we will apply clinical judgement in deciding on length of treatment of oral/intranasal NRT. The advice on patch duration and oral NRT discontinuation will be the same in both arms. At week +8 participants will be given a month supply of NRT and advised to contact either their general practitioner or local stop smoking service should they need further support and/or prescriptions beyond week +12.

Stopping rules/modification of medication regime

- Participants who have problems with insomnia or difficulties with vivid dreams will use the patch for 16 hours daily, not 24 hours

- Participants who have skin reactions to the patch that are not controlled by switching preparations, emollient and hydrocortisone cream will switch to acute NRT only.

- Participants who become pregnant may have their dose adjusted in line with the National Institute for Health and Clinical Excellence guidance and in accord with the wishes of the participant.

- Participants who show symptoms of overdose will have the dose reduced.

• Participants who fail or give up on their quit attempt will cease using NRT.

Evidence of safety of smoking whilst using NRT

The safety of using transdermal NRT while smoking was investigated in a review by Fagerstrom & Hughes[37], which is summarised in Table 2. In addition to this review, we have recently systematically reviewed the Cut Down to Stop (CDTS) studies mentioned in the literature review[19]. As part of this, we performed a meta-analysis of adverse events in people smoking and using NRT versus those smoking and using placebo NRT. Overall, 1384 predominantly middle-aged smokers were treated with NRT for 6 to 18 months, while 1383 were treated with placebo. Four deaths occurred in those randomised to NRT and four in those randomised to placebo; Odds ratio (OR) 1.00 95%CI 0.25–4.02. Serious adverse events occurred in fewer than 8% of participants in both arms; OR 1.09 95%CI 0.79–1.50. In no cases were these were judged likely to have been due to treatment. Discontinuation of treatment due to adverse events was rare with 1.7% and 1.3% in the NRT and placebo groups; OR 1.27 95%CI 0.64–2.51. Nausea was selected as an index symptom to indicate possible nicotine overdose. It was slightly and significantly more common in the NRT group with 8.6% versus 5.3% on placebo experiencing nausea; OR 1.69 95%CI 1.21–2.36.

Lifestyle advice

There is no special dietary or life-style advice that is imposed by using NRT and the associated regimes for using it proposed in the protocol. However, participants using oral NRT will be advised to avoid acidic drinks 15 minutes prior to using oral NRT.

Concomitant Medication

All medications will be permitted for use concurrently, except those that are proven to help smoking cessation (bupropion, nortriptyline, mecamylamine, reserpine, varenicline), or medications that are unlicensed and for which no interaction data with NRT are available. No rescue therapies will be permitted in treatment, in accordance with the National Institute for Health and Clinical Excellence guidance on smoking cessation pharmacotherapy[32]. The NRT itself is aimed at the relief of symptoms of nicotine withdrawal. Should adverse skin reactions occur with the use of the patch, advice will be given on the use of over the counter emollients and 1% hydrocortisone cream, as is standard. Data on all concomitant medication will be recorded.

Trial Outcomes

Primary trial outcome

• Abstinence at four weeks, measured according to the Russell standard[20,42]. The Russell standard allows a two week grace period from quit day for slips[43].

Secondary trial outcomes

• Point prevalence at each follow up and prolonged abstinence at 8 weeks and 6 months. Half of those sustaining abstinence for six months sustain it for life, the goal of treatment[44,45].

Table 2: Summary of Fagerstrom & Hughes review of the safety of smoking and concomitant NRT use[37]

Study reviewed	NRT treatment given	Blood nicotine concentrations	Safety conclusions
Foulds et al, 1992	16+ cigarettes per day (cpd) & 15 milligram (mg) transdermal patch (TP) over 16 hrs	Baseline: 37 nanograms per millilitre (ng/ml), Placebo: 36 ng/ml, 15 mg TP: 44 ng/ml.	Participants experienced almost no subjective toxic effects whilst wearing the patch
Pickworth, Bunker & Henningfield, 1994	13+ cpd & 22 mg, 44 mg TP over 24 hrs	Baseline: 30 ng/ml, Placebo: 19 ng/ml, 22 mg TP: 39 ng/ml, 44 mg TP: 63 ng/ml.	No adverse subjective experiences were reported.
Mahmarian et al, 1997	8+ cpd & 14 mg TP over 24 hrs	Baseline 16 ng/ml, 14 mg TP: 24 ng/ml, 21 mg TP: 30 ng/ml.	Only adverse effects noted were nausea & vomiting in 2 patients.
Zevin, Jacob & Benowitz, 1998	Smoking ad libitum & 21 mg, 42 mg, 63 mg patch over 8 hours	Placebo: 20 ng/ml, 63 mg TP: 60 ng/ml.	No additional haemodynamic effects of TP on heart rate, blood pressure, noradrenaline, white blood cell count, fibrinogen, haematocrit, cortisol, or lipids. No adverse reactions.
Carpenter et al, 2000	11+ cpd & TP, gum or inhaler	Lower than 22 mg TP: 54% increase, Higher than 22 mg TP: 190% increase.	Number of cpd reduced by 43% and CO by 31%.

• Urges to smoke and nicotine withdrawal symptoms will be measured after cessation. Urges to smoke are an important proxy of return to smoking.

Other trial outcomes (non-efficacy)

• Exhaled carbon monoxide using a CO monitor is a measure of smoke inhalation. We will compare smoke exposure before quit day in both arms of the study.

• Cotinine levels, to show whether nicotine intake rises from normal when smoking in both arms, as we expect, and whether the rise in cotinine relates to the success of treatment. We propose measuring cotinine at baseline, week -1, quit day, and at week +1 on all participants to examine whether reduction leads to higher self-medication with nicotine. It could be that reduction treatment gets people used to using high doses of NRT and therefore some of the effect of treatment could be explained by post-quitting NRT dose. These data will also provide valuable evidence on nicotine consumption while smoking and using NRT.

• Participant rating of the reward from their cigarette while smoking using the modified Cigarette Evaluation Questionnaire (mCEQ)[46,47]. The mCEQ measures satisfaction, taste, mood, cognitive, and sensory sensations to smoking particular cigarettes. Twice each week prior to quitting (to keep participant burden reasonable), we will ask participants to rate satisfaction from smoking from the first cigarette of the day and one other key cigarette. We routinely ask participants to rate cigarette satisfaction in one specimen day so as to anticipate danger periods for lapsing after cessation. Typical rewarding cigarettes are after dinner. Additionally, participants will be asked to rate a cigarette smoked in a negative affect situation. It is possible that the mechanism of benefit may be the reward from smoking, and this study will allow investigation of this. We will also rate satisfaction from smoking after cessation, should slips occur.

• Confidence in quitting is a predictor of abstinence and might be modified by reduction and will be used in mediation analysis. This will be measured by a single question used in other trials that has been shown to predict success. How high would you rate your chances of giving up smoking for good at this attempt? (Circle one response)

Extremely high

Very high

Quite high

Not very high

Low

Very low

• Smoking stereotypy is a measure of the degree to which smoking is prompted by cues to smoke[48]. Perhaps reduction might work by disrupting stimulus control and this scale could measure this. Two questions from this scale will be used to measure smoking stereotypy because the other questions in the scale are either forced to change or could not be assessed over a short period.

There are no specific outcomes proposed when comparing methods of reduction. This analysis will focus on the above measures and is exploratory. See Table 3 for a breakdown of which outcomes are to be measured at specific time-points [49].

In addition to the weekly clinic measures, participants will complete a daily diary for the first three weeks of the trial from week -2 to week +1. This will record whether or not the patch is worn, the amount of acute NRT used, the number of cigarettes smoked, and the two urge to smoke questions from the Mood and Physical Symptoms Scale (MPSS). Once a week, the diary will include the mCEQ, with the other measure being taken in clinic.

Trial Statistics

Power calculation

We propose a non-inferiority trial following the Consolidated Standards of Reporting Trials (CONSORT) statement for such trials[29]. With a one-sided alpha of 0.05 we have 80% power to detect inferiority of 9.5% in the quit rate at four weeks if we enrol 343 in each arm, assuming 50% 4-week abstinence. Therefore the trial sample size shall be N = 700. Analyses will be carried out on an intention-to-treat basis, according to the Russell Standard, where participants lost to follow up are assumed to be smokers [20].

Arguably, differences of 5% at 4 weeks would be worthwhile detecting[50], but a trial would need to enrol 2500 participants for this, which would make it impractical and unlikely to be funded. If the reduction produced abstinence rates not worse than 9.5% less at four weeks, this is probably sufficient for stop smoking services to implement the programme.

Analysis

The analysis will compare the proportions stopping smoking, calculating confidence intervals and relative risks and confidence intervals. We will calculate differ-

Table 3: Schedule of trial measures

Follow-up	Trial measures
Baseline (wk -2)	Smoking history, demographics, nicotine dependence using Fagerstrom Test for Nicotine Dependence (FTND)[49], urges and withdrawal (MPSS[51]), confidence in quitting, smoking stereotypy[48], cigarette satisfaction[47], future orientation questionnaire, exhaled carbon monoxide (CO), salivary cotinine, Give out diaries.
Pre-quit visit (wk -1)	CO, cotinine, MPSS, confidence, smoking stereotypy, cigarette satisfaction, adverse events. Collect diaries with daily smoking, NRT use, MPSS urge questions. Give out diaries.
Extra pre-quit visit (wk -1a)	**Only applicable if delays quit date by 1 week** CO, MPSS, confidence, smoking stereotypy, cigarette satisfaction, adverse events. Collect diaries with daily smoking, NRT use. Give out diaries.
Extra pre-quit visit (wk -1b)	**Only applicable if delays quit date by 2 weeks** CO, MPSS, confidence, smoking stereotypy, cigarette satisfaction, adverse events. Collect diaries with daily smoking, NRT use. Give out diaries.
Quit day (wk 0)	CO, cotinine, MPSS, confidence, smoking stereotypy, cigarette satisfaction, adverse events. Collect diaries with daily smoking, NRT use, MPSS urge questions. Give out diaries.
One week after quit day (wk +1)	CO, cotinine, MPSS, confidence, cigarette satisfaction if lapsed, adverse events Collect diaries with daily smoking, NRT use, MPSS urge questions
Post-quit visits (wks +2, +3, +4)	Smoking in past week, CO, MPSS, confidence, cigarette satisfaction if lapsed, future orientation questionnaire at week 4, amount NRT used, adverse events
+8 wk visit	Smoking in past 4 weeks, CO, MPSS, cigarette satisfaction if lapsed, confidence, amount NRT used, adverse events
6-month telephone call	Smoking status over past 5 months, use of NRT. Those claiming 7-day abstinence will be invited to a validation visit for exhaled CO and to complete the future orientation questionnaire. Serious adverse events (SAEs)

ences in withdrawal scores using regression, controlling for baseline differences, as is standard using the MPSS[51]. We will investigate possible mechanisms of action (NRT dose, satisfaction from smoking, withdrawal, self-efficacy) using mediation analysis within a regression framework. Mediation analysis is outlined in more detail by the RIPL research group at the Arizona State University[52].

In comparing methods of reduction, we have no specified hypotheses. We will compare changes in confidence, stereotypy, and urges to smoke calculating differences in mean changes and confidence intervals for the difference. We will compare the proportion abstinent using point prevalence and prolonged abstinence as in the comparison between reduction and abrupt cessation. The primary analysis of abrupt cessation versus reduction will not be adjusted by method of reduction used.

Trial schedule

With two fulltime nurses who will also act as trial co-ordinators and liaise with practices, and do follow ups, and the support of a PhD student, we can see the 700 participants in 24 months (bearing in mind that clinical contacts span 10 weeks).

Definition of end of trial

End of trial is defined as the final 6 month patient follow-up measuring carbon monoxide level of the last participant undergoing the trial.

Safety Reporting

Assessment of safety

Potential participants' safety will be ensured by screening for eligibility using a structured form completed by the trial nurse. This will record evidence of eligibility and exclusion criteria. In addition, the nurse will take a general medical history to assess for other complicating diseases. Any queries remaining as a result of this process will be resolved by discussion between the trial nurse, chief investigator and the relevant physicians providing routine medical care, usually the participant's general practitioner. Such concerns are unusual but not rare. Typically, they arise from a participant's hazy knowledge or under-

standing of their past medical history and are usually readily resolved. No blood or further medical testing will be necessary to ensure safety.

NRT has been investigated in several hundred previous clinical trials and is widely prescribed worldwide and subject to safety monitoring, and is replacing a product, nicotine, which the participants are already consuming and will have consumed for many years in cigarettes. Thus, there is every reason to expect that treatment in this trial will be safe. Participants will be warned about the side-effects of NRT and advised not to stop taking the medication without consulting with an NHS professional, preferably the trial team. To this end, all participants will be given a credit card-sized card with the trial team's contact details on that will allow participants to receive advice on medication or to report perceived serious adverse effects and receive advice on medication as required. Participants will record the occurrence of side-effects of medication as specified on the summary of product characteristics for relevant NRT preparations, by completing a checklist. The checklist will be given to the trial nurse and the nurse will enquire about recorded adverse events, so as to determine the severity of any adverse event and ensure that appropriate advice is given for its management (such as rotating the patch site or use of emollients for skin reactions). Minor adverse reactions will be monitored and managed in this way. For each known side effect listed in the summary of product characteristics, the trial nurse will have a definition of clinical severity. For example, a mild skin site reaction to the patch will be defined as burning sensation that does not interfere with normal activities, redness or swelling at the site of application, or mild blistering. Any reaction beyond that will be classified as potentially moderate or severe and will be reported to and discussed with the principal investigator. A decision on stopping therapy will then be made with the participant, attending clinician, principal investigator, and other relevant parties as appropriate. Nicotine has a short half life (2 hours), meaning that the blood concentration will not build up during the course of treatment so that new side-effects are not expected after the first few weeks. In addition, with reactions relating to local use, such as skin discomfort from patches, or bad taste from oral use, either treatment will have been switched or people become accustomed to the side-effects after a short time of using the preparation. At the last meeting (week 8 of the quit attempt), the participant will be advised to phone the contact number to report side-effects that occur after this. The advice given will depend upon the severity of the reported reaction and those with moderate reactions will be invited to an ad hoc consultation.

Participants will also complete a schedule of nicotine overdose symptoms at each visit. On completion of this questionnaire, the schedule will be handed to the nurse and thus any symptoms of overdose will be assessed. In addition, based on her/his enquiry, the nurse will make an assessment of whether the NRT dose is too high or not, and then what action was taken, such as continue with prescribed dose, or direct the participant to use a lower dose, which will be recorded.

The summary of product characteristics for the relevant NRT products contain no warnings about serious adverse reactions except rare allergic reactions, such as angioedema, and cardiac arrhythmias, occurring in less than 1/1000 users. Thus we expect no or very few suspected unexpected serious adverse reactions (SUSARs) in this trial. The long history of use in and outside of trials for NRT means that SUSARs are unlikely. On the reverse of the trial card given the contact number for advice on side-effect management, there will be instructions for the reporting of serious adverse events. Through direct contact from the participant or contact from their attending physician, we expect to become aware of serious adverse events. If any member of the trial team becomes aware, they will inform the PI within 24 hours. The principal investigator will then assess the seriousness, causality, expectedness and severity of the adverse effects. An immediate decision will be made on the interim use of medication for that participant. If an event is judged severe, it will be reported to the trial sponsor, who will report the event to the Research Ethics Committee and Medicines and Healthcare Regulatory Authority. Participants will be asked weekly to report inter-current illnesses and the response recorded. If any of these inter-current illnesses contra-indicates NRT, this will be immediately reported to the principal investigator and a decision made about continued use of the NRT product. The reporting procedures and definitions are presented in Additional file 1.

Monitoring and audit

The progress of the trial will be monitored by quarterly review of records. This will ensure that consent is being obtained and the inclusion and exclusion criteria are adhered to. The medication dispensed and the instructions for using it will also be assessed.

Data cleaning will take place by a series of logical checks on the electronic data. (For example, a person cannot be recorded as prolonged abstinent smoker at 6 months if they were not in such a state at 8 weeks). Discrepant records will be checked with the source documents and the database amended if necessary.

The trial will be potentially subject to audit by the appropriate regulatory authorities and therefore participants will be asked to consent to allow their records to be viewed.

Data management

The trial is being run as part of the portfolio of trials in the Primary Care Clinical Research and Trials Unit (PCCRTU), a National Institute for Health Research (NIHR) recognised trials unit in Primary Care Clinical Sciences at the University of Birmingham. The data management will be run in accord with the standard operating procedures, which are fully compliant with the Data Protection Act and International Conference on Harmonisation (ICH) Good Clinical Practice (GCP). The source documents for the trial will be the case report forms which will be stored in the trials unit in a locked cabinet in a locked office in a locked department. The trial database will be securely held and maintained by the PCCRTU. On completion of the trial and data checking, the case report forms will be transferred to Modern Records, a secure archiving facility at the University of Birmingham, where they will be held for 15 years and then destroyed. The database will be anonymised and a secure compact disc containing the link between identification number and patient identifiable information will be stored in modern records.

Data protection and confidentiality

Data will be kept in accordance with the Data Protection Act and the trial registered with the Data Protection Act website at the University of Birmingham. The standard operating procedures of the trials unit will be followed, which are designed to protect patient confidentiality. Patient identifiable data will be shared only within the clinical team on a need-to-know basis to provide clinical care and ensure good and appropriate follow up. Patient identifiable data will also be shared with the general practitioner and approved auditors from the Research Ethics Committee, NHS Research and Development, or the Medicines and Healthcare Regulatory Authority will also be able to see patient identifiable information. Otherwise, confidentiality will be maintained and no one outside the trial team will have access to either the case report forms or the database.

Ethics and Research Governance

The trial will be conducted in compliance with the principles of the Declaration of Helsinki (1996), the principles of ICH-GCP and run in accord with EU Clinical Trials Directive and all of the applicable regulatory requirements. The study protocol and other documentation have been reviewed and approved by the National Research Ethics Committee (08/H0408/213), the Medicines & Healthcare Regulatory Authority, and local NHS Research & Development offices. Any subsequent protocol amendments will be submitted to the Research Ethics Committee for approval, and the other bodies if necessary. We will comply with ICH-GCP Guidelines over the reporting of adverse events, serious adverse events and suspected unexpected serious adverse reactions (SUSARS). In addition we will provide the Research Ethics Committee with progress reports as well as a copy of the Final Study Report.

Finance

The study will be funded by the British Heart Foundation and service support costs will be claimed via the Comprehensive Clinical Research Network.

Publication

The trial results will be written up for submission to a peer reviewed journal and the trial is registered with controlled-trials.com. No data relating to individuals will be identified in these publications.

Competing interests

PA has done consultancy work for Pfizer, McNeil, and Xenova/Celtic. NL has no competing interests. JTI has no competing interests. JI has no competing interests. JB has no competing interests. RW undertakes research and consultancy for companies that develop and manufacture medications for smoking cessation including nicotine replacement therapy. He also has a share of a patent on a novel nicotine delivery device. SM has no competing interests.

Authors' contributions

NL participated in the design of the study and drafted the manuscript. PA conceived of the study, participated in its design and helped to draft the manuscript. JTI participated in the design of the study and helped to draft the manuscript. JI, JB, RW, and SM all participated in the design of the study. All authors read and approved the final manuscript.

Additional material

Additional file 1
Appendix 1. Adverse Event Reporting.
Click here for file
[http://www.biomedcentral.com/content/supplementary/1745-6215-10-69-S1.doc]

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APPENDIX 2: PUBLISHED COCHRANE REVIEW (LINDSON ET AL. 2010)

Reduction versus abrupt cessation in smokers who want to quit (Review)

Lindson N, Aveyard P, Hughes JR

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[Intervention Review]

Reduction versus abrupt cessation in smokers who want to quit

Nicola Lindson[1], Paul Aveyard[1], John R Hughes[2]

[1]Primary Care Clinical Sciences, University of Birmingham, Birmingham, UK. [2]Dept of Psychiatry, University of Vermont, Burlington, Vermont, USA

Contact address: Nicola Lindson, Primary Care Clinical Sciences, University of Birmingham, Edgbaston, Birmingham, West Midlands, B15 2TT, UK. nll839@bham.ac.uk.

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ABSTRACT

Background

The standard way to stop smoking is to quit abruptly on a designated quit day. A number of smokers have tried unsuccessfully to quit this way. Reducing smoking before quitting could be an alternative approach to cessation. Before this method is adopted it is important to determine whether it is at least as successful as abrupt quitting.

Objectives

1. To compare the success of reducing smoking to quit and abrupt quitting interventions. 2. To compare adverse events between arms in studies that used pharmacotherapy to aid reduction.

Search strategy

We searched the Cochrane Tobacco Addiction Review Group specialised register, MEDLINE, EMBASE and PsycInfo for topic specific terms combined with terms used to identify trials of tobacco addiction interventions. We also searched reference lists of relevant papers and contacted authors of ongoing trials. Date of most recent search: November 2009.

Selection criteria

We included randomized controlled trials (RCTs) that recruited adults who wanted to quit smoking. Studies included at least one condition which instructed participants to reduce their smoking and then quit and one condition which instructed participants to quit abruptly.

Data collection and analysis

The outcome measure was abstinence from smoking after at least six months follow-up. We pooled the included trials using a Mantel-Haenszel fixed-effect model. Trials were split for two sub-group analyses: pharmacotherapy vs no pharmacotherapy, self help therapy vs behavioural support. Adverse events were summarised as a narrative. It was not possible to compare them quantitatively as there was variation in the nature and depth of reporting across studies.

Main results

Ten studies were relevant for inclusion, with a total of 3760 participants included in the meta-analysis. Three of these studies used pharmacotherapy as part of the interventions. Five studies included behavioural support in the intervention, four included self-help therapy, and the remaining study had arms which included behavioural support and arms which included self-help therapy. Neither reduction or abrupt quitting had superior abstinence rates when all the studies were combined in the main analysis (RR= 0.94, 95% CI= 0.79 to 1.13), whether pharmacotherapy was used (RR= 0.87, 95% CI= 0.65 to 1.22), or not (RR= 0.97, 95% CI= 0.78 to 1.21), whether studies included behavioural support (RR= 0.87, 95% CI= 0.64 to 1.17) or self-help therapy (RR= 0.98, 95% CI= 0.78 to1.23). We were unable to draw conclusions about the difference in adverse events between interventions, however recent studies suggest that pre-quit NRT does not increase adverse events.

Authors' conclusions

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. Further research needs to investigate which method of reduction before quitting is the most effective, and which categories of smokers benefit the most from each method, to inform future policy and intervention development.

PLAIN LANGUAGE SUMMARY

Comparing reducing smoking to quit with abrupt quitting.

The standard way to quit smoking is to smoke as normal until a quit day at which point the smoker stops using all cigarettes. Most smokers who try to quit end up relapsing, therefore there are a number of people who have tried to quit abruptly in the past without success, and are disillusioned with this approach. An alternative way to give up could be to reduce the amount of cigarettes smoked before going on to quit completely. There is evidence to suggest that reducing smoking before quitting would be popular with smokers. This means that offering this approach to quitting could encourage more smokers to give up, however before offering this approach it is important to ensure it is at least as successful as abrupt quitting. This is because given a choice smokers who would otherwise have quit abruptly may choose to reduce first instead. If reduction isn't as effective, smokers who choose that method will be at a disadvantage. The aim of this review was to compare quit rates in reduction to quit and abrupt quitting interventions to see if reducing to quit is at least as successful as abrupt quitting. Ten studies were found which compared reducing smoking before quitting with abrupt quitting. Pooled results found that neither reducing or abrupt quitting produced superior quit rates. This was true whether nicotine replacement therapy was used as part of the intervention or not, and whether participants were offered self-help materials or behavioural support. These results suggest that smokers should be given a choice of quitting methods, either reducing smoking before quitting or abrupt quitting, however, to inform the development of new interventions more research is needed into which method of reducing smoking is the most effective.

BACKGROUND

Description of the condition

Tobacco use is the largest preventable cause of death in the world, as a risk factor for six of the eight leading causes of death. A survey of a sample of 893 English smokers (Jarvis 2002) found that most were disenchanted with smoking and, if they were given their time again, they would not have started smoking in the first place. Most of these smokers expected to be quit within a few years, but historical data on quit rates suggest this is extremely unlikely because most people who try to quit relapse quickly (Hunt 1973). The authors interpreted this as a delusion gap between expectations and likely reality. Such a gap means we need to find new ways to encourage smokers, most of whom have tried to quit repeatedly, to keep on trying. Finding new ways to quit would be helpful to this endeavour.

Description of the intervention

The standard way to stop smoking is to quit abruptly. This means that a person smokes as normal until a designated quit day, from which point forward they try to abstain and avoid any smoking whatsoever.

An alternative method is to quit gradually. Such gradual reduction methods, when used as a means of achieving cessation, typically have a quit day as in abrupt cessation. The key difference is that smokers aim to reduce smoking prior to this day. Some researchers have investigated the relative efficacy of different methods of reducing smoking on the likelihood of achieving reduction and of subsequently achieving abstinence, but this is not the focus of this review. All such different methods are pooled here.

How the intervention might work

There are a number of ways that reducing the amount of cigarettes smoked prior to total abstinence might help a smoker give up completely. The first of these is a principle of psychopathology, which suggests that, as the dose of nicotine received by the individual each day is reduced, drug dependence and therefore craving is reduced in response. Another is 'shaping', a conditioning procedure, whereby making successive approximations of the target behaviour (gradually cutting down the number of cigarettes smoked) the desired behaviour (abstinence) is eventually achieved. The third is the cognitive psychology principle that completing a step toward a goal (reducing smoking) increases self efficacy, which increases the likelihood that the goal (abstinence) will be achieved. The fourth is the classical and operant conditioning principle that reducing the frequency of a behaviour decreases the association with environmental cues, which in turn weakens the urge to partake in that behaviour when those cues are present. Finally reducing provides a goal which is more in-line with the smokers current behaviour than complete abstinence and therefore appears more achievable. However, the standard assumption of smoking cessation treatment is that cessation begins on a quit day and that cutting down prior to quitting is not advised. This is based on nicotine addiction theory, which claims that the user has impaired control over their drug use, and that it should therefore be difficult for them to control their usage in any way, e.g. by reducing. It also assumes that with reduction each remaining cigarette will become more rewarding and harder to give up, and that the smoker will suffer a loss of motivation before attaining total abstinence. However medication to reduce withdrawal, such as nicotine replacement therapy (NRT), could be used to counteract this effect, and has successfully been used to do so in smokers who are not yet ready to quit (McRobbie 2006; Wang 2008). Wang et al conducted an assessment report which examined the effectiveness and cost- effectiveness of NRT alongside 'cut down to quit' (CDTQ) smoking in people who were either unwilling or unable to quit (Wang 2008). The approach was found to be both effective, and cost effective, although abstinence rates were not as high as those documented in abrupt quitting regimes. Studies which utilise the CDTQ approach, and therefore people who are unable or unwilling to quit, have already been included in the Cochrane review of harm reduction (Stead 2007). Our review will focus only on those smokers who want to quit. Surveys have been carried out across England and Wales (West 2001) and the UK, US, Canada and Australia (Cheong 2007), investigating the success of quit attempts when smokers reduce cigarettes smoked with an aim to quitting completely. Both of these observational studies found that abrupt quitting was almost twice as successful as quitting gradually in those sampled. However participants in these studies were from the general population and hadn't used a particular service or intervention. They could potentially have used a wide range of gradual quitting techniques, ranging from no structure, no reduction goals and no set quit day to highly structured, with set reduction goals and a target quit day to work toward, which may have influenced success rates.

Although British (NICE 2008) and American (Fiore 2008) national guidelines for smoking cessation services do not recommend reducing smoking before quitting, both conclude that further research is needed into whether it could be used as a successful intervention to help those who have tried unsuccessfully to quit in the past. The US Medicines Regulator, and some other pharmaceutical regulators, have not approved the use of NRT for smokers who wish to cut down the amount they smoke without wanting to quit. However, the Medicines and Healthcare Regulatory Authority (MHRA) in the UK and other medicines regulators have licensed the use of NRT for this purpose. UK guidelines suggest that, until further evidence is available, this strategy should only be used in properly designed and conducted research studies. New Zealand's smoking cessation guidelines (NZ MoH 2007) mention cutting down cigarettes smoked, but as a strategy that should only be implemented in those unwilling to quit. Cutting down is therefore a strategy that is either not recommended by national guidelines or is only recommended for smokers not ready to stop.

Why it is important to do this review

Without help, most people who try to stop smoking relapse within one week and only 4% sustain abstinence for one year (Hughes 2004). The UK is the only country with a truly nationwide network of smoking cessation clinics, although a growing number of countries are developing a variety of free or subsidised services to help smokers to quit. Although these clinics, substantially increase rates of abstinence, most people who try to stop smoking will fail to do so. For example, the evaluation of the UK National Health Service (NHS) specialist stop smoking services showed that 15% of patients achieved abstinence for a whole year (Ferguson 2005). Thus, while treatment substantially improves the number who achieve abstinence, a return to smoking is the norm for the majority, whatever method of stopping is used. Consequently there is a cadre of patients who have been through treatment services

a number of times. Smoking cessation services currently recommend abrupt cessation for all quit attempts (first or repeated), whereas alternative methods might be more successful or at least give renewed hope and encourage cessation in those who have given this up as impossible. Gradual cessation could offer a new way to quit for those who have failed previously, but it can only be recommended by therapists if it is an effective strategy for cessation.

There is evidence to suggest that some people feel that reducing the number of cigarettes they smoke is an important first step towards quitting completely. In the English Smoking Toolkit Study, 40% of quit attempts included cutting down first (West 2006). A survey of respondents to an advertisement for people interested in cessation found that 66% planned to stop by cutting down gradually, while 13% planned to stop abruptly. In a survey of people responding to an advertisement for those planning to reduce smoking, 57% planned to reduce and then stop (Hughes 2006). A survey of US daily smokers showed that in their most recent quit attempt 35% tried to stop gradually while 65% tried to stop abruptly (Hughes 2007). Those who chose gradual cessation were as motivated to stop and as confident of success as those who used abrupt cessation. A random sample of US smokers showed that nearly half of smokers planning to quit would choose reduction over abrupt cessation (Shiffman 2007). There was little interest among these smokers in reduction as an end in itself, only as a means to abstinence. Reducing the number of cigarettes smoked as a means to giving up smoking may prove to be a popular approach, and may draw people into treatment services. Given behavioural support and pharmacotherapy increase the likelihood of achieving abstinence (Lancaster 2005; Stead 2005; Stead 2008) this would have public health benefits.

OBJECTIVES

- To compare the success of smoking cessation interventions that instruct the smoker to reduce the amount they smoke before quitting with interventions that instruct the smoker to stop smoking abruptly.
- To compare adverse events by arm, stratified by whether they use pharmacotherapy.

METHODS

Criteria for considering studies for this review

Types of studies

Randomized controlled trials. We included a trial where allocation to treatment arms was cluster randomized, and carried out a sensitivity analysis to adjust for this clustering. To meet the second objective we examined adverse events only in those trials which had a reduction arm utilising pre-quit pharmacotherapy and an abrupt quitting arm that did not utilise pre-quit pharmacotherapy.

Types of participants

Cigarette smokers of any age who intended to stop smoking soon. Participants demonstrated their commitment to quitting by enrolling in a smoking cessation programme. Trials that enrolled smokers who did not intend to quit soon were excluded, as they are covered by the Cochrane review of harm reduction (Stead 2007).

Types of interventions

We compared any instruction to participants to reduce the amount of cigarettes smoked before quitting, with any instruction to stop smoking abruptly without prior reduction. We did not include trials with arms where participants spontaneously reduced before quitting without being advised to do so, versus arms where participants stopped abruptly.

Interventions included anything from no behavioural support to extensive behavioural support, but studies were excluded if behavioural support differed substantially in type or duration between arms. Behavioural support pre- and post-quit could vary between the reduction and abrupt quit arms as long as overall contact was roughly equal. Trials could also include concomitant pharmacotherapy to support cessation, as long as it was equivalent in all trial arms after cessation. Pharmacotherapy used prior to quit day could vary as a necessary component of the intervention i.e. to support smoking reduction.

Types of outcome measures

Primary outcomes

The primary outcome was abstinence from smoking at least six months after the quit day. We excluded trials with a follow up of less than six months.

In trials with more than one measure of abstinence, we preferred the measure with the strictest criteria. We used prolonged or continuous abstinence over point prevalence abstinence, and preferred biochemically validated abstinence, such as by exhaled carbon monoxide, over self-report.

Secondary outcomes

The secondary outcome was the type and number of adverse events recorded.

Search methods for identification of studies

We searched the Cochrane Tobacco Addiction Review Group specialised register, which has been developed from electronic searches of MEDLINE, EMBASE and PsycINFO, together with handsearching of specialist journals, conference proceedings and reference lists of previous trials and overviews. We also searched MEDLINE, EMBASE and PsycINFO for possible trials to include in the review, searched the reference lists of relevant trials, and where necessary contacted the authors of ongoing trials.

We searched MEDLINE (Ovid, 1966 to 5th November 2009), EMBASE (Ovid, 1980 to 2009 week 44) and PsycINFO (Ovid, 1967 to 23rd November 2009) using the following topic-specific terms:

- cold turkey.mp
- (schedul* adj3 smok*).mp
- (cut* down or cut-down).mp
- (({Gradual* or abrupt*}) adj3 (reduction or reduce* or quit* or stop* or abstin* or abstain* or cessat*)).mp
- fading.mp
- taper*.mp
- (controlled adj smoking).mp

[mp=title, original title, abstract, name of substance word, subject heading word]

We combined these with the terms used for the regular searches of MEDLINE, EMBASE and PsycINFO to identify trials of tobacco addiction interventions for the Tobacco Addiction Review Group specialised register. Full strategies are shown in the Appendices. We also searched the specialised register in November 2009 using the following terms: Cold turkey or schedul* or Cut* down or cut-down or Gradual* or abrupt* or fading or reduction or reduce* or taper* or controlled smoking.

Data collection and analysis

Selection of studies

One author checked the titles and abstracts of studies generated by the search strategy for relevance, and obtained copies of papers reporting relevant trials. Two authors then independently assessed the reduced trials list for inclusion in the review. Any disagreements were resolved through discussion with the remaining review author. We based eligibility decisions on the following questions:

1. Is the study described as randomized or quasi- randomized?
2. Were the participants cigarette smokers who wanted to quit?
3. Did the study include at least two groups, i.e. one group advised to reduce their smoking before quitting and one advised to quit abruptly on quit day?
4. If the intervention includes behavioural support with or without pharmacotherapy, is overall contact for behavioural support and post-quit pharmacotherapy similar between both groups?
5. Is the intervention an instruction to reduce the number of cigarettes smoked, rather than an instruction to reduce harm, e.g. smoking cigarettes with lower levels of nicotine?
6. Does the study report smoking abstinence at least six month after the quit date?

If the answer to any of the above questions was 'No' then the trial was not included in the review.

Data extraction and management

For each included trial one author extracted the data and another author checked them. The only included paper published in Spanish was translated into English (Roales-Nieto 1992). We extracted the following information for inclusion in the Characteristics of included studies table:

Methods:

- The design of the trial, for example randomized or quasi-randomized.
- Country and setting
- Method by which participants were selected
- The definition of a smoker
- Duration of the study
- Time to follow up(s)

Participants:

- The number of participants randomized to each intervention group
- Demographics of participants (age, gender, ethnicity)
- The average number of cigarettes per day, and number of past quit attempts
- Average Fagerstrom Test of Nicotine Dependence (FTND) or equivalent score
- Particular preference for abrupt or gradual cessation

Interventions:

- The method of rapid reduction intervention used
- The method of abrupt quitting intervention used
- Whether pharmacotherapy was used as part of the intervention, and if so details of use
- Details of any behavioural support provided
- Duration of reduction period
- Who delivered the intervention?

Outcomes:

- Did the trial examine whether the reduction arm reduced as instructed, and that the abrupt arm did not reduce?
- Outcomes measured
- The strictest definition of abstinence used
- Whether abstinence was biochemically verified, and if so, how
- whether enough data are available for an intention-to-treat analysis
- the proportion of quitters in each intervention arm
- the number of adverse events in each arm
- Amount of reduction in cigarettes per day in each arm (self report and/or chemical biomarkers)
- Additional outcome results
- Drop-out rates
- Information about withdrawals
- Further information about adverse events
- Missing data in both arms.

Assessment of risk of bias in included studies

Risk of bias for each trial was assessed within the domains of sequence generation, allocation concealment and incomplete outcome data, using the risk of bias table, as outlined in the Cochrane Collaboration Handbook (Handbook 2008).

Measures of treatment effect

We compared quit rates between the abrupt cessation and reduction groups, calculated on an intention-to-treat (ITT) basis, including all participants originally randomized to a trial arm. Any participants lost to follow up were treated as relapsed, excluding any deaths. We used relative risk as the summary statistic in any meta-analyses, using the Mantel-Haenszel fixed-effect model for pooling results, checking for no significant heterogeneity. We also compared the number of adverse events between arms, however no meta-analysis was carried out for this outcome as data was sparse and not consistently measured across studies.

Assessment of heterogeneity

Any inconsistency across study results was identified and assessed by examining forest plots for poor overlap of confidence intervals, and by examining the I-squared statistic.

Subgroup analysis and investigation of heterogeneity

We conducted sub-group analyses comparing trials which used pharmacotherapy as part of the interventions with those that did not. We also grouped interventions by whether or not the instruction on how to quit smoking was given alongside behavioural support or by self-help methods.

Sensitivity analysis

We tested study design by investigating the sensitivity of the main effect, when adjusting for the only cluster randomized trial eligible for inclusion in the meta-analysis and when excluding the studies where non-validated self-report data was used for the meta-analysis,

RESULTS

Description of studies

See: Characteristics of included studies; Characteristics of excluded studies; Characteristics of ongoing studies.
See Characteristics of included studies, Characteristics of excluded studies, Characteristics of ongoing studies.

Results of the search

The searches of the Cochrane Specialised Register, MEDLINE, EMBASE and PsycINFO resulted in 543 unduplicated references. Additionally one of the authors of this review has just completed a study comparing reduction to abrupt quitting and has written a study report (Hughes 2009), which cited two further studies possibly relevant for inclusion. These 543 references were screened for eligibility based on their titles and abstracts, resulting in a reduced total of 30 studies. These studies were then independently assessed by two authors for eligibility, based on the questions specified above. We found 10 studies which were relevant for inclusion in the review based on these criteria; seven of these took place within the United States of America (Flaxman 1978; Cummings 1988; Curry 1988; Cinciripini 1995; Jerome 1999; Riley 2005; Hughes 2009), the remaining three were situated in Austria (Gunther 1992), Switzerland (Etter 2009) and Spain (Roales-Nieto 1992). We also discovered three ongoing studies (Riley 2001; Cinciripini 2006; Lindson 2009) which, when completed, may also be relevant for inclusion. The authors of eight studies (Cummings 1988; Curry 1988; Jerome 1999; Riley 2001; Riley 2005; Roales-Nieto 1992; Cinciripini 2006; Etter 2009) provided additional information when contacted.

Included studies

Characteristics of participants

The 10 included studies all recruited adult cigarette smokers with an aim to quit. Seven studies recruited participants from the community using advertisements (Flaxman 1978; Cummings 1988; Curry 1988; Cinciripini 1995; Riley 2005; Etter 2009; Hughes

2009). One study recruited work-sites to take part and then recruited their employees by posting advertisements and internal memos (Jerome 1999). Another recruited students using advertisements at a university (Roales-Nieto 1992), and another recruited patients consulting a hospital based smoking counselling service (Gunther 1992).

In one study these participants were then randomized in clusters (work-sites) to study arm (Jerome 1999), however for all other included studies participants were individually randomized. In the eight studies where participant gender was reported participants were on average evenly split between males and females, and the average reported age of participants (averaged across seven studies) was 42.8 years. Eight studies reported average baseline cigarettes per day in all participants, and this ranged from 23 to 28 cigarettes per day, with an average of 25.4.

Sample sizes

The total sample size across the 10 included studies ranged from 23 to 1895, with a mean sample size of 487. However not all conditions in all of the studies were used in the meta-analysis. When only the conditions relevant to this review were taken into account, sample sizes ranged from 14 to 1277, with a mean of 376. In five of the included studies all conditions randomized were relevant to the current review and were therefore included in the meta-analysis, however five of the studies randomized participants to interventions which were not relevant. Cummings 1988, Jerome 1999 and Hughes 2009 all included a control condition, which did not provide specific advice on how to quit, but provided information about the health implications of smoking, praise for quitting, and material emphasizing the importance of a general program of physical health (including quitting smoking) respectively. Flaxman 1978 included an immediate quit condition where participants were asked to quit the day after enrolling in the study and received substantially less behavioural support then the other conditions. Roales-Nieto 1992 included two conditions where the participants' goal was to reduce their smoking and control it rather than to reduce and quit completely. All of these conditions were deemed not relevant to this review and were excluded from any meta-analyses.

Interventions

All of the included studies had at least one group of participants who were instructed to reduce the amount they smoked before they quit, and at least one group instructed to quit smoking abruptly. In four of the studies, participants were advised on either abrupt or gradual cessation by self-help manuals or a handheld computer programme (Cummings 1988, Jerome 1999, Riley 2005, Etter 2009). Participants in another five studies were given face-to-face (Flaxman 1978, Gunther 1992, Roales-Nieto 1992; Cinciripini 1995) or telephone based (Hughes 2009) behavioural support as a means to assist either reduction or abrupt cessation. In the remaining study one reduction arm and one abrupt arm consisted of self-help therapy, and participants in the other reduction and abrupt arms were provided with behavioural support (Curry 1988). The behavioural support varied in terms of the overall length of time for which support was provided, the length of support sessions, number of support sessions, whether these were provided to individuals or groups, and who provided the support, however they all included pre-quit sessions where participants were taught strategies to help them avoid smoking when tempted, such as strategies to maximise self-control, and post-quit sessions focusing on relapse prevention. Most of the self-help interventions consisted of information booklets, some of which provided the participants with written activities. However the reduction interventions in Jerome 1999 and Riley 2005 gave participants the LifeSign handheld computer (PICS Inc); LifeSign structures a gradual reduction schedule, prompts users to smoke and allows them to record each cigarette they smoke. In the Jerome 1999 study this computer was provided, with a 48 page manual, which consisted of instructions on how to use the computer and information about behaviour modification strategies and relapse prevention. In the Riley 2005 study participants only received brief instructions on how to use the device and no further information. This was designed as a minimal contact intervention, which matched the minimal instructions provided to the abrupt quitting intervention group members, who received a calender log to record their smoking.

The abrupt quitting method advised for participants did not vary much across the ten studies. Participants were either given a quit date or asked to choose one themselves, and then asked to smoke as normal and quit abruptly on this date, with no prior cutting down. Quit dates ranged from zero to five weeks following baseline assessment. The smoking reduction interventions were more varied across studies as follows, however all reduction methods culminated in a quit day:

- Cummings 1988 gave participants unspecific advice on how to quit; they were simply advised to reduce the amount smoked over two weeks before quitting. Suggestions were provided on how they could reduce, such as setting daily goals, switching brands, changing habits and delaying the first cigarette; but ultimately it was left to participants to choose by how much to reduce and which, if any, strategies to use to achieve this.
- Three studies asked participants to reduce cigarettes per day by a certain quota over a set time interval without providing participants with any particular strategy to do so. Etter 2009 asked participants to reduce their smoking to 50% of baseline over four weeks and then quit completely. Gunther 1992 asked participants to reduce their smoking by five to ten cigarettes per week, depending on how much they were smoking at baseline, over five weeks until they were not smoking at all. Roales-Nieto 1992 instructed participants to reduce by 25% of baseline in week one, 50% in week two, 75% in week three and to quit completely in week four.

- In the Cinciripini 1995 study two groups of participants were asked to reduce their smoking; one of the groups reduced smoking by a set quota but did not use a specific technique to achieve this, as in the three studies above. Participants cut down to 66% of their baseline smoking rate in the first week of reduction, to 33% of baseline in the second week, and to 22% of baseline in the third week, until they reached two to four cigarettes per day. The second reduction group reduced by the same quota of cigarettes, but this was structured. Each week the advised smoking rate was divided by the number of hours in the participants' waking day to calculate an inter-cigarette interval. Participants were then able to smoke only in the first five minutes of each interval, and any missed cigarettes could not be accumulated for later use. Both groups quit in the week following the third week of reduction, and were combined for the purposes of our meta-analysis.
- Jerome 1999 and Riley 2005 also used inter-cigarette intervals to reduce smoking to nil. They implemented this using a handheld computer called LifeSign, which developed a smoking reduction schedule, lasting between 10 to 28 days, depending on each individual's baseline smoking rate and progress through the programme. The machine beeped and put a reminder on its screen to prompt participants to smoke.
- Hughes 2009 advised participants to reduce their smoking by 25% of baseline in week one, 50% in week two and 75% in week three, before quitting completely. They were also provided with four structured ways to do this, which they could choose between. The first was scheduled reduction where participants were advised to gradually increase the time between cigarettes (the inter-cigarette interval). The second asked participants to rate each cigarette of the day in terms of how difficult it would be to give up and then eliminate each in turn starting with the most difficult first. The third was the same as the second but participants started with the easiest first. The fourth involved the participant increasingly delaying the time from waking to the first cigarette of the day. Abstinence results did not appear to differ across the methods and so the data was pooled.
- Flaxman 1978 differed from the previous approaches as participants were not asked to reduce by a certain quota of cigarettes, but to identify situations that caused them to smoke. They were then asked to rate these situations in terms of how difficult it would be to abstain from smoking and then to eliminate smoking in one situation every three days, starting with the easiest situation and proceeding to the most difficult. In one reduction group participants continued this until they were not smoking at all and in the other they reduced until they were smoking in 50% of their baseline smoking situations and then quit abruptly. These two reduction groups were combined into an overall reduction group in our meta-analysis.
- One study gave very limited information as to how reduction took place (Curry 1988); the method was described as cigarette tapering and a gradual acquisition of coping skills. The author confirmed that this was a reduction method relevant for inclusion in this review, however no further detail could be provided.

Pharmacotherapy

Three of the studies included in this review gave participants pharmacotherapy as a part of their interventions. In all cases this was in the form of nicotine replacement therapy (NRT); one study used gum (Etter 2009), another lozenges (Hughes 2009) and the third nasal spray (Riley 2005). In the reduction arm of each study participants used the NRT both pre- and post- quit, and in the abrupt quitting arm post-quit only. In the pre-quit period Etter 2009 advised participants to use at least 10 pieces of 4mg nicotine gum per day, Hughes 2009 requested that participants replace each cigarette missed with a 2mg or 4 mg lozenge (4mg for those who smoked within 30 minutes of waking and 2mg for others). Riley 2005 signalled when participants should use the nasal spray using the same LifeSign handheld computer as was used to signal smoking. The appropriate nasal spray dosage was determined for each individual user depending on their recorded baseline smoking rate.

Outcomes

Nine of the 10 studies reported smoking abstinence as an outcome at either six month follow-up (Flaxman 1978; Cummings 1988; Hughes 2009), 12 month follow-up (Gunther 1992; Curry 1988; Etter 2009) or both (Cinciripini 1995; Jerome 1999; Riley 2005). The remaining study (Roales-Nieto 1992) reported cigarettes per day over seven days at six month, nine month and 12 month follow-ups for individual participants; it was possible to calculate abstinence rates from this information. Where abstinence was measured at six and 12 month follow-ups the 12 month rates were used in the meta-analysis. In three studies smoking abstinence was reported as point prevalence (Roales-Nieto 1992; Jerome 1999; Riley 2005), and in six studies as prolonged/continuous (Cummings 1988; Curry 1988; Gunther 1992; Cinciripini 1995; Etter 2009; Hughes 2009). Flaxman 1978 did not report how abstinence was defined. Abstinence was verified in eight of the included studies, by either expired carbon monoxide (Jerome 1999; Riley 2005; Etter 2009; Hughes 2009), saliva cotinine (Cinciripini 1995; Etter 2009), saliva thiocyanate (Curry 1988), or asking a relative or friend to confirm the participant had stopped smoking (Cummings 1988; Roales-Nieto 1992). However verified data were not used for one of the studies (Cummings 1988), as there were problems with the naming of a friend or relative to verify participants' self report. If participants did not name a person to verify their self-report, or if their self-report contradicted with their friend/relative's then they were classed as smoking, however 20% of those claiming abstinence did not provide a friend/relative. Participants who lived alone were four times more likely not to name a

person for verification than those who lived with others. All of the study reports either reported ITT analysis or provided sufficient information to allow us to calculate this, apart from Cummings 1988 where the author provided this information when contacted. Only two studies (Etter 2009, Hughes 2009) reported information about adverse events. Further information was obtained from these authors and some limited information was also obtained from the authors of Riley 2005. Reporting was not consistent across studies and so it was not possible to carry out a meta-analysis, therefore these data are synthesised qualitatively.

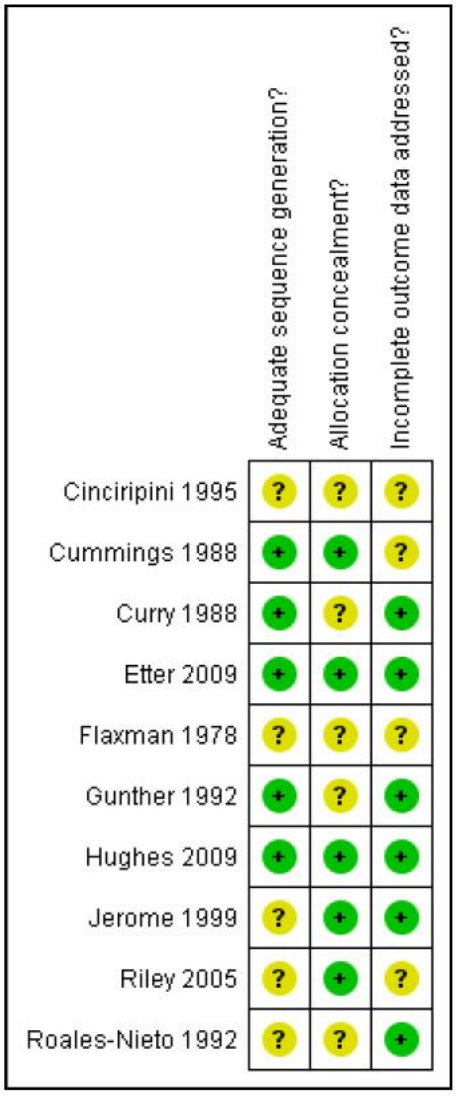
Excluded studies

Studies which were identified as potentially relevant but later excluded are listed, with reasons for exclusion, in the Characteristics of excluded studies table. The primary reasons for exclusion fell into one of three categories: 1) The goal of the intervention was to reduce smoking and control it, rather than quit (Hatsukami 1988; Bolliger 2000b), 2) the main outcome was smoking rates, and it was not possible to calculate abstinence rates from the data presented or to get these from the authors (Marston 1971), 3) both of the trial arms quit in the same way (Bernard 1972; Glasgow 1989; Cinciripini 1994; Herrara 1995; Daughton 1998; Jerome & Fiero 1999; Rose 1998; Bolliger 2000a; Schuurmans 2004; Rose 2006; Rezaishiraz 2007; Bullen 2008; Rose 2009; Shiffman 2009). Five of the excluded studies examined pre-treatment with NRT vs placebo prior to the quit date, and did not instruct smokers to reduce pre-quit. Three of these reported that participants spontaneously reduced whilst using the NRT (Rose 1998; Rose 2006; Rose 2009), two of which found that participants who reduced their smoking the most were more likely to achieve abstinence (Rose 2006; Rose 2009). However, as none of the studies instructed subjects to reduce their smoking during the pre-cessation phase of the treatment, this success cannot be attributed to an instruction to reduce and so the studies were excluded.

Risk of bias in included studies

We extracted information from each study to assess the risk of biased randomization, whether allocation concealment took place, and whether incomplete outcome data was addressed. This was assessed as either likely to cause bias (No), unlikely to cause bias (Yes) or unclear, if insufficient information was present to make a judgment (Figure 1).

Figure 1. Methodological quality summary: review authors' judgements about each methodological quality item for each included study.



• Randomization sequence generation. Five studies reported adequate information on sequence generation to be classified as having minimal chance of bias in this regard. Five of the studies (Flaxman 1978; Roales-Nieto 1992; Cinciripini 1995; Jerome 1999; Riley 2005) did not describe the method of randomization used, and so were classified as unclear in this category. All of the studies randomized individual participants, apart from Jerome 1999 who randomized work-sites to trial arms. Trials that randomize clusters to treatment arms can be given a higher weighting than they should if data on individuals are entered in the meta-analysis. This is because the analysis assumes there is no connection between individuals in the same group in the likelihood of them stopping smoking successfully. However when we carried out an analysis adjusting for the clustering in Jerome 1999, although the study weighting decreased from 22% to 17% the main result was not sensitive to the adjustment (Risk ratio (RR)= 0.93, 95% CI= 0.78 to 1.12). This adjustment used an intra-class correlation of 0.0105 (as recommended by Martinson 1999 for an outcome of percentage quit in the work place) and an average number of people per group of 18.3 (design effect = 1.18).

• Allocation concealment. When rated in terms of allocation concealment from clinicians enrolling participants into studies, four studies (Cummings 1988; Jerome 1999; Riley 2005; Etter 2009) were rated as unlikely to cause bias, as all interventions consisted of self-help therapy and there was either no or minimal contact with investigators/enrolling clinicians. Consequently, participants enrolment in the studies could not depend on knowledge of the allocation sequence as there was no clinician deciding on whether to enrol or which treatment to give. Hughes 2009 was also rated as unlikely to cause bias in this category as a statistician generated a concealed allocation sequence. The five remaining studies did not report on allocation concealment and were therefore classed as unclear.

• Incomplete outcome data. In the category of incomplete outcome data six studies were classed as unlikely to cause bias, as participant attrition was reported as similar in all trial arms. The four remaining studies were classed as unclear; three of the studies (Flaxman 1978; Cinciripini 1995; Riley 2005) did not provide any information about participant attrition or missing data, and the abstinence rates table in the Cummings 1988 report appeared to leave 18 participants unaccounted for. Due to the length of time since the study had been completed the author could not confirm why this was the case, but did provide further information so that an intention-to-treat analysis could be carried out, in which the missing participants were classified as not abstinent. Participants attrition in general was similar across arms, however the study was classified as unclear as we didn't know the allocation of the missing participants and whether this was similar across arms.

Two of the included studies (Flaxman 1978; Cinciripini 1995) were rated as unclear for all three of the above bias categories and another two were rated as unclear for two (Roales-Nieto 1992; Riley 2005). We carried out a sensitivity analysis to establish whether the main result was sensitive to the exclusion of these four studies and found that it was not (RR= 0.94, 95% CI= 0.76 to 1.16).

Other potential sources of bias were failure to verify smoking abstinence by biochemical means and whether participants conformed to their allocated intervention.

• Biochemical verification. Studies that did not validate self-reports of abstinence (Flaxman 1978; Gunther 1992), or where validation was potentially flawed, and therefore not used in this review (Cummings 1988) could potentially over-estimate abstinence. However we would not expect this to differ between arms, and a sensitivity analysis confirmed that the main findings were not sensitive to the exclusion of studies where abstinence was not validated (RR= 0.91, 95% CI= 0.74 to 1.12). SRNT 2002 concludes that population based studies with limited face-to face contact, and where data collection is optimally by mail, telephone, or on the Internet are unlikely to benefit from biochemical verification. Population studies have much higher biochemical verification refusal rates than clinic based studies, if all participants who refused were classed as smoking then this would be likely to overestimate smoking rates. In reality the extent that self-reports inflate abstinence rates is small and rarely differs across conditions. Also, in studies where there is very little contact with an investigator or therapist this reduces demand characteristics, meaning there is little incentive to lie.

• Adherence to method of quitting allocated. Six of the 10 studies assessed whether participants followed the instructions they had been given on how to quit i.e. to reduce or quit abruptly without prior reduction. Three of these studies (Roales-Nieto 1992; Etter 2009; Hughes 2009) found that participants followed instructions; the participants in the reduction group reduced before quitting and the participants in the abrupt group quit abruptly with no prior reduction. Cinciripini 1995 found that the reduction group complied well with their instructions but the abrupt group also reduced by seven to eight cigarettes per day less than baseline before quitting. However the reduction group smoked significantly fewer cigarettes than the abrupt group before quit day. The two remaining studies to report on adherence to the intervention allocation found that participants did not abide by intervention instructions. In Flaxman 1978 the group which reduced until they were not smoking at all reduced by a mean of 6 cigarettes per day, and the group who reduced to 50% of baseline then quit reduced by a mean of 3.5 cigarettes per day. However the abrupt quit group also reduced by an average of 3.4 cigarettes per day before they quit, meaning there

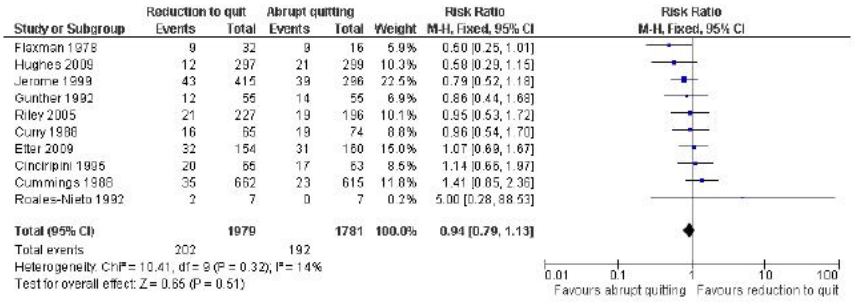
was little difference between reduction in the partial reduction group and the abrupt quit group. Cummings 1988 asked participants after quit day whether they had quit abruptly. 39% of participants in the abrupt group quit abruptly and 40% of the reduction group also quit abruptly, therefore there appeared to be little difference between the arms in the methods of quitting that were actually used. As is the case with all ITT analyses, it is only ever possible to examine the effect of allocation to a quitting method, not the effectiveness of actually following it.

Effects of interventions

Abstinence Outcome

The meta-analysis included 10 trials with a total of 3760 participants. There was evidence that reduction produced similar quit rates to abrupt cessation and that any difference in effectiveness was small. The overall rate ratio for abstinence for reduction versus abrupt cessation was 0.94, 95% CI= 0.79 to 1.13 (Figure 2). There was low heterogeneity (I^2 = 14%), suggesting that the effect of reduction relative to abrupt cessation did not differ across trials. For all studies confidence intervals spanned one, indicating no study achieved statistically significant superiority of either gradual or abrupt cessation. We have not reported pooled quit rates because studies varied on a number of factors, such as definition of abstinence (point prevalence or prolonged), length of abstinence (6 months or 12 months), whether or not behavioural support was provided , and whether pharmacotherapy was provided, meaning that average rates would not be useful.

Figure 2. Reduction to quit versus abrupt quitting. Outcome: abstinence



The effect of gradual versus abrupt cessation in participants using pharmacotherapy

The studies were split into two sub-groups to assess whether the effect of gradual cessation depended on whether people used smoking cessation pharmacotherapy or not. One sub-group included studies that didn't use any pharmacotherapy as part of the interventions (Flaxman 1978; Cummings 1988; Curry 1988; Gunther 1992; Roales-Nieto 1992; Cinciripini 1995; Jerome 1999). The other sub-group included the remaining studies (Riley 2005; Etter 2009; Hughes 2009), which utilised nicotine replacement therapy pre- and post-quit in the reduction interventions and post-quit in the abrupt interventions. There was no evidence of the superiority of either gradual or abrupt cessation whether pharmacotherapy (NRT) was used (RR= 0.89, 95% CI= 0.65 to 1.22), or not (RR= 0.97, 95% CI= 0.78 to 1.21), and neither was there evidence that pharmacotherapy modified the effect of reduction versus abrupt cessation (Analysis 1.2).

The effect of the type of behavioural support utilized

We also conducted a sub-group analysis by the type of therapy provided. Some of the included studies used self-help therapy (Cummings 1988; Jerome 1999; Riley 2005; Etter 2009), and some behavioural support (Flaxman 1978; Gunther 1992; Roales-Nieto 1992; Cinciripini 1995; Hughes 2009). Curry 1988 included study arms that were self-help and others that were behavioural, so these were split accordingly for the sake of this analysis. Again the risk estimates were similar whether the instruction in how to quit and support for achieving this was given by self-help (RR= 0.98 95% CI= 0.78 to 1.23) or by behavioral support (RR=

0.87 95% CI= 0.64 to 1.17), and neither reduction nor abrupt quitting resulted in superior quit rates in either case (Analysis 1.3).

Adverse Events Outcomes

The secondary objective of this review was to compare adverse events between arms, however no attempt has been made to do this quantitatively as there was a a lot of variation in nature and depth of reporting. The seven studies that did not utilise pharmacotherapy did not report information about adverse events. Of the three studies using pharmacotherapy, Riley 2005 reported no information on adverse events in the study report, but the author kindly supplied further information for this review. Etter 2009 and Hughes 2009 also provided additional information as well as data reported in the publications. Etter 2009 and Riley 2005 reported that no participants in these studies experienced serious adverse events. Etter 2009 also provided data obtained in response to the question: "If you experienced undesirable effects due to the nicotine gum, please describe them" (open ended question), asked two months after target quit day. Overall the most commonly reported symptoms were mouth pain/dry mouth/throat burns, hiccups, stomach pain/heartburn- the most common side-effects from oral NRT. Nine of the total symptoms reported occurred more frequently in the reduction groups (mouth pain/dry mouth/throat burns, hiccups, stomach pain/heartburn, pain/cramp in jaws, mouth ulcers, headache, eructation, heart palpitations, cough) four in the abrupt groups (nausea, bad taste, insomnia, vomiting) and three were reported as frequently in both groups (malaise, constipation, diarrhoea). Hughes 2009 reported that the incidence of adverse events rated severe was small and similar across conditions. 3% of participants randomized to the reduction to quit group reported severe adverse events and 5% of the abrupt quit group; the incidence of discontinuation was 1% for both groups.

DISCUSSION

The 10 studies included in this review compared interventions that instructed participants to quit smoking gradually by reducing the amount they smoke with interventions that instructed participants to quit smoking abruptly without prior reduction. The results provide evidence that reduction to quit provides similar quit rates to abrupt quitting with no evidence that one method is significantly superior to the other in adults trying to quit smoking. This applies whether therapy is self-help or includes behavioural support and whether the quit attempt uses NRT or not. The similarity of the result in the NRT sub-group and the non NRT subgroup suggests that the success of the reduction interventions relative to the abrupt quit interventions is not due to the use of pre-quit NRT. We were unable to combine data on absolute quit rates as studies varied on a number of factors expected to influence quit rates, for example length of follow-up, and so can not provide meaningful estimates of average quit rates as a result of reduction to quit and abrupt quit interventions.

We were unable to combine statistically the adverse events data, and therefore could not determine whether adverse events differed significantly between the intervention groups that reduced and used NRT pre- and post-quit, and the intervention groups where participants quit abruptly and used NRT post-quit. However a recent review conducted a meta-analysis (Moore 2009) of seven placebo controlled RCTs, which used NRT to assist reduction to stop smoking and found that there were no significant differences in deaths (odds ratio (OR)= 1.00, 95% CI= 0.25 to 4.02), serious adverse events (OR= 1.16, 95% CI= 0.79 to 1.50), and discontinuation due to adverse events (OR= 1.25, 95% CI= 0.64 to 2.51), between the placebo and NRT interventions. The only adverse event that was more common in the NRT interventions was nausea (OR= 1.69, 95% CI= 1.21 to 2.36), which is a common side effect of nicotine replacement therapy. Taken with other safety data on concurrent smoking and use of NRT (Fagerstrom 2002), there appears to be no reason to recommend against the practice of gradual reduction assisted by NRT. At least one trial shows that among smokers trying to quit smoking by gradual reduction, using NRT is more effective than use of placebo in supporting abstinence (Shiffman 2008), and a Cochrane Review of smoking harm reduction (Stead 2007) found that people who did not originally want to quit smoking were more likely to be abstinent from cigarettes at long-term follow-up when NRT was used as an aid to reduction than when a placebo was used (OR= 1.90, 95% CI= 1.46 to 2.47). On this basis, if reduction is to be used as a means of quitting, use of NRT or other pharmacotherapy appears desirable. NRT is licensed for use in this way in the UK and Australia, however the US Medicines Regulator, along with other pharmaceutical regulators have not yet licensed NRT for this purpose.

An important limitation of any meta-analysis is that methods vary across studies and the underlying assumption that the meta-analysis is trying to estimate a single true rate ratio might not hold. In this instance patient populations, outcome definitions, provision of pharmacotherapy and the behavioural support provided varied across the included trials. Despite this, the measure of heterogeneity was low suggesting that heterogeneity of these elements did not translate into heterogeneity of effectiveness of reduction. One of the studies also varied because it used cluster randomization, but sensitivity analysis suggested that allowing for this or not had little influence on the result of the meta-analysis. Four of the studies included in the meta-analysis (Flaxman 1978; Cummings 1988; Curry 1988; Cinciripini 1995) had more than one intervention that qualified as reduction and/or abrupt quitting, and we combined these to create one reduction arm and one abrupt quit arm per study. We considered entering the data for each trial arm separately to see if this would give us any more detailed information about the relative success of different reduction meth-

ods, however the methods used differed in each study (scheduled, non scheduled, group behavioural support, individual behavioural support, reduction to zero cigarettes before quit, reduction to 50% of baseline before quit etc), so they could not be pooled for a subgroup analysis, and therefore would be no more informative than the original studies.There is however some evidence that structured methods of reduction are more effective than simple advice to cut down without following specific methods (Levinson 1971; Cinciripini 1995).

Two of the 10 included studies (Etter 2009; Hughes 2009) were assessed as unlikely to cause bias for all three categories assessed. These studies were the most recent of the 10 studies, which may suggest that their increased reporting, relative to the other eight studies, is due to awareness of the revised CONSORT reporting guidelines (Moher 2001), which were published in 2001, and advise reporting methods of sequence generation and allocation concealment, and a flow diagram illustrating the flow of participants through the study. Seven of the studies rated in at least one bias category as 'No' or 'Unclear' were published before 2001 and the remaining study was not written up for publication. Therefore lack of reporting may be for these reasons rather than because bias is present. This may also explain why the reporting of adverse events was only present in the most recent studies. The main results of the two most recent studies do not differ much from the main results of the eight older studies, therefore there is no evidence that studies reporting better randomization procedures produced different results. Many of the older studies did not propose a hypothesis that favoured either a reduction or an abrupt quitting intervention (Flaxman 1978; Curry 1988; Gunther 1992; Roales-Nieto 1992; Cinciripini 1995) so in the cases where allocation concealment was not reported, and so may not have occurred, there is no reason why allocation would have been carried out to favour any particular arm.

Whilst assessing studies for eligibility there were two studies (Curry 1988; Jerome 1999) where uncertainty arose about whether the intervention methods were abrupt or reduction to quit. Curry 1988 reported that one method of quitting used in the study was "cold turkey" and that the other was "tapering and nicotine fading". There is no further detail given on these methods so we contacted the authors who confirmed that one of these methods was an abrupt quit method and the other was a reduction to quit method, which met our inclusion criteria. Jerome 1999 consisted of a study arm where participants reduced and then quit using a handheld computer, and an arm where participants were provided with an American Lung Association self-help booklet called "Freedom From Smoking For You and Your Family". The study report did not specify whether this booklet advised an abrupt quitting method or a reduction to quit method and the authors and the American Lung Association were unable to provide additional information. However Davis 1992 includes a table comparing the content of three self-help guides including this one, which reported that the topic of cutting down smoking is not covered. We therefore believe that including these studies in the review is appropriate. The failure of studies to clarify methods used to achieve abstinence does raise the possibility that studies could have been missed because authors described them in terms we did not expect. We followed up included studies reference lists to check for other studies that came up in our search and we found no other studies. Nevertheless, we could have failed to include all extant studies but there is no reason why publication bias or failure to find less clearly described or less prominent studies would be expected to bias the results towards reduction or abrupt cessation methods.

Surveys carried out in the general population (West 2001; Cheong 2007) have found that gradual quitting isn't as effective as abrupt quitting, however these differ from the RCTs included in this meta-analysis in ways that may explain the difference in outcomes. The participants quitting gradually in the RCTs (whether support was behavioural or self-help) were all provided with some instructions as to how to quit, which included setting quotas of cigarettes to reduce by, and setting time intervals at which participants could smoke. All of the included studies also appeared to require participants to set a target quit day providing them with a goal to work toward. However the participants included in the observational studies will have quit using a number of methods of gradual reduction, and it is likely that these will vary in their levels of success. The UK and US national guidelines do not recommend cutting-down before quitting and therefore services such as the UK NHS Stop Smoking Services (NHS SSS) only offer abrupt quitting as a cessation method. This means that those participants who chose gradual cessation were less likely to have benefited from any kind of support whilst quitting (behavioural or self-help materials), which in the case of the NHS SSS has been found to increase quit rates by up to four times. Therefore quitters choosing gradual reduction are automatically put at a disadvantage. A person who quits without support is also more likely to use an unstructured method, with no reduction goals, no particular method of reducing, and no target quit day. Cinciripini 1995 found that those participants that quit using unstructured reduction were less successful than those who used a more structured method. Two previous meta-analyses (Law 1995; USPHS 2008) have looked at nicotine fading as a smoking cessation intervention. These, however, differ from the current analysis, because as well as including studies where participants were asked to reduce nicotine intake by reducing the number of cigarettes they smoked, they also included studies where participants were asked to use graduated filters to remove progressively more nicotine from inhaled smoke, and studies where participants changed brands to cigarettes of successively lower nicotine yield. We chose not to combine all of these approaches in the current analysis as there is reason to believe that these methods do not all work by the same mechanisms. For example, one of the ways reducing cigarettes smoked may work is by weakening links between environmental cues (e.g. socialising) and smoking a cigarette. This wouldn't be applicable to using nicotine filters as

the person is still smoking in all the same situations and therefore still associates smoking with the same environmental cues. One of the reviews (Law 1995) compared the gradual quitting interventions with sudden or abrupt cessation as we have done in this case, however the second (USPHS 2008) compared nicotine fading with untreated control conditions and therefore the relative effectiveness of reducing nicotine intake and abrupt quitting was not reported. USPHS 2008 found that there was no effect of using nicotine fading techniques when compared to no treatment, however Law 1995 found that gradual cessation was 5% (95% CI= -2% to 11%) more effective than abrupt quitting, although this difference was not significant (p>0.10). Therefore as in this analysis neither abrupt quitting or reducing to quit provided superior quit rates.

The result of this analysis suggests that public health messages on cessation and cessation services supporting individuals who smoke could advocate or offer reduction as a way to quit for people who intend to quit soon. They can be confident that if people choose to quit by reducing before stopping entirely, this would not put them at a disadvantage compared with those who choose to smoke as normal and then quit abruptly. Reduction to quit might help those who have tried to quit a number of times without success and are disillusioned with the abrupt quit method. Having a new way to quit could give renewed hope, especially as many smokers see reduction as an intuitive first step toward stopping smoking completely. Offering reduction to quit may also appeal to those who would otherwise not have sought behavioural support and pharmacotherapy because they want to pursue gradual cessation and this is not currently supported. This would then enhance the proportion of the population that make assisted quit attempts and boost population cessation rates . Without help, around 4% of people who try to stop smoking sustain abstinence for one year (Hughes 2004), but with the aid of cessation treatment in the UK, around 15% of quitters abstain for a year (Ferguson 2005). This increase in success when behavioural support is provided suggests that we should be trying to encourage as many people as possible into cessation services. Our sub-group analysis, however, suggests that reduction is as successful as abrupt quitting whether the intervention consists of behavioural support or is self-help. Therefore this result could also benefit people who want to quit smoking on their own without behavioural support. If people who smoke are aware of an additional effective quitting method then this could also encourage more of them to quit who want to do so independently.

Reduction versus abrupt quitting risk ratios vary across the studies included in this meta-analysis (from Flaxman 1978: RR= 0.50, 95% CI= 0.25 to 1.01 to Roales-Nieto 1992: RR= 5.00, 95% CI= 0.28 to 88.53). We would expect the effect of the abrupt interventions to be constant across studies as abrupt quit instructions did not vary, therefore there may be a difference in the success rates of different reduction methods. This is supported by the fact that gradual reduction has been found to be less successful than abrupt quitting in observational studies, but as successful in RCTs. The studies included in this review used a number of different methods, including scheduled reduction, non-scheduled reduction, reducing to zero cigarettes before quitting, reducing to 50% of baseline before quitting. There are conceivably many more ways that people could reduce before going on to quit completely. Trials that have been carried out so far to compare different reduction methods are small and often participants aim to reduce rather than to quit completely. There has been no attempt to combine all of these studies into a review so that conclusions can be drawn and applied to policy development. Therefore further research needs to be carried out to investigate the methods of gradual reduction that smokers in the general population are using, and whether they are using any type of support alongside, to see whether this accounts for the difference in results between observational studies and RCTs. Further work is needed to identify the most effective reduction methods in those wanting to quit. Ideally this would be a review which amalgamates existing evidence and identifies literature gaps, leading to large-scale RCTs that directly compare different methods. In turn, this could inform policy and service development as to the most successful reduction to quit method(s). If there are marginal differences in the effects of different reduction methods then quitters could choose from a number of options. However, if there are methods shown to be significantly less effective, quitters should not be advised to use them as this might disadvantage them. It may prove useful to establish whether different quitting methods benefit different groups of smokers, e.g. a particular method may benefit a highly addicted smoker more than a less addicted one. If so, then a person could use a quitting method tailored to their individual profile, to produce the optimal likelihood of abstinence.

In summary, we found no big differences in effectiveness between advising people who smoke to quit abruptly or advising them to reduce cigarette consumption prior to quit day i.e. gradual quitting. These results apply to gradual quitting methods that all employed a definite quit day and it is not clear whether telling people to cut down and quit when they are ready would achieve the same results. Given these findings, it seems reasonable to offer smokers a choice of whether to cut down in preparation for quitting or to continue to smoke as normal and quit abruptly.

AUTHORS' CONCLUSIONS

Implications for practice

- Patients can be given a choice to quit smoking either by reducing cigarettes smoked before quitting or by quitting abruptly with no prior reduction.
- Reduction to quit can be implemented via self-help therapy or with the aid of behavioural support.
- NRT can be used to aid pre-quit reduction.

Implications for research

- Further research should focus on methods of reduction that smokers in the general population use to quit and whether they utilise behavioural or self-help support alongside these.
- A review of the existing literature on methods of smoking reduction is needed, and RCTs developed to determine which methods of reduction are the most effective.
- Research is needed to try and establish people who may benefit most from the abrupt and gradual approach to quitting smoking, in order to tailor smoking cessation to individuals.

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* *Indicates the major publication for the study*

CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Cinciripini 1995

Methods	Country: USA Recruitment: participants recruited from the community, method not stated.
Participants	128 smokers randomized to 4 groups, with at least 3 years smoking history, consumption of 15+ cigarettes per day (CPD), no current cessation treatment, psychiatric disorder or uncontrolled systemic illness. 58% F, av. age 45, av. CPD 24, av. 4 previous quit attempts.
Interventions	1. Scheduled reduced: inter-cigarette interval progressively lengthened, until quit day at week 5. 2. Non-scheduled reduced: CPD reduced using same quota as scheduled group but participants were free to choose when they smoked their cigarettes, until quit day at week 5. 3.Scheduled non-reduced: participants instructed to smoke at regular time intervals but the time intervals were not progressively reduced to quit day at week 5. 4. Non-scheduled, non-reduced: No manipulation of inter-cigarette interval or cigarette frequency, until quit day at week 5. Pharmacotherapy: No pharmacotherapy Type of support: Two-hour weekly group meetings; cognitive behavioural intervention weeks 2-5; relapse prevention weeks 5-9.
Outcomes	Abstinence: Prolonged abstinence (defined as smoking on fewer than 5 days between assessments) at treatment end (week 9) & 1, 6 and 12 month post-treatment. (PP at quit week (week 5) also reported). Validation: CO <6ppm at quit week, cotinine <14 mg/ml at treatment end & 1,6 and 12 month follow-up Other outcomes: CPD, coping behaviour, withdrawal score, tension & fatigue mood states, urge frequency, self-efficacy.
Notes	Groups 1 and 2 combined to create reduction group and Groups 3 & 4 combined to create abrupt quitting group.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Randomized, method not stated.
Allocation concealment?	Unclear	No information given.
Incomplete outcome data addressed? All outcomes	Unclear	Information on attrition/exclusions not given. Those with missing data were counted as non-abstainers.

Cummings 1988

Methods	Country: USA Recruitment: callers responding to advertisement of stop smoking hotline, who accepted a free stop smoking booklet.
Participants	1895 randomized to 4 experimental groups and 1 control group. 18+ year old current smokers. 65% F, av. age 42, av. CPD 28, av. 3 previous quit attempts.
Interventions	1. Booklet instructing smokers to gradually reduced cigarettes smoked before quitting. Day by day structured guide. 2. Booklet instructing smokers to gradually reduced cigarettes smoked before quitting. No day by day instructions. 3. Booklet instructing smokers to quit abruptly. Day by day guide. 4. Booklet instructing smokers to quit abruptly. No day by day instructions. 5.Control: booklet providing information on the health hazards of smoking and the nature of tobacco addiction, but did not give specific advice on how to stop smoking. Pharmacotherapy: No pharmacotherapy. Type of support: Self-help booklet.
Outcomes	Abstinence: Continuous between 1 month & 6 month follow-up. (1 week PP at 1 & 6 months post-enrolment, 1 month prolonged at 6 months post-enrolment also reported) . Validation: surrogate interview conducted with family member or friend. Other outcomes: report of cessation attempt, cigarettes per day, percentage of booklet read, booklet evaluation, actions taken in preparation for quit and after quit, method of quitting.
Notes	Groups 1 and 2 combined to create reduction group and Groups 3 & 4 combined to create abrupt quitting group. Surrogate interview validation data not used as there were problems with allocation of a surrogate- 20% of the quit participants refused to provide a surrogate, and participants were less likely to give a surrogate if they lived alone.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	"randomization was done from a pre-randomized list so subjects were randomized as they called into the study and were defined as eligible" (email communication).
Allocation concealment?	Yes	Self-help intervention involving minimal contact with investigators/enrolling clinicians, risk of bias assessed as low.
Incomplete outcome data addressed? All outcomes	Unclear	19.1% of total randomized lost to follow-up, reported not to vary by arm. 18 additional participants missing from report results table, these participants are in-

Cummings 1988 *(Continued)*

		cluded in the current analyses and treated as non abstainers, however their allocation to treatment arms is unknown.

Curry 1988

Methods	Country: USA Recruitment: from the community via radio announcements and newspaper adverts offering stop smoking program.
Participants	139 cigarette smokers randomized to 4 experimental groups. 51% F, av. age 40.6, av. CPD 28, av. 3.7 previous quit attempts.
Interventions	1. Reduction (Absolute abstinence)-group based: cigarette tapering and nicotine fading before quit day in week 5. Groups met once a week for two hours, for 8 weeks. 2. Reduction (Absolute abstinence)-self-help: cigarette tapering and nicotine fading before quit day in week 5. Provided with work books with written exercises. 3. Abrupt (Relapse prevention)-group based: quit abruptly at week 3. Groups met once a week for two hours, for 8 weeks. 4. Abrupt (Relapse prevention)-self-help: quit abruptly at week 3. Provided with work books with written exercises. Pharmacotherapy: No pharmacotherapy Type of support: Self-help booklet and group behavioural support.
Outcomes	Abstinence: Prolonged abstinence from at least month 9 to month 12 at 12 month follow-up (PP at EOT and 3 months post treatment also reported) Validation: saliva thiocyanate test during final week of treatment and at 12 month follow-up. Other outcomes: time to relapse, number of quit attempts, returns to abstinence after lapse.
Notes	Groups 1 and 2 combined to create reduction group and Groups 3 & 4 combined to create abrupt quitting group for the main analysis. For sub-group analysis this study was split back into 4 groups to look at self-help and behavioural support interventions separately.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	"Participants were stratified by availability for day or evening group meetings. Within each stratum a total of 24 participants were picked randomly and were grouped into pairs of 12. A coin toss determined assignment to the RP or AA program."
Allocation concealment?	Unclear	No information given.

Curry 1988 *(Continued)*

Incomplete outcome data addressed? All outcomes	Yes	Significantly more participants assigned to self-help treatment withdrew (64% vs 36% in group condition) before treatment began suggesting assignment to self-help was the overriding contributor to attrition. It is reported that there was no difference in participation rates between the reduction and abrupt quit groups.

Etter 2009

Methods	Country: Switzerland Recruitment: from the community through advertisements on a smoking cessation web site (http://www.stop-tabac.ch), via newspaper advertisements, and by physicians in private practice.
Participants	314 participants randomized to 2 groups, smoking at least 15+ CPD, aged 18+, with a commitment to quit smoking on a target date in the next two months, and to use 10+ pieces of nicotine gum per day. 41.3% F, av. age 43.1, av. CPD 23.7, 42.4% had made a 24hr quit attempt in the past 12 months.
Interventions	1. Pre-cessation treatment group: received recommendation to decrease cigarette consumption by half before quitting roughly 2 months after baseline, whilst using nicotine gum. 2. Usual care: received instruction to quit abruptly on a target quit date, roughly 2 months after baseline. Pharmacotherapy: Unflavoured 4 mg nicotine gum. 4 weeks pre-quit in pre-cessation arm and 8 weeks post-quit in pre-cessation and usual care arm. Type of support: Self-help- booklet in the mail and a smoking cessation web site.
Outcomes	Abstinence: 7 day, 4 week, 6 month, and 12 month prolonged abstinence at 12 months post-quit (PP at 3 days post-quit. 7 day , 4 week, 2 month prolonged abstinence at 8 weeks post-quit (EOT) also reported) Validation: CO and saliva cotinine at 12 month follow-up. Other outcomes: self-efficacy, preference for study group, method of quit, gum use, CPD in pre-quit week, cravings, dependence, attitudes toward smoking, appetite, hunger, withdrawal, anxiety and depression, weight gain.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	"Randomization was based on a list of random numbers generated by a computer."

Etter 2009 *(Continued)*

Allocation concealment?	Yes	Self-help intervention involving minimal contact with investigators/enrolling clinicians, risk of bias assessed as low.
Incomplete outcome data addressed? All outcomes	Yes	Participation rates were similar in both arms at all time points: 11% of reduction group and 12.5% of abrupt group lost to follow-up at 12 months.

Flaxman 1978

Methods	Country: USA Recruitment: by means of public service announcements of a smoking cessation clinic on television, radio and in local newspapers
Participants	64 cigarette smokers randomized to 4 groups. 50% F, av. age not reported, av. CPD 26, 42.4% av. 3 previous quit attempts.
Interventions	1. Gradual reduction: stimulus hierarchy technique- situations leading to smoking were categorised and rank ordered according to anticipated difficulty of not smoking in each. Participants were instructed to give up in the easiest situation first, progressing to the hardest. Adding one situation every three days. 2. Partially gradual reduction: Same as gradual reduction, however participants quit abruptly when their smoking rates dropped to half of baseline. 3. Target date: a date approximately 2 weeks from the first session was selected for abrupt quitting. 4. Immediate quit: participants were scheduled to quit smoking the next day. Pharmacotherapy: No pharmacotherapy. Type of support: Behavioural. Participants met with experimenters twice a week for 0.5 hour sessions pre-quit and were presented with self-control techniques.
Outcomes	Abstinence: measured at 1 week and 6 months post-treatment. No further definition of abstinence given. Validation: No information given. Other outcomes: mean daily post-treatment smoking rates (weeks1-8 and 6 months). percentage of baseline smoked.
Notes	Groups 1 and 2 combined to create reduction group and Group 3 abrupt quitting group. Group 4 data was not used as this group received a lot less behavioural support than the other groups. Participants in each group were also split into one of two phase 2 post-quit interventions, however there was no difference between these two conditions at 6 month follow-up so this is not taken into account.

Risk of bias

Item	Authors' judgement	Description

Flaxman 1978 *(Continued)*

Adequate sequence generation?	Unclear	Randomized; "Sixty-four subjects were blocked by sex and number of cigarettes smoked per day and randomly assigned to one of the eight treatment cells and to two of the six experimenters", precise method not described.
Allocation concealment?	Unclear	No information given.
Incomplete outcome data addressed? All outcomes	Unclear	No information given.

Gunther 1992

Methods	Country: Austria Recruitment: patients consulting a hospital based smokers' counselling service between Februaury and December 1988.
Participants	110 participants randomized to 2 groups, examined by a psychiatrist to determine tobacco dependence, value of 6+ on Fagerstrom tolerance questionnaire. Av. CPD 26.4.
Interventions	1. Gradual stopping: From the second hour of counselling the number of cigarettes was reduced, depending on initial consumption the number of cigarettes was reduced by 5-10 cigarettes per week. 2. Sudden stopping: a quit date was set on which participants quit abruptly. Pharmacotherapy: No pharmacotherapy. Type of support: Behavioural - Total of 12 hours of counselling (1 hour per week).
Outcomes	Abstinence: 1 year prolonged (relapse during the 1 year follow-up period= resumption of nicotine use for more than 3 days at follow-up date). Validation: No validation at 1 year follow-up. Other outcomes: response rates, number of CPD at 1 year follow-up, relapse.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	"computer generated randomized list".
Allocation concealment?	Unclear	No information given.
Incomplete outcome data addressed? All outcomes	Yes	Only the participants initially abstinent were followed to one year (76% sudden, 73% gradual). Of these, loss to follow-up was 36% in the sudden stopping group and 22% in the gradual stopping group (non

Gunther 1992 *(Continued)*

		statistically significant difference).

Hughes 2009

Methods	Country: USA Recruitment: respondents to local newspaper and radio advertisements.
Participants	746 daily smokers randomized to 3 groups, smoking at least 15+CPD, with no increase or decrease in CPD by 20%+ in last month. 54% F, av.age 48, av. CPD 23.
Interventions	1. Gradual: participants could choose from four reduction methods to reduce smoking by 25% week 1, 50% week 2, 75% week 3, quit week 4 2. Abrupt: participants advised not to change their CPD prior to set quit day. 3. Brief Advice: praised on decision to quit, not advised how to do so. Pharmacotherapy: NRT (lozenges) used pre-quit in gradual group, participants were advised to substitute one lozenge for each cigarette missed. All participants used lozenges post-quit contingent upon abstinence. Type of support: Behavioural - over the telephone. Both gradual and abrupt groups received 5 calls (90 minutes).
Outcomes	Abstinence: prolonged abstinence from 2 weeks-6 months follow-up (7-day PP at 6 m also reported). Validation: CO at 6 month follow-up. Other outcomes: quit attempts, self-efficacy, severity of dependence, stereotypy, craving, motivation to quit.
Notes	Only the data from the gradual and abrupt groups are of interest to this review as participants in the brief advice group were not advised to quit in any particular way.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Yes	"..our statistician generated a concealed allocation sequence and randomized the participant to the gradual, abrupt or brief advice conditions in a 2:2:1 ratio using blocked randomization (stratified by city and counsellor) based on the SAS procedure PLAN (Cary, NC: SAS Institute, Inc) "
Allocation concealment?	Yes	"..our statistician generated a concealed allocation sequence.."
Incomplete outcome data addressed? All outcomes	Yes	The incidence of adverse events was similar and small across conditions (3% gradual, 5% abrupt, 3% brief intervention), and in-

Hughes 2009 (*Continued*)

		cidence of discontinuation was lower than 1% in total. Drop out rates were also similar across groups; loss to follow-up was 20.7% in the abrupt group and 23.6% in the gradual group at 6 months.

Jerome 1999

Methods	Country: USA Recruitment: work-sites recruited smokers who wanted to quit to a free work-site self-help smoking cessation program. Recruitment was via posted advertisements and internal memos to employees.
Participants	1025 adult smokers from 61 work-sites randomized to 3 groups. 61.8% F, av. age 37.5, av. CPD 24.
Interventions	1. Computerized, scheduled, gradual reduction (with LifeSign program): Handheld computer used to increase the inter-cigarette interval until quit and record smoking. General advice on coping with urges and maintaining abstinence provided by a manual. 2. American Lung Association (ALA) quit smoking manual provided to participants: 'Freedom From Smoking For You and Your Family'. Includes standard behavioural techniques but not cutting down before quit. 3. General wellness information: printed material provided emphasizing the importance of a general program of physical health that included quitting smoking , exercise and sound nutrition. No specific quitting techniques provided. Pharmacotherapy: No pharmacotherapy. Type of support: Self-help materials.
Outcomes	Abstinence: 7-day PP at 12 month follow-up (from treatment initiation) (PP at EOT, & 6 m also reported) Validation: CO at all follow-ups. Other outcomes: program use, ease of use, effectiveness of program.
Notes	Only the data from the gradual reduction and ALA groups are of interest to this review as participants in the general wellness group were not advised to quit in any particular way.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Cluster randomized: "Work-sites were randomly assigned to one of three treatment conditions," precise method not described.
Allocation concealment?	Yes	Self-help intervention involving minimal contact with investigators/enrolling clinicians, risk of bias assessed as low.

Jerome 1999 *(Continued)*

Incomplete outcome data addressed? All outcomes	Yes	Loss to follow-up was comparable in the two arms of interest;13% gradual reduction, 17% ALA at 12 months. Analysis undertaken as intention to treat.

Riley 2005

Methods	Country: USA Recruitment: Respondents to local television spots who were then screened by phone to determine eligibility.
Participants	423 daily cigarette smokers randomized to 2 groups. Had been smoking for at least 1 year, aged between 18 and 67, smoking 10+ CPD, and not using any other type of tobacco. 44% F, av. age 43.4.
Interventions	1. LifeSign- Nicotine nasal spray (NNS): provided with handheld computer which decreased the use of cigarettes and increased the use of nicotine nasal spray over 10 days. Ps were then expected to quit smoking and use the nasal spray only. After 3 weeks of NNS use the program decreased usage. 2. Nicotine nasal spray only: participants instructed to set a quit date , quit smoking and begin using NNS as instructed on packet. Pharmacotherapy: Nicotine nasal spray was used pre and post quit in LifeSign-NNS arm and only post quit in the NNS only arm. Type of support: Self-help- minimal contact with little/no behavioural support.
Outcomes	Abstinence: 7 day PP at 12 month follow-up (PP at 5 weeks (mid-treatment), 10 weeks (EOT) & 6 m also reported) Validation: CO ≤8 ppm at 10 weeks (EOT), 6 & 12 month follow-ups. Other outcomes: CPD, nasal spray use, reasons for ceasing nasal spray use.
Notes	

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Randomized, method not described.
Allocation concealment?	Yes	Self-help intervention involving minimal contact with investigators/enrolling clinicians, risk of bias assessed as low.
Incomplete outcome data addressed? All outcomes	Unclear	Loss to follow-up was 43% at 6 months, and 57% at 12 months. This data wasn't split by groups so no comparison of loss to follow-up between groups could be carried out. Analysis was carried out as intention to treat.

Roales-Nieto 1992

Methods	Country: Spain Recruitment: students voluntarily responded in answer to announcements made in diverse academic centres of the university and through people who upon learning of the study suggested participation to relatives or friends.
Participants	23 participants took part and chose the goal of abstinence or reduction (controlled smoking), within each goal these participants were then randomized. 14 participants chose abstinence as their goal, and were randomized into 2 groups. Had been smoking for at least 5 years, and smoking 15+ CPD.
Interventions	1. Reduction (with goal of abstinence): received instructions to reduce cigarette consumption over 4 weeks (25% week 1, 50% week 2, 75% week 3, abstinence week 4) 2. Abrupt quitting (with goal of abstinence): received instructions to stop smoking completely on the first day of treatment 3. Reduction (with goal of controlled smoking): participants set reduction goal and received instructions to reduce their consumption to this goal. 4. Abrupt quitting (with goal of controlled smoking): participants set reduction goal and were asked to abruptly drop to this goal consumption Pharmacotherapy: No pharmacotherapy. Type of support: Behavioural.
Outcomes	Abstinence: 1 week PP at 1 year follow-up (also reported at EOT, 3 month, 6 month, 9 month and. Validation: for some participants a verifier they didn't know about was also asked to report CPD. Participant and verifier ratings corresponded in all cases. Other outcomes: Smoking rates at baseline and follow-ups, treatment compliance.
Notes	Only groups 1 and 2 are of interest and included in this meta-analysis as we are only interested in interventions with a goal to quit.

Risk of bias

Item	Authors' judgement	Description
Adequate sequence generation?	Unclear	Randomized, method not described.
Allocation concealment?	Unclear	No information given.
Incomplete outcome data addressed? All outcomes	Yes	All bar one participant, were followed up for the whole year. Therefore loss to follow-up was 14.3% in the abrupt group and 0% in the reduction group at 12 months. This is a small loss to follow-up, however there were only 14 participants randomized and these were all students at the University where the research took place, and so were potentially easy to follow-up.

CPD - cigarettes per day
EOT - end of treatment
PP - point prevalence abstinence

Characteristics of excluded studies *[ordered by study ID]*

Bernard 1972	All study arms reduced- two with a goal of quitting, one with a goal of controlled smoking.
Bolliger 2000a	The CEASE trial included participants who were all asked to quit in the same way (with NRT or placebo).
Bolliger 2000b	The Rossette study included participants who were all asked to reduce with a goal of controlled smoking in the same way (with NRT or placebo).
Bullen 2008	There was no reduction arm. Both arms were asked to smoke as they wished before quitting.
Cinciripini 1994	The control group was not an abrupt quit intervention. Participants received a complete 'I Quit Kit' (American Cancer Society,1977), which included a 7-day smoking reduction schedule.
Daughton 1998	All participants quit in the same way, either using nicotine patches or placebo patches.
Glasgow 1989	Reduction occurred in both trial arms. The key difference between arms was post-quit.
Hatsukami 1988	The reduction arm had a goal of reduced controlled smoking rather than quitting smoking.
Herrara 1995	All groups reduced using nicotine gum or placebo gum.
Jerome & Fiero 1999	Reduced scheduling was with regard to nicotine gum use. Both arms quit abruptly before beginning to use the nicotine gum.
Marston 1971	Main outcome was smoking rates. Abstinence rates were not reported and not possible to calculate from reported results.
Rezaishiraz 2007	Participants were asked to restrict themselves to one pack of reduced nicotine cigarettes per day during the 2 weeks pre-quit. However this instruction was given to both study arms.
Rose 1998	Neither arm was asked to reduce before quitting.
Rose 2006	Neither arm was asked to reduce before quitting.
Rose 2009	Neither arm was asked to reduce before quitting.
Schuurmans 2004	Neither arm was asked to reduce before quitting.
Shiffman 2009	Neither arm quit abruptly. Both study arms reduced before quitting.

Characteristics of ongoing studies *[ordered by study ID]*

Cinciripini 2006

Trial name or title	Scheduled smoking with transdermal nicotine.
Methods	Country: USA Recruitment: from the community. Randomization: method not stated.
Participants	Over 700 daily smokers randomized to 3 groups.
Interventions	1. SSNP: scheduled smoking with concurrent transdermal nicotine replacement. Smoking scheduled using a hand-held computer, which signals smoking at progressively increasing inter-cigarette intervals. 2. SS: scheduled smoking alone plus nicotine replacement therapy post-quit. Smoking scheduled using a hand-held computer, which signals smoking at progressively increasing inter-cigarette intervals. 3. UCC: usual care control, instructed to quit smoking within a few days of study entry and begin using the nicotine patch on their quit day. They are provided with no instructions to reduce and monitor their smoking behaviour using a hand-held computer. Pharmacotherapy: Transdermal nicotine patch in all groups. Both pre and post quit in SSNP group and only post-quit in SS and UCC groups. Type of support: Self-help materials
Outcomes	Abstinence: at 4 weeks post quit, long-term quit rates (no further detail known). Validation: Unknown Other outcomes: Unknown
Starting date	01/04/1998
Contact information	Dr Cinciripini, Director Tobacco Treatment Program and Deputy Chair University of Texas MD Anderson Cancer Center Department of Behavioral Science-Unit 1330 PO Box 301439, Houston Texas [pcinciri@mdanderson.org]
Notes	Data analysis is currently being carried out for this study.

Lindson 2009

Trial name or title	Rapid Reduction Trial.
Methods	Country: UK Recruitment: General practitioner's practices and NHS Stop Smoking Services write to patients recorded as smokers and offer them treatment. Randomization: Stata used to accomplish stratified randomization by therapist with blocking within each stratum. The blocks are randomly ordered blocks of 2, 4, and 6. Each therapist opens sealed numbered envelopes in turn to determine allocation to abrupt cessation or rapid reduction.
Participants	700 participants randomized to two arms. Males and females 18 years+, smoking at least 15 cigarettes or 12.5 grams of loose tobacco daily as roll your own cigarettes, or blows 15 parts per million or above on exhaled

Lindson 2009 *(Continued)*

	carbon monoxide (CO) reading, willing to stop smoking completely in two weeks.
Interventions	1. Abrupt cessation arm: participants instructed to smoke as normal for two weeks before quitting abruptly on a designated quit day. 2. Rapid reduction arm: participants instructed to reduce their smoking over to weeks and then quit completely on a designated quit day. Participants choose from one of three reduction methods: 1) Scheduled reduction- time between cigarettes gradually increased so smoking 50% of baseline end of week 1, and 25% end of week 2, 2) Hierarchical reduction- cigarettes usually smoked identified and eliminated, hardest or easiest first, until smoking 50% of baseline end of week 1, and 25% end of week 2, 3) Smoke-free periods- participants reduce the number of time periods in which they usually smoke by 50% in week 1 and by a further 50% in week 2. Pharmacotherapy: nicotine patches used in both arms pre- and post-quit. Acute NRT (type chosen by participant) used pre- and post-quit in reduction arm and post-quit only in the abrupt arm. Type of support: Behavioural support weekly from 2 weeks pre-quit to 4 weeks post-quit.
Outcomes	Abstinence: PP and prolonged at 4 weeks, 8 weeks and 6 months post quit Validation: Exhaled carbon monoxide Other outcomes: Cotinine levels pre-quit and 1 week post-quit, cigarette reward, urges to smoke, withdrawal, confidence in quitting, smoking stereotypy.
Starting date	01/01/2009
Contact information	Nicola Lindson (nll839@bham.ac.uk), Paul Aveyard (p.n.aveyard@bham.ac.uk) at: Primary Care Clinical Sciences, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK
Notes	This study is in the participant recruitment and data collection stages and aims to be completed by 31/12/2012.

Riley 2001

Trial name or title	Combining scheduled reduction with nicotine replacement.
Methods	Country: USA Recruitment: through television media advertising. Randomization: method not stated
Participants	337 smokers desiring to quit randomized to 2 conditions. Aged between 18 and 65, had been smoking over 15 CPD for at least 1 year, no current nicotine product use, no Zyban or other antidepressant use for over 1 month, no medical condition which would preclude the use of the nicotine patch. 44% F, av.age 41, av. CPD 24.4, av. 3.2 previous quit attempts.
Interventions	1. Computerised scheduled gradual reduction + patch: a handheld computer was used to schedule the reduction of smoking rate by increasing the interval between smoking of cigarettes. When smoking rate was down to 10 CPD participants were advised to stop smoking completely and start the use of nicotine patches. 2. Patch only: participants advised to stop smoking abruptly, with no reduction, and then begin using nicotine patch. Pharmacotherapy: nicotine patches were used in both arms post-quit. Type of support: Self-help- minimal contact with little/no behavioural support.

Riley 2001 *(Continued)*

Outcomes	Abstinence: 7 day pp and continuous abstinence at EOT (12 weeks post study entry), unknown at 6 & 12 month follow-up. Validation: CO at EOT, unknown at 6 & 12 month follow-ups. Other outcomes: time to relapse, patch use, satisfaction with patch, computer program use.
Starting date	01/05/1997
Contact information	Dr Riley, NHLBI [William.Riley@nih.gov]
Notes	Data analysis is currently being carried out on 6 & 12 month follow-up data for this study.

DATA AND ANALYSES

Comparison 1. Reduction to quit versus abrupt quitting

Outcome or subgroup title	No. of studies	No. of participants	Statistical method	Effect size
1 Abstinence: Main analysis	10	3760	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.79, 1.13]
2 Abstinence: Sub-group analysis split by use of pharmacotherapy	10	3760	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.79, 1.13]
2.1 Pharmacotherapy (NRT) used	3	1333	Risk Ratio (M-H, Fixed, 95% CI)	0.89 [0.65, 1.22]
2.2 No pharmacotherapy used	7	2427	Risk Ratio (M-H, Fixed, 95% CI)	0.97 [0.78, 1.21]
3 Abstinence: Sub-group analysis split by type of behavioural support	10	3760	Risk Ratio (M-H, Fixed, 95% CI)	0.94 [0.78, 1.13]
3.1 Self-help therapy	5	2816	Risk Ratio (M-H, Fixed, 95% CI)	0.98 [0.78, 1.23]
3.2 Behavioural support	6	944	Risk Ratio (M-H, Fixed, 95% CI)	0.87 [0.64, 1.17]

HISTORY

Protocol first published: Issue 4, 2009

Review first published: Issue 3, 2010

CONTRIBUTIONS OF AUTHORS

NL & PA checked references against eligibility criteria and extracted data and any disagreements were resolved through discussion with JH. NL drafted the review, with review and contributions from PA & JH.

DECLARATIONS OF INTEREST

Dr Aveyard has done consultancy work for Pfizer, McNeil, and Xenova/Celtic who make products for smoking cessation.

Dr Hughes is currently employed by The University of Vermont and Fletcher Allen Health Care. He has also received grants and consulting fees from many for-profit and non-profit companies that market smoking cessation products and services. He is an author of one trial included in this review.

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INDEX TERMS

Medical Subject Headings (MeSH)

Randomized Controlled Trials as Topic; Smoking [psychology; *therapy]; Smoking Cessation [*methods; psychology]

MeSH check words

Adult; Humans

APPENDIX 3: PUBLISHED NICOTINE PRELOADING REVIEW (LINDSON & AVEYARD 2011[a])

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REVIEW

An updated meta-analysis of nicotine preloading for smoking cessation: investigating mediators of the effect

Nicola Lindson · Paul Aveyard

Received: 6 August 2010 / Accepted: 22 October 2010 / Published online: 9 November 2010

Abstract
Rationale Using nicotine replacement therapy (NRT) whilst smoking, prior to quitting, is called preloading. Two reviews have estimated the effect of preloading on abstinence, but need updating. Neither investigated possible mediators or moderators of the effect, which could have implications for individual treatment plans.
Objectives To update the nicotine preloading efficacy estimate and test four hypotheses: (1) Efficacy is mediated through reduced smoking reward, (2) efficacy is mediated through increased NRT adherence post-quit, (3) efficacy is mediated through increased confidence, and (4) behavioural support modifies efficacy.
Methods Randomised controlled trials were included that allocated cigarette smokers attempting to quit to either a preloading or control condition. A Mantel–Haenszel fixed-effect model was used to calculate risk ratios from quit rates at short- and long-term follow-ups. We carried out subgroup analyses and synthesised the data available on possible mediators and moderators qualitatively.
Results Eight relevant studies were included, with 2,813 participants. The risk ratio (RR) for short-term abstinence was 1.05, 95% confidence intervals (CI)=0.92, 1.19, and for long-term abstinence 1.16, 95% CI=0.97, 1.38. There was a marginal benefit of using nicotine patch rather than gum for preloading, significant at short-term follow-up, and no significant benefit of more intensive pre-quit behavioural support.
Conclusions We found a weak non-significant effect of nicotine preloading on abstinence. None of our mediational hypotheses received strong support, however evidence suggests that efficacy was enhanced by the patch over acute NRT. Future research needs to investigate the mechanisms of preloading by carrying out mediational analysis.

Keywords Meta-analysis · Systematic review · Cigarette smoking · Nicotine dependence · Preloading · Nicotine replacement therapy · Smoking cessation · Treatment efficacy · Pre-cessation treatment

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N. Lindson (✉) · P. Aveyard
UK Centre for Tobacco Control Studies,
Primary Care Clinical Sciences, University of Birmingham,
Edgbaston,
Birmingham B15 2TT, UK
e-mail: nll839@bham.ac.uk

Introduction

Nicotine preloading means using nicotine replacement therapy (NRT) prior to quitting smoking. Two systematic reviews of nicotine preloading reported very positive results, with Shiffman and Ferguson (2008) giving an odds ratio (OR) of 1.96, 95% confidence intervals (CI): 1.31, 2.93 for 6 weeks abstinence, and an OR of 2.17, 95% CI: 1.46, 3.22 for 6 months, and a Cochrane review (Stead et al. 2008) giving a risk ratio (RR) of 2.03 (95% CI: 1.22–3.38) for long-term abstinence. Since these reviews were published the results of three more trials have become available (Bullen et al. 2010; Etter et al. 2009; Hughes et al. 2010), as well as 6 month quit rates from a study by Rose et al. (2009), which is cited as Rose et al. 2007 in Shiffman and Ferguson's (2008) review.

Neither published review (Shiffman and Ferguson 2008; Stead et al. 2008) investigated possible mediators of the efficacy of preloading. Knowing the mechanisms of action

could have clinical implications. For example, in this article, we propose that preloading could reduce the reward from smoking, help extinguish the learned need to smoke, and lead to reduced withdrawal intensity after cessation of smoking. One hypothesis that flows from this is that lengthening the preloading period might enhance efficacy. Furthermore, a clinician could measure reward from smoking and lengthen preloading or advise quitting depending upon responses of individual patients.

We developed three mediational hypotheses to test in this review. The first is that preloading reduces reward from smoking which facilitates the extinction of learned associations between cues to smoke and smoking. This would lead to reduced dependence, reduced withdrawal symptoms and craving on stopping smoking, and enhance the likelihood of cessation success. If this mechanism holds, we would expect nicotine patches to be more effective than short-acting forms of NRT. This is because nicotine patches used concurrently with smoking lead to supra-normal blood nicotine concentrations (Fagerstrom and Hughes 2002), that we expect would blunt reward, reduce the need to smoke to avoid withdrawal, and hence undermine the learned basis of tobacco addiction. Short-acting NRT, such as gum, used concurrently with smoking produces blood nicotine concentrations similar to those while smoking only (Fagerstrom and Hughes 2002). We expect in this situation that the natural fall in blood nicotine concentrations will mean that smoking is more rewarding than on a patch and that preloading with a short-acting form of NRT will be less effective. It follows from this that higher blood nicotine concentrations (usually measured by cotinine) will be associated with greater cessation efficacy. It also follows that we would expect reduced exhaled carbon monoxide (CO) concentrations as preloading reduces smoking intensity due to reduced reward.

The second mediational hypothesis is that preloading accustoms patients to using NRT which leads to greater use of NRT after quit day. Greater use of NRT after quit day is associated with increased likelihood of abstinence (Stead et al. 2008, Shiffman 2007). If this hypothesis holds, we would expect to see higher use of NRT in the intervention arm than the control arm. However, NRT use after quit day is contingent on participants' intentions. Once a participant decides continuing to quit is futile or no longer desired, s/he usually stops NRT. A trial showing higher abstinence in one arm than another could show higher use of NRT for this reason alone, so we need to account for this.

Our third mediational hypothesis is that smoking while using NRT leads to reduced cigarette consumption which will increase a person's confidence that he or she can stop smoking. Confidence or self-efficacy is associated with increased likelihood of cessation (Gwaltney et al. 2009).

In addition to these mediational hypotheses, we also examined the evidence that behavioural support modifies the effectiveness of preloading, by testing the hypothesis that until recently, smokers were warned even by the package inserts that smoking while wearing the nicotine patch was dangerous and there is no intuitive reason for people to assume that smoking while using a patch would help. Behavioural support is assumed to be effective partly by enhancing adherence to medication, as users are able to voice their doubts about their medication and be directly reassured by therapists. If this is the case, we would expect that more intensive pre-quit behavioural support would be associated with better adherence in the pre-quit period. However, if adherence is high during preloading even without behavioural support, we would expect behavioural support not to modify the effectiveness of preloading. In addition, we assessed evidence of moderation in any trial reports.

Method

Inclusion criteria

Studies were included if they were randomised controlled trials, if participants were cigarette smokers attempting to quit, if the intervention was a smoking cessation intervention with a pre-quit phase during which participants were randomised to receive active nicotine replacement therapy daily for at least a week or a control of either placebo or no nicotine replacement therapy, if the nicotine content of cigarettes smoked pre-quit were comparable across conditions, if post-quit NRT and overall behavioural support was comparable across conditions, and if abstinence was reported at 6 month follow-up or later.

Search strategy

Studies relevant for inclusion were sought from already published reviews of preloading, and from the MEDLINE, EMBASE and PsycINFO databases, using the following topic-specific terms: nicotine or NRT, combined with any of the following: pre-cessation, precessation, pre cessation, pre-loading preloading pre loading, pre-treatment, pretreatment, pre treatment, pre-quit, prequit, pre quit, before treat*, before quit*, before cessation. The titles and abstracts generated from this search, as well as the reference lists of relevant papers, were checked for relevance using the inclusion criteria above. Data on the following was then extracted from each relevant paper: study design, setting of study, method of participant recruitment, type of NRT, type of support/participant contact, follow-up point, number of participants randomised to each group, participant characteristics at baseline, definition of abstinence, whether abstinence was biochem-

ically verified, the number of quitters in each arm, and secondary outcomes.

Outcomes

Primary outcomes were both short-term abstinence and long-term abstinence at least six months after quit day. In trials with more than one measure of abstinence, we preferred the measure with the strictest criteria. We used prolonged or continuous abstinence over point prevalence abstinence, and preferred biochemically validated abstinence over self-report for both short-term outcomes and abstinence at least 6 months from quit date. We also extracted data on the possible mediators and moderators of the effect of preloading.

Quality assessment

The quality of each included study was assessed within the domains of randomisation sequence generation, concealment of allocation to study arm, blinding to study arm allocation, and incomplete outcome data. This assessment was carried out according to procedure outlined in the Cochrane Collaboration Handbook (Higgins and Green 2009). Whether studies validated self-reported abstinence was also considered. A sub-group analysis was used to compare the effect of preloading in double-blinded studies using placebo NRT in the control groups, with studies that were unblinded. We also examined funnel plots to investigate possible publication bias.

Analysis

We compared both short- and long-term quit rates between treatment arms using pre-quit NRT and the arms using placebo/no pre-quit NRT, calculated on an intention-to-treat basis. Participants lost to follow-up were classified as smokers. Relative risk was used as the summary statistic in all meta-analyses, using the Mantel–Haenszel fixed-effect model and checking for heterogeneity by examining forest plots for poor overlap of confidence intervals and the I^2 statistic and the chi-squared Q statistic.

To test our hypotheses we carried out the following analyses. Where analysis is qualitative this is because insufficient quantitative data was provided to conduct meta-analyses.

Hypothesis 1. Efficacy is mediated through reduced reward and hence reduced dependence

We synthesised the data qualitatively to examine the effects of preloading on reward, negative reinforcement, cigarette smoking, and post-quit withdrawal intensity. Furthermore, we split the studies into those providing 2 and 4 weeks preloading and those using patch and gum consistent with the hypothesis above, using meta-analyses.

Hypothesis 2. Efficacy is mediated through increased post-quit adherence

We synthesised the data qualitatively to examine whether post-quitting adherence was higher in the group who continued to try to quit in those who had used preloading.

Hypothesis 3. Efficacy is mediated through increased confidence

We examined qualitatively whether confidence before quitting increased in the preloading group relative to the control group.

Hypothesis 4. Behavioural support modifies the effect of preloading

We qualitatively examined whether the degree of behavioural support provided was associated with enhanced adherence to pre-quit NRT. We also examined whether studies that provided less support in the pre-quit period were associated with reduced smoking cessation efficacy using meta-analysis.

Finally we examined baseline individual differences, as potential moderators of the effect of preloading on abstinence, and synthesised the available data.

Results

Included studies and participants

Our database searches retrieved 129 references and after title and abstract searches we were left with 15 full-text papers. After checking the full-text against the inclusion criteria we found eight studies relevant for inclusion (Bullen et al. 2010; Etter et al. 2009; Hughes et al. 2010; Rose et al. 1994; Rose et al. 1998; Rose et al. 2006; Rose et al. 2009; Schuurmans et al. 2004) (Table 1). Four of these were included in Stead et al.'s (2008) review (Rose et al. 1994; Rose et al. 1998; Rose et al. 2006; Schuurmans et al. 2004), and four were included in the Shiffman and Ferguson's (2008) review (Rose et al. 1998; Rose et al. 2006; Rose et al. 2009; Schuurmans et al. 2004). We found three studies published since these reviews were conducted (Bullen et al. 2010; Etter et al. 2009; Hughes et al. 2010). Another potentially relevant study was identified where a small subgroup of the participants were allocated to preloading as we defined it, however the quit rate data

was not available at long-term follow-up for this group (Herrera et al. 1995). The total sample size in the preloading arms was 1,403 across the eight studies, ranging from 24 to 549 in individual studies. In the control arms total sample size was 1,410, ranging from 24 to 551 across studies. All of the studies recruited participants attempting to quit smoking. On average participants were evenly split between males and females, mean age 42 years, average cigarettes per day (cpd) ranged between 19 to 30 across studies with a median of 25 cpd, and a median Fagerstrom Test for Nicotine Dependence of 6. In all but one of the studies (Hughes et al. 2010), all trial arms were relevant and included in our analyses, however Hughes et al. (2010) included a third arm where participants were randomised to a minimal treatment condition. As this trial arm received a different level of behavioural support to the preloading condition this could impact on the resulting effect and so we did not include it in our analyses.

Interventions

All studies included at least one group randomised to receive nicotine replacement therapy before quitting smoking; three included another group who received a preloading placebo pre-quit (Rose et al. 2006; Rose et al. 2009; Schuurmans et al. 2004), and five studies were unblinded (Bullen et al. 2010; Etter et al. 2009; Hughes et al. 2010; Rose et al. 1994; Rose et al. 1998). Preloading was given for 2 weeks in five studies (Bullen et al. 2010; Rose et al. 1994; Rose et al. 2006; Rose et al. 2009; Schuurmans et al. 2004), 4 weeks in two studies (Etter et al. 2009; Rose et al. 1998), and 3–5 weeks in the remaining study (Hughes et al. 2010). Four studies provided participants with 21 mg/24 h patches pre-quit (Rose et al. 1994; Rose et al. 1998; Rose et al. 2006; Rose et al. 2009), one with 15 mg/16 h patches (Schuurmans et al. 2004), and Bullen et al. (2010) gave participants a choice of nicotine patch only, patch and gum, or gum only where the dose depended on the advisor's assessment. Another study provided participants with 4 mg gum pre-quit (Etter et al. 2009), and the final study (Hughes et al. 2010) sent participants 2 or 4 mg lozenges depending on how soon they smoked their first cigarette on waking. Post-quit day NRT was provided for 4–12 weeks, varying across studies.

In addition to NRT treatment three included studies provided participants with mecamylamine (a nicotinic antagonist) or placebo either pre and post-quit (Rose et al. 1994; Rose et al. 1998) or post-quit only (Rose et al. 2006), and two studies provided participants with cigarettes with manipulated nicotine content (Rose et al. 2006; Rose et al. 2009). Five studies asked participants to smoke freely whilst preloading (Bullen et al. 2010; Rose et al. 1994; Rose et al. 1998; Rose et al. 2006; Rose et al. 2009), one asked participants to smoke as they normally did (Schuurmans et al. 2004), and two asked participants to reduce their smoking in the preloading arm and quit abruptly in the control arm (Etter et al. 2009; Hughes et al. 2010).

Outcomes

The follow-up point for short term abstinence varied across studies from 4 to 12 weeks, with a median of 7 weeks. Seven of the eight studies reported short-term continuous abstinence: two as self-report only (Bullen et al. 2010; Etter et al. 2009) and five studies using CO validation to confirm self-report (Rose et al. 1994; Rose et al. 1998; Rose et al. 2006; Rose et al. 2009; Schuurmans et al. 2004). The eighth study (Hughes et al. 2010) defined short-term abstinence as self-reported prolonged abstinence.

Six studies reported long-term abstinence at six month follow-up (Bullen et al. 2010; Hughes et al. 2010; Rose et al. 1998; Rose et al. 2006; Rose et al. 2009; Schuurmans et al. 2004), one at 12 month follow-up (Etter et al. 2009), and the remaining study reported abstinence at both 6 and 12 month follow-up (Rose et al. 1994); in this case the 12 month abstinence was used. Four of the included studies supplied continuous abstinence rates, verified by either CO and/or cotinine (Rose et al. 1994; Rose et al. 1998; Rose et al. 2009; Schuurmans et al. 2004), one prolonged CO-verified rates (Hughes et al. 2010) and another defined abstinence as 7-day point prevalence at six months, verified by CO measurement (Rose et al. 2006). Etter et al. (2009) provided 4-week prolonged abstinence rates verified by cotinine and CO, as well as continuous self-reported rates at 12 month follow-up. In this case the verified rates were used as these were most stringent. Bullen et al. (2010) attempted cotinine verification in a sample of participants only, and for point prevalence rates. For this study we used self-reported continuous abstinence.

Quality assessment

Each included study was rated on whether they might cause bias in terms of randomisation sequence generation, concealment of the allocation sequence, blinding to study arm allocation, and incomplete outcome data. For each criteria a study was rated as 'yes' if unlikely to cause bias, 'no' if they may cause bias, and 'unclear' if there was insufficient information to make a judgment. In terms of sequence generation all studies claimed to be randomised, three of these reported acceptable sequence generation methods

(Bullen et al. 2010; Etter et al. 2009; Hughes et al. 2010). The remainder did not specify the method used to generate the randomisation sequence so were rated 'Unclear' (Rose et al. 1994; Rose et al. 1998; Rose et al. 2006; Rose et al. 2009, Schuurmans et al. 2004). Although Schuurmans et al. (2004) did specify that randomisation was performed with a computer generated list, in order to have allocated exactly 100 participants to each arm a special system would need to have been used, which was not described.

When rated in terms of concealment of participant allocation from researchers, the same four studies were rated as unlikely to cause bias, as they specified that allocation was concealed (Bullen et al. 2010; Hughes et al. 2010; Schuurmans et al. 2004) or they involved no therapist contact (Etter et al. 2009). The remaining four studies did not report on allocation concealment and thus were rated as 'Unclear' (Rose et al. 1994; Rose et al. 1998; Rose et al. 2006, 2009).

In the blinding category three studies were classified as unlikely to cause bias (Rose et al. 2006; Rose et al. 2009; Schuurmans et al. 2004). They were all double-blinded, using placebo nicotine patches in the control arm, so that participants and researchers were unaware of who was receiving active treatment. None of the remaining studies (Bullen et al. 2010; Etter et al. 2009; Hughes et al. 2010; Rose et al. 1994; Rose et al. 1998) used placebos, therefore it was impossible to conceal treatment arm after allocation had occurred. As a result these studies may have caused bias in this respect. To investigate this possibility we conducted a sub-group analysis on the main meta-analysis, comparing the effect of preloading in the double-blinded studies with the effect of preloading in the unblinded studies. For short term outcome there was a significant sub-group difference ($p<0.001$) with an RR of 1.78 (95% CI= 1.33, 2.39) for the double-blind studies and an RR of 0.91 (0.79, 1.05) for the unblinded studies. The difference was smaller but still significant ($p=0.01$) for the long term outcome with an RR of 1.80 (95% CI=1.21, 2.68) in the blinded studies and an RR of 1.02 (0.84, 1.25) in the unblinded studies.

When rated in terms of incomplete outcome data five studies were classified as unlikely to cause bias for the meta-analysis, (Bullen et al. 2010; Etter et al. 2009, Hughes et al. 2010; Rose et al. 1994; Schuurmans et al. 2004) as they all had reasonable and similar attrition rates across conditions at follow-up points. Hughes et al. (2010) did have differential drop-out over the pre-quit period, reporting the rate of completion of baseline and pre-quit surveys as 57% in the preloading arm and 82% in control arm ($p<$ 0.0001). Although data on abstinence are based on intention to treat, we had to use data on responders only for assessing the effect of the intervention on the mediators and this potential bias should be borne in mind. The remaining three studies (Rose et al. 1998; Rose et al. 2006; Rose et al. 2009) were rated as 'unclear' for incomplete outcome data, either because they did not report drop-out past the quit day, or because they did not give drop-out for each group separately.

Another potential bias relates to biochemical validation of abstinence (Table 1). Studies that did not validate abstinence could potentially over-estimate it. Five studies (Rose et al. 1994, Rose et al. 1998; Rose et al. 2006; Rose et al. 2009; Schuurmans et al. 2004) validated abstinence at both short- and long-term follow-ups, and two studies validating at long-term follow-up only (Etter et al. 2009; Hughes et al. 2010). Bullen et al. (2010) was the only study that did not verify abstinence biochemically. Validation had occurred in a small subset of the participants and was then generalised to the whole population, however this was only for point prevalence not continuous abstinence. We chose not to use these rates over self-reported continuous abstinence rates, based on the assumption that we would not expect the proportion of participants claiming abstinence, but failing validation to differ between arms, and the conclusion of the SRNT Subcommittee on Biochemical Verification (2002) that studies with limited face-to-face contact, and where data collection is by telephone are unlikely to benefit from biochemical verification because of higher refusal rates. In reality the extent that self-report inflates abstinence rates rarely differs across conditions. This is supported by the only two included studies that allowed comparison of validated and non-validated quit-rates in this analysis (Etter et al. 2009; Hughes et al. 2010) who both found that the proportion of biochemically non-validated participants who claimed to be abstinence did not vary significantly across conditions ($p=0.86$ and $p=0.61$ respectively).

Finally we examined funnel plots to establish whether our results may be subject to publication bias. These plots were largely asymmetric with the smaller studies providing more positive results and the larger studies indicating less positive effects (see Online Resource 1).

Effect of preloading on abstinence

There was a very weak positive effect of preloading on short-term abstinence (RR=1.05, 0.92, 1.19), however the effect was not significant ($p=0.49$) (Fig. 1). There was marked heterogeneity with an I^2 of 69%, $p=0.002$. Based on this large amount of heterogeneity we re-ran the analysis using a random-effects model; however the results were similar (See Online Resource 2).

The effect on long-term abstinence gave a slightly larger RR of 1.16 (0.97, 1.38) (Fig. 2), and there was less heterogeneity with an I^2 of 36%, $p=0.14$. However, again the effect was non-significant.

Table 1 Study characteristics

Study ID	Total *N*	Preloading *N*	Control *N*	Mean age	% female	Mean baseline FTND	Mean baseline cpd	Length of preloading (weeks)	Pre-quit NRT	Preloading smoking instructions	Measure of short-term abstinence	Measure of long-term abstinence
Bullen et al. (2010)	1,100	549	143	40	60	6	19	2	Patch +/or gum	Smoke freely	12 week self-reported, continuous	6-month self-reported, continuous
Etter et al. (2009)	314	154	160	Preloading=42 Control=44	Preloading=35 Control=47	Preloading=5.5 Control=5.4	Preloading=24 Control=23.4	4	4 mg Gum	Reduce	8 week self-reported continuous	12 month, commit and CO verified, 4 week prolonged
Hughes et al. (2010)	596	297	299	48	54	5.9	23	3–5	2 or 4 mg Lozenge	Reduce	12 week self-reported, prolonged	6 month CO verified, prolonged
Rose et al. (1994)	48	24	24	34	60	6	28	2	21 mg/24 h patches	Smoke freely	7 week CO verified, continuous	12 month CO verified, continuous
Rose et al. (1998)	80	40	40	41	49	6.4	29.9	4	21 mg/24 h patches	Smoke freely	6 week CO verified, continuous	6 month CO verified, continuous
Rose et al. (2006)	96	48	48	45	53	6.5	28.6	2	21 mg/24 h patches	Smoke freely	4 week CO verified, continuous	6 month CO verified, 7-day point prevalence
Rose et al. (2009)	379	191	188	42	57	5.9	23.1	2	21 mg/24 h patches	Smoke freely	6 week CO verified, continuous	6 month CO verified, continuous
Schuurmans et al. (2004)	200	100	100	44	44	6.1	24.8	2	15 mg/16 h patches	Smoke as normal	6 week, CO verified, continuous	6 month, CO verified, continuous

FTND Fagerstrom Test for Nicotine Dependence, *cpd* cigarettes per day, *NRT* nicotine replacement therapy, *CO* carbon monoxide

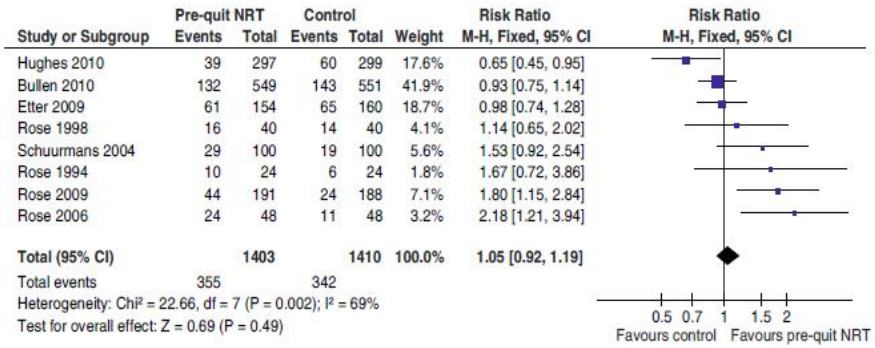

Fig. 1 Effect of NRT preloading on short-term abstinence

Hypothesis 1. Efficacy is mediated through reduced reward and hence reduced dependence

Two studies measured reward, satisfaction or enjoyment from smoking during preloading (Rose et al. 1994; Rose et al. 1998). Rose et al. (1994) reported that preloading significantly reduced smoking satisfaction good taste of cigarettes, and the calming effect of smoking relative to control, but there was no main effect of preloading on enjoyment of respiratory tract sensations when smoking. It was not possible to calculate effect sizes from the report. Rose et al. (1998) reported that nicotine preloading did not affect the reward from cigarettes pre-quit with almost identical reductions in reward in both active and placebo groups. Taken together, there is little evidence that preloading influences the positive reward from smoking.

Four studies reported data on the effect of preloading on variables relevant to negative reinforcement from smoking during the pre-quit period (Rose et al. 1994; Rose et al. 1998; Rose et al. 2006; Schuurmans et al. 2004). Rose et al. (1994) reported some evidence that nicotine patch treatment reduced negative affect in smokers with high baseline ratings, but effect sizes were not calculable. Rose et al. (1998) reported that negative affect increased in nicotine treatment compared to placebo during the first week only of 4 weeks preloading, but no effect size was calculable. Rose et al. (2006) measured negative affect pre-quitting but results presented do not enable the reader to determine whether there was an effect of nicotine preloading. Schuurmans et al. (2004) reported no effect of preloading on a composite (Wisconsin) scale of withdrawal symptoms. Overall we found no evidence that preloading influenced negative reinforcement.

Reduced positive or negative reinforcement from smoking should reduce cravings during the pre-quit period and four studies had data. Rose et al. (1994) and Rose et al. (1998) found no effect of preloading on craving. Rose et al. (2006) reported an approximate 20% reduction in craving during preloading, and Hughes et al. (2010) a 10% reduction. Therefore the effect on pre-quit cravings is small if it exists.

Our hypothesis was that reduced craving would be associated with reduced dependence scores and lower

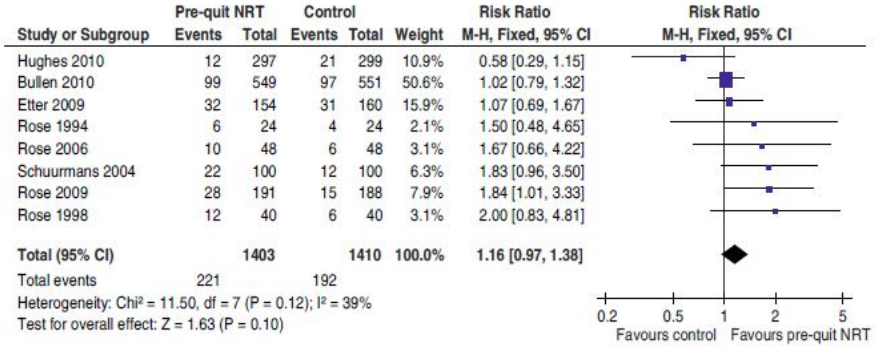

Fig. 2 Effect of NRT preloading on long-term abstinence

cigarette consumption (cigarettes/day, CO, and cotinine) during preloading. In five studies participants were advised to smoke as they chose (Bullen et al. 2010; Rose et al. 1994; Rose et al. 1998; Rose et al. 2006; Rose et al. 2009) Rose et al. (1994) showed participants reduced cigarette consumption by more than half in the nicotine preloading condition, whereas there was little change in the placebo group. Rose et al. (1998) showed an approximate one third reduction in cigarettes/day in the active patch condition compared with placebo where there was little reduction pre-quit. There was no apparent reduction in CO but plasma nicotine derived from smoking fell by around 20% in the nicotine treated group and was steady in the placebo group. Rose et al. (2006) showed an approximate 20% reduction in daily cigarette consumption in the nicotine preloading vs 10% reduction without preloading. CO levels declined by about 10% in the active group and did not change in the non-nicotine group. Bullen et al. (2010) found the preloading group reduced daily cigarette consumption by 63% and the no preloading group reduced by 16%. Schuurmans et al. (2004) reported almost no reduction in cigarettes per day in both active and placebo groups and CO declined little (12% vs 3%), but the investigators had asked participants not to change their smoking behaviour. Etter et al. (2009) and Hughes et al. (2010) both asked the preloading group to reduce their smoking. Etter et al. (2009) reported a 48% reduction in consumption and 9% in the group who received no preloading. Hughes et al. (2010) found that cigarettes per day reduced by 54% (13 cpd), as well as CO levels by 21% (6 ppm), in the preloading condition, in comparison to a 1% (0.3 cpd) reduction in cigarettes per day and a 0% (0 ppm) reduction in CO in the control group. Only one study reported on cotinine concentration while smoking (Rose et al. 2006). Cotinine concentration rose by about 60% during preloading with patch compared with almost no change on placebo. Taken together the data indicate that preloading reduces smoking consumption moderately and variably across studies, but this seems partly related to the instructions given on how to smoke. Reduction in smoke intake measured by CO is less affected than cigarettes per day.

Only two studies reported change in dependence over the pre-quit period (Hughes et al. 2010; Rose et al. 2006). Hughes et al. (2010) reported that participants in the preloading condition decreased their dependence by increasing the time to first cigarette after waking from 15 to 28 min, whereas this measure of dependence did not change in the control group. They also reported that similar outcomes occurred when dependence was measured using the FTND and self rated addiction; the change in scores is not specified, however the difference between the preloading condition and control was significant in both cases ($p<0.0001$). Hughes et al. (2010) also reported that the regularity of smoking (stereotypy) decreased in the preloading condition by 10%, but stayed the same in the control condition during the pre-quit period. Rose et al. (2006) showed a decline of about two FTND points (20%) in the group receiving nicotine preloading and one point in the group on placebo. In both of these studies cigarette consumption declined on average and this contributes to FTND score so, in the case of FTND, it is not possible to know whether other indices of dependence declined or whether these changes were accounted for by reduction in consumption. However the decline in other measures of dependence (self-rated addiction and stereotypy), that do not depend on cigarette consumption in Hughes et al. (2010) supports the theory that dependence was reduced by preloading.

We hypothesised that reduced positive or negative reward from smoking would manifest as reduced pre-quit consumption, reduced dependence, and hence reduced intensity of withdrawal *after* quitting. Rose et al. (1994) showed similar levels of craving after cessation in nicotine preloading and placebo groups. Rose et al. (1998) showed an approximate 10% reduction in craving after cessation in both the active and placebo groups. Bullen et al. (2010) reported that craving was 0.24 units (3% of the whole scale) lower in the preloading group than the no preloading group. Etter et al. (2009) reported similar craving levels in smokers receiving preloading compared to those who did not. Overall withdrawal scores were measured by Schuurmans et al. (2004) and Etter et al. (2009), both showing almost no difference in active or comparator groups. Some studies (Rose et al. 1994; Rose et al. 1998; Rose et al. 2006; Etter et al. 2009) reported scores for some individual withdrawal symptoms. These indicated no large differences and when these were compared statistically (Etter et al. 2009) the differences were not significant. Overall there appears to be reasonable evidence that nicotine preloading does not reduce post-quit smoking withdrawal.

A subsidiary hypothesis arising from this proposed mechanism is that patch, which leads to supra-normal nicotine blood concentrations when smoking, would be more effective than short-acting NRT, in which nicotine concentration is typical of smoking alone (Fagerstrom and Hughes 2002). We tested this by carrying out a sub-group analysis, splitting the studies in terms of whether they used gum/lozenge (Etter et al. 2009; Hughes et al. 2010) or patch (Bullen et al. 2010; Rose et al. 1994; Rose et al. 1998; Rose et al. 2006; Rose et al. 2009; Schuurmans et al. 2004) pre-quit. Bullen et al.'s (2010) study included participants that used patch and participants that used gum only, but did not present results split this way for the continuous cessation outcome. As 9% used nicotine gum, for the purposes of this analysis, we included all participants in the patch category. For short-term abstinence the RR for the patch group was

1.17 (95% CI=1.00, 1.37) and for gum/lozenge was 0.82 (95% CI=0.66, 1.02), p=0.009 for the difference in RRs. Splitting the studies in this way for short-term outcomes did not remove heterogeneity which was still 66% for the patch subgroup and 67% for the gum/lozenge subgroup. For long-term cessation, the nicotine patch also appeared somewhat more effective than gum with an RR of 1.26 (95% CI=1.03, 1.55), compared to a RR of 0.87 (95% CI= 0.60, 1.26), although the difference between the sub-groups was not statistically significant (p=0.09). Heterogeneity was still present, with I^2 at 28% in the patch group and 55% in the gum/lozenge group. This supports the hypothesis that preloading using nicotine patch is more successful than preloading with short-acting NRT only, and that there is no benefit to preloading using short-acting NRT, although this latter conclusion is clouded by unexplained heterogeneity.

A second subsidiary hypothesis is that longer preloading would lead to better cessation. Five studies that used patches had a preloading period of 2 weeks (Bullen et al. 2010; Rose et al. 1994; Rose et al. 2006; Rose et al. 2009; Schuurmans et al. 2004) and 1 of 4 weeks (Rose et al. 1998). For short-term outcome the RRs of the two groups were similar, with a 2 week RR of 1.18 (95% CI=1.00, 1.39), and 4-week RR of 1.14 (95% CI=0.65, 2.02). For long-term cessation the RRs were 1.23 (95% CI=1.00, 1.52) and 2.00 (95% CI=0.83, 4.81), but in neither case was the test for difference in subgroups significant (p=0.91 and p=0.29 respectively). The wide confidence intervals show the data are insufficient to examine the effect of length of preloading.

Hypothesis 2. Efficacy is mediated through increased post-quit adherence

In all included trials, participants were randomised to NRT or placebo/no NRT pre-quit, but all participants used active NRT after quit day. Our hypothesis was that preloading would enhance post-quit adherence to NRT relative to control. Adherence to NRT treatment was measured using a variety of measures in all eight of the studies, however only four of these studies made between-group, post-quit comparisons (Etter et al. 2009; Hughes et al. 2010; Rose et al. 2009; Schuurmans et al. 2004). Two studies used placebo patch pre-quit as a control (Rose et al. 2009; Schuurmans et al. 2004), therefore we would expect that adherence would be similar across the groups, which was the case. Rose et al. (2009) found that overall adherence was high post-quit and that there was no difference between groups. Schuurmans et al. (2004) found that at quit day, 2, 6 and 10 weeks follow-up 95%, 79%, 58% and 38% of participants in the active patch group complied with nicotine treatment respectively and in the placebo patch group 87%, 77%, 57% and 39%. In Etter et al. (2009) and Hughes et al. (2010)—the only studies to compare preloading with no preloading and report post-quit adherence between groups—there was no significant differences in adherence post-quit. Etter et al. (2009) found that at 8 weeks follow-up preloading participants had used gum for 68% and control participants for 67% of the past 60 days (p=0.80), 41% of the preloading condition and 40% of the control condition (p=0.45) were still using nicotine gum daily, and of these daily users preloading participants were using an average of 7.6 pieces of gum per day and control participants 7.5 (p=0.92). Hughes found that at 1 week post-quit preloading participants had used NRT for an average of 6.5 days of the week, and the control condition for 6.2 days of the week. The available evidence on adherence does not support the hypothesis that preloading achieves efficacy by enhancing adherence to post-quit NRT.

Hypothesis 3. Efficacy is mediated through increased confidence

We hypothesised that if preloading reduces cigarettes smoked per day pre-quit then this will increase confidence in quitting. Only Etter et al. (2009) and Hughes et al. (2010) reported on confidence in quitting. Etter et al. (2009) showed that the preloading group reduced consumption by 48% compared with 9% in the group who received no preloading. Confidence ratings, however, were not affected with scores measured on a 0–100 scale 3 days after quitting being 73 in both groups, p=0.88. Hughes et al. (2010) found that the preloading group reduced cigarette consumption by 54% and the control group by 1%, and that this corresponded to an increase in self-efficacy (measured using the nine-item, form of Velicer's scale) in the preloading group from 18 at baseline to 23 out of a possible 45 at pre-quit (an 11% increase), with minimal change in the control (data for the control condition alone were not provided). A similar effect occurred when confidence was measured using the five-point confidence in quitting scale, however data are not reported. Therefore there was contrasting and inconclusive evidence that reduced smoking enhanced confidence in ability to quit.

Hypothesis 4. Behavioural support modifies the effect of preloading

Our fourth hypothesis was that the intensity of behavioural support provided pre-quit moderates the effect of preloading on adherence. Providing support during preloading could increase adherence, and in turn the efficacy of preloading because participants can raise any misunderstandings, worries and/or problems with the regimen. To investigate this we carried out a sub-group analysis to assess cessation outcomes, by splitting the studies into two sub-groups based on whether or not behavioural support was provided during the pre-quit period. All included studies provided participants with behavioural support, which varied from minimal with no in-

person support to moderate intensity. The studies offering clinic visits (Rose et al. 1994; Rose et al. 1998; Rose et al. 2006; Rose et al. 2009; Schuurmans et al. 2004) all included support part-way through the preloading period bar one (Schuurmans et al. 2004), which provided support at baseline and 1–2 days before quit day. One trial provided telephone support (Bullen et al. 2010), but not during the pre-quit period (Bullen et al. 2008). Hughes et al. (2010) provided telephone support three times for 10 min each during the pre-quit period, in addition to a session at baseline. The remaining study was a self-help study (Etter et al. 2009) with support only by a booklet and/or website. The mid pre-quit support group therefore included five studies (Hughes et al. 2010; Rose et al. 1994; Rose et al. 1998; Rose et al. 2006; Rose et al. 2009) and the no mid pre-quit support group contained three studies (Bullen et al. 2010; Etter et al. 2009; Schuurmans et al. 2004) (Table 2).

For short-term abstinence, splitting by the type of behavioural support (mid pre-quit support vs no mid pre-quit support) resulted in a RR of 1.15 (95% CI=0.93, 1.44) for mid-pre-quit support, and an RR of 0.99 (95% CI=0.85, 1.16) for no mid pre-quit support; p=0.26 for subgroup difference. Heterogeneity was lowered to 38% in the no mid pre-quit support group, but was high in the other group at 78%. The result was similar using long-term abstinence, when the RR was 1.30 (95% CI=0.93, 1.83) for the mid-pre-quit support group and 1.10 (95% CI=0.90, 1.36) for no mid pre-quit support, p=0.40 for subgroup difference. Again this analysis did not eliminate heterogeneity (49% mid pre-quit support, 26% no mid pre-quit support). Given the imprecision of these estimates, the data are insufficient to conclude whether pre-quit support enhances the effectiveness of preloading, though there is very modest support for this hypothesis.

The evidence that behavioural support enhances effectiveness would be supported by data showing that such support enhanced adherence to preloading. All studies that offered support part-way through the pre-quit period (Hughes et al. 2010; Rose et al. 1994; Rose et al. 1998; Rose et al. 2006; Rose et al. 2009) reported that pre-quit NRT use was high, ranging from 90–100% of patches applied in the Rose studies, and 93% of participants using lozenges on a median of 83% of days, and on average using four to five lozenges (18.6 mg) per day in Hughes et al. (2010). The three studies providing no support reported mixed adherence. Bullen et al. (2010) reported that 61% of participants used all of their NRT in the preloading arm pre-quit. However, both Etter et al. (2009) and Schuurmans et al. (2004) also reported adherence was high. In Etter et al. (2009) participants used 7.9 gums per day on average pre-quit. Schuurmans et al. (2004)) reported 95% of participants were using preloading active or placebo patches at quit day. This suggests that participants generally adhered to treatment well in the preloading arms and so the addition of support during preloading did not enhance adherence, and, in turn, the effectiveness of preloading.

Additional moderators of the preloading effect

We also extracted any available results from the included studies, of analyses investigating whether differences in participants' characteristics at baseline were associated with differences in the effect of preloading on abstinence. Five included studies carried out an analysis of this. Bullen et al. (2010) conducted sub-group analyses splitting participants by ethnic group (Maori/non-Maori), age group (<40 years old/≥40 years old), sex (male/female), and social economic group (left school below year 12 or with no qualification/attained year 12 and above), and found that there was no significant differences in the effect of preloading on abstinence for any of these distinctions. Hughes et al. (2010) investigated the interaction of baseline age, sex, race, cigarettes per day, FTND, self-rated addiction, confidence in ability to quit, intention to quit, confidence could quit gradually/abruptly, quitting method preference, self-efficacy and regularity of smoking on abstinence, and found no interaction between any of the moderators and either point prevalence or prolonged abstinence. Rose et al. (2006) also found that age and FTND at baseline did not interact with the effect of preloading on abstinence. However, Rose et al. (2009) did find that baseline FTND interacted with 10-week continuous abstinence rates (p=0.03), with NRT preloading showing a greater effect for those with scores less than 6 compared with 6 or higher. Thirty-four percent of smokers with lower FTND scores achieved abstinence in the preloading arm and 9% in the control arm, whereas 14% of smokers with high FTND scores achieved abstinence with preloading compared with 11% in the control arm. Rose et al. (2009) also specified that they would investigate an interaction for age, sex, withdrawal, smoking satisfaction, cigarettes per day, CO and cotinine levels at baseline, however the results of these analyses were not reported, which might imply none were significant. Finally, Schuurmans et al. (2004) reported that smokers of fewer than 16 cigarettes daily who received preloading had similar rates of abstinence whether or not they received active or placebo patches. However, among heavier smokers, active patch users were significantly more successful (p=0.01) than placebo users. This cut-off was based on an exploratory technique and therefore no test for sub-group differences was appropriate or performed. The data from Schuurmans et al. (2004) and Rose et al. (2009) are somewhat contradictory and therefore there is no strong evidence that any characteristics discernable at the start of treatment identify participants who might benefit more than others from preloading.

Table 2 Details of support provided as part of included studies

Study ID	Method of contact	Support facilitator	Pre-quit support contacts	Minutes per contact	Content of contact
Bullen et al. (2010)	Established telephone quit-line	Trained advisors	Control condition quit immediately. Preloading condition received pre-quit support at baseline only (Bullen et al. 2008)	Not specified	Content of support calls not specified
Etter et al. (2009)	Mailed NRT and booklet. Smoking cessation website	No person contact	Could use booklet and website as required	Not applicable	Booklet included instructions to participants (no further details). Website: www.stop-tabac.ch
Hughes et al. (2010)	Telephone and US National Cancer Institute's "Clearing the Air" booklet	Counsellors with a bachelor's degree in psychology or counselling	Control condition: Baseline, 2 days pre-quit. Preloading condition: Baseline, 1 week after baseline, 2 weeks after baseline, 2 days pre-quit.	All participants received 30–90 min in total. Preloading received at least 1 h pre-quit.	Manuals used by counsellors can be found at: http://www.uvm.edu/~hbpl/?Page=data.html
Rose et al. (1994)	Clinic visits and self-help booklet	Research assistant	Baseline, mid-way through pre-quit (wk 1), quit day	15	Participants interviewed about difficulties and offered encouragement and behaviour change strategies. Booklet advised on quitting strategies
Rose et al. (1998)	Clinic visits and self-help booklet	Research assistant	Baseline, wk 1, wk 2 and wk 3 pre-quit, quit day	10–15	Participants interviewed about difficulties and offered encouragement and behaviour change strategies. Booklet advised on quitting strategies
Rose et al. (2006)	Clinic visits	Not specified	Baseline, mid-way through pre-quit (wk 1), quit day	5–10	Brief supportive counselling. Booklet advised on quitting strategies and quitting benefits
Rose et al. (2009)	Clinic visits	Not specified	Baseline, mid-way through pre-quit (wk 1), day before quit day	Not specified	Not specified
Schaumans et al. (2004)	Clinic visits	Experienced nurse	Baseline, 1–2 days before quit day	20	Counselling given. (No further details specified)

NRT nicotine replacement therapy, *wk* week

Discussion

This updated meta-analysis reports modest evidence of a weak favourable effect of nicotine preloading on abstinence. However, this effect did not achieve significance for short- or long-term abstinence rates and is substantially weaker than the effects reported in previous meta-analyses (Shiffman and Ferguson 2008; Stead et al. 2008). Furthermore, results were clouded by heterogeneity, particularly for short-term outcomes.

The evidence also suggested little apparent effect on users' positive or negative reinforcements for smoking and minimal effect on reported cravings during preloading. Despite this, some studies (Bullen et al. 2010; Etter et al. 2009; Rose et al. 1994, Rose et al. 1998; Rose et al. 2006) reported reductions in smoking intensity, daily cigarette consumption and dependence, but this varied from study to study. It was hypothesised that after quitting a reduction in these variables would lead to a reduction in withdrawal intensity post-quit, thought to drive return to smoking, however there was no evidence of this, and there was reasonable evidence that preloading did not enhance adherence to post-quit NRT. The two studies (Etter et al. 2009; Hughes et al. 2010) that reported reductions in cigarette consumption and measured change in self-efficacy showed contrasting results, therefore we are unable to conclude whether preloading increased self-efficacy, mediated by the decrease in cigarette consumption pre-quit. There was weak evidence that preloading with patch was more effective than with gum, reaching significance for short-term abstinence, but only approaching significance for long-term abstinence, and a very weak non-significant effect of intensity of pre-quit behavioural support on the effect of preloading. Overall, none of our mediational hypotheses received strong support, but many studies did not report on these mediators and none have conducted tests of mediation. Similarly there was very little evidence of any influence of moderators on the effect of preloading, and the only studies that did report an effect appeared to be contradictory, with one study (Rose et al. 2009) reporting that preloading was more effective than control in less dependent smokers with no difference in effect in highly dependent smokers, whereas another (Schuurmans et al. 2004) reported that preloading was more effective than control in heavier smokers with no difference in effect in lighter smokers.

We believe that this review incorporates all extant literature and represents an update on previously published reviews (Shiffman and Ferguson 2008; Stead et al. 2008). These previous reviews both resulted in substantially more positive effect estimates of preloading with large confidence intervals, although in the case of Shiffman and Ferguson (2008) this may be partly caused by the fact that a random-effects model was used rather than fixed-effects. However, Stead et al. (2008) carried out a fixed-effect analysis, as used in this study; therefore the more precise effect estimate produced in this case could be portrayed as a relative strength of this meta-analysis. Our more negative result appears to be due to including recent large, negative studies. There are several reasons why these studies could be more negative than the earlier studies. Two of the three studies provided short-acting NRT for preloading and the strongest evidence of sub-group differences was from dividing studies by whether or not they used a nicotine patch. These two studies also asked participants to use the (short-acting) NRT to reduce their smoking. This could undermine the efficacy of preloading because it is likely to retain the natural rise and fall of blood nicotine levels and mean participants experience the positive and negative reinforcement that is thought to be related to the development and maintenance of tobacco addiction. However, the evidence that NRT preloading with patches did not have marked effects on positive or negative reinforcement casts some doubt on this. A further reason relates to the intensity of behavioural support because two of the three studies provided very limited support pre-quit or self-help only. There was very weak support for the hypothesis that support intensity matters and therefore that this explains the more negative findings of later studies. A final issue is that the funnel plots were noticeably asymmetric, with large negative studies and small positive studies, raising the possibility of publication bias. However, as there were potentially important methodological differences between the studies, this does not itself prove publication bias. Overall, there were too few studies to simultaneously control for several key methodological differences in meta-regression to investigate these issues further.

Another way that this analysis builds on previous investigations is the focus on potential mediators and moderators of the effect of preloading on abstinence. However, these data were sometimes incompletely reported. For example, data had to be extracted from graphs and/or they were reported insufficiently to allow meta-analysis, by not reporting numbers in the analysis or standard deviations. In some studies, data on mediators and moderators were collected and we believe analysed but not reported, fuelling concerns that only statistically significant results were presented. The extracted mediators and moderators, however, do not appear to be convincing explanations for the effect of preloading or differences between trials and therefore this weakness is unlikely to be giving a false picture. This finding highlights that this is an area where measurement and reporting could be improved and that the question of whether preloading is effective, how it might be effective, and in whom it might be most effective is still largely unanswered.

Although the evidence was weak, we believe that the most plausible hypothesis is that preloading undermines the learning process that led to addiction and it is this that leads to enhanced cessation. Weak support was provided for this with our comparison of nicotine patches with short-acting NRT. However it is important to note that the type of NRT used was not the only substantial difference between the studies in each of the subgroups of this analysis. As previously mentioned the studies that used short-acting NRT for preloading both also asked participants to reduce their cigarette consumption during the pre-quit period, whereas the control group were asked to quit abruptly. Therefore there is no way of knowing whether the effect detected in these studies is a function of instructions of how to quit, type of NRT used, or both. To investigate this it would be useful to examine the effect of preloading using acute NRT in participants asked to smoke as normal.

If NRT preloading does work in the way outlined above then longer preloading could be more helpful. Evidence of this was too scanty to draw conclusions, because nearly all studies used the same length of preloading. Taking the evidence as a whole, we believe that future randomised trials of preloading might reasonably choose to use a patch and a longer period of preloading. A full mediation analysis of theoretically possible mediators perhaps using the framework we propose and appropriate moderators would also be helpful.

The efficacy of preloading could depend on the intensity of behavioural support. Until recently, people were advised not to smoke and use NRT concurrently, and, as a result, they may feel reluctant to use nicotine preloading and behavioural support could address this. Behavioural support during preloading could address these concerns increasing the likelihood of adherence to treatment, and thus increasing the likelihood of abstinence. However there was little evidence for this. Perhaps participants were not worried about smoking and using NRT at the same time, or this issue was addressed satisfactorily at the baseline behavioural support session. Regardless of this finding, it seems important to have a counselling protocol which encourages therapists to elicit patients' concerns and seeks to address these.

To assess whether issues in the design, conduct, or reporting of studies affected the apparent efficacy of preloading we carried out a quality assessment. In most cases judgements indicated that studies were either unlikely to cause bias or that the evidence was unclear. The only studies that were judged to be a potential cause of bias were those that were unblinded, where participants and therapists (where used) knew whether they had been allocated to preloading treatment or not. We carried out sub-group analysis to test whether this could influence the effect estimate, which showed a significant difference between those studies that blinded participants and those that did not. If a placebo effect had occurred then we would expect that the effect of preloading would be higher in the unblinded studies, however the opposite was the case, with preloading more effective than placebo in blinded studies but only as effective as control in the unblinded studies. This suggests that failure to blind was not a bias in this review. However, there were differences between the blinded and the unblinded studies—for example two of the three largest unblinded studies used short-acting NRT—which was associated with lower efficacy, and it could be this or other differences between studies that partly explain this unexpected finding.

Based on the previous apparently conclusive meta-analyses, some smoking cessation clinics have routinely recommended preloading treatment. This update gives no strong evidence of efficacy and suggests routine use is not supported by evidence. Nor does this review give any basis for selecting a subgroup of patients who might benefit more from preloading. If preloading is used, we would select the patch over a short-acting form of NRT. Patients could be told to smoke freely, to try to smoke as normal, or to reduce their consumption, but there are no data to suggest which instruction would be most efficacious. Other data indicate that concurrent smoking and NRT use is safe and patients could be strongly reassured (Fagerstrom and Hughes, 2002). However, further trials are required to improve the precision of the estimate of effect of preloading, to try and establish the cause(s) of the heterogeneity in the current trials and to enhance our understanding of the mechanisms and moderators of action. By improving understanding of these mechanisms clinicians may have a basis for deciding which patients would benefit from preloading, and therefore be able to offer targeted cost effective treatment.

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Conflicts of interest NL has received hospitality from Pfizer, manufacturers of smoking cessation medication. PA has done consultancy and research on smoking cessation for Pfizer, McNeil, and Celtic Biotechnology.

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APPENDIX 4: PUBLISHED RESPONSE TO ROSE'S (2011) LETTER TO THE EDITORS (LINDSON & AVEYARD 2011[b])

Psychopharmacology
DOI 10.1007/s00213-011-2351-z

LETTER TO THE EDITORS

Response to Rose (2011): nicotine preloading: the importance of a pre-cessation reduction in smoking behavior

Nicola Lindson · Paul Aveyard

Received: 27 April 2011 / Accepted: 29 April 2011

In response to our review of nicotine preloading trials (Lindson and Aveyard 2011) Rose (2011) raises two discussion points. Firstly, that the effect of nicotine preloading may be correlated with the extent to which smokers reduce smoking during preloading, and secondly that the use of measures of non-continuous abstinence may underestimate the effect of preloading.

Rose (2011) cites within study data supporting the first point. For example, Rose et al. (2010) found that participants who reduced cotinine concentration more than 50% were three times more likely to be abstinent than those who reduced less. This was also observed in a recent trial of 4 weeks of varenicline preloading. (Hajek et al. 2011). We agree that these findings could offer insight into the mechanisms by which preloading has its effects. Therefore, we investigated this further using data from our meta-analysis (Lindson and Aveyard 2011) to make between study comparisons, using sub-group analysis. Four of the eight studies asked participants to smoke freely during the preloading period, and provided data on pre-quit reduction in smoking in the preloading arm. The only common marker of reduction reported was cigarettes per day (cpd). The two studies reporting reduction <50% baseline cpd gave a risk ratio (RR) of 1.83 (95% confidence intervals (CI)=0.97, 3.47), while those reporting >50% reduction gave a RR of 1.04 (95% CI=0.81, 1.34). However the difference between sub-groups was not significant (Online Resource 1). These data therefore do not suggest that the ability of preloading to suppress smoking is a good explanation for the between study heterogeneity we observed in our review.

In response to Rose's (2011) second point, we investigated the suggestion that "studies finding the largest effects of nicotine preloading used as an outcome measure continuous and complete smoking abstinence assessed from the quit date on.", again using sub-group analysis. When measuring long-term abstinence prolonged or point prevalence rates were used for three studies resulting in a pooled RR of 0.95 (95% CI=0.68, 1.34), and an RR of 1.25 (95% CI=1.01, 1.53) for the studies using continuous abstinence. However the test for sub-group differences was not significant (Online Resource 2).

Rose et al. (2009) suggest that trials not reporting continuous abstinence underestimate the true benefit of preloading because in a real-life setting participants will not be supported to continue NRT during lapses after quit day. This may be so, but it is also likely that adherence to preloading would be lower outside a trial than within it for the same reasons. Until recently, people were advised not to smoke and use NRT concurrently. The message to the contrary is not widely accepted as we have witnessed in our own trial (Lindson et al. 2009). Instructions to preload or to continue NRT during a lapse are party to the same discriminations by smokers. In fact, preloading may present more of an issue due to the prolonged nature of the concomitant usage.

In conclusion, we agree that both points raised by Rose (2011) are important but they do not appear to explain

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N. Lindson (✉) · P. Aveyard
UK Centre for Tobacco Control Studies,
Primary Care Clinical Sciences, University of Birmingham,
Edgbaston, Birmingham B15 2TT, UK
e-mail: nll839@bham.ac.uk

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heterogeneity between studies. Further within trial analyses are needed, in particular focusing on differences between active and placebo conditions, as in Rose's recent studies. It would be useful to understand why those people who reduce their smoking do so—the mediators of reduction. Given the uncertainty over the size of the benefit and mechanism of action, we suggest a further trial of nicotine preloading is needed.

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Conflicts of interest NL has received hospitality from Pfizer Ltd, manufacturers of smoking cessation medication. PA has done consultancy and research on smoking cessation for Pfizer, McNeil, and Celtic Biotechnology.

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APPENDIX 5: RRT PARTICIPANT INFORMATION SHEET

UNIVERSITY OF BIRMINGHAM

If you are a smoker wanting to quit, we are inviting you to take part in a research study

We are inviting smokers in the West Midlands to take part in a study aimed at increasing the effectiveness of NHS stop smoking services by offering an alternative to the current method of abrupt quitting (without cutting down), and by providing nicotine replacement therapy (NRT) before quit day as well as after. If you decide to take part, you will be invited to meet a stop smoking advisor who will provide help for you in stopping smoking. You will receive NRT both before and after your quit date and will be asked to quit smoking either abruptly on a quit day without cutting down, or on a quit day after cutting down over 2 weeks.

Joining the study will involve:

- Answering a small number of questions over the phone to ensure you are eligible to take part.
- Attempting to quit smoking (either abruptly or after cutting down)
- Attending seven weekly sessions with a member of the Stop Smoking research team at a local clinic
- Taking part in a short telephone interview about study methods
- Attending a follow-up session 8 weeks after quit day
- Receiving a follow-up phone call 6 months after quit day
- Taking NRT as prescribed (before and after quit day)
- Completing some short questionnaires
- Giving saliva samples and carbon monoxide readings using a carbon monoxide monitor.

Stopping smoking: Assessing the effectiveness of reducing smoking before quitting

You are being invited to take part in a research study. Before you decide whether or not to take part, it is important for you to understand why the research is being done and what it involves. Please take time to read the following information carefully and discuss it with others if you wish. If anything is unclear or you would like more information, please ask us.

What is the purpose of the study?

The purpose of this study is to look at how successful smokers are at giving up smoking when they rapidly reduce their smoking in the two weeks before quit day. We want to compare a group of smokers who cut down before quitting with a group of smokers who don't cut down, and stop abruptly on their quit day. Both groups will receive nicotine replacement therapy (NRT) for 2 weeks before their quit day and for roughly 12 weeks

afterwards. Abrupt quitting is currently the only method of stopping smoking that the NHS Stop Smoking Service offers and using this service greatly increases smokers' chances of successfully quitting. Research suggests that cutting down the number of cigarettes smoked prior to quitting may also be an effective way of giving up and this research wishes to explore this. At present the NHS only use NRT after quit day as part of their treatment, however this study will use NRT before and after quit day in both groups as this has been found to be more effective.

Why have I been chosen?
We are inviting smokers in the West Midlands who want to stop smoking to take part in this study.

What does taking part involve?

- If you decide to take part you will be invited to attend seven sessions with a stop smoking advisor who is trained to help smokers to succeed in their quit attempt. The seven week course is based on the standard stop smoking treatment provided by the NHS.
- The sessions will all take place in (or close to) your GP surgery. You will be able to attend the sessions at times that suit you.
- You will be randomly allocated to one of two groups that will differ only in behaviour for the 2 weeks before quit day. One group will reduce the amount of cigarettes they smoke in the 2weeks before quit day and will be instructed how to do this. This group will use nicotine patches and another type of NRT (e.g. gum) for this period. The other group will continue smoking as normal for the two weeks before quit day and will use only nicotine patches in this period.

Session 1
A member of the research team will talk to you about the study and ask you for your consent to take part. If you have agreed to take part, you will also be asked to provide a sample of your saliva, provide an exhaled carbon monoxide reading using a carbon monoxide monitor, and complete a short questionnaire. On this visit a quit day (in 2 weeks time) will be decided between yourself and your stop smoking advisor and you will be randomly allocated to one of the two treatment groups. You will be given instructions on whether to reduce smoking or not over the next week, and on how to use the NRT. Enough NRT will be supplied at this session to last until the next session. You will also be provided with and taught to use a simple diary which to record the amount of cigarettes smoked and NRT used each day up until the quit day.

Session 2
The stop smoking advisor will discuss how reduction and/or use of NRT have gone so far and help prepare you for stopping smoking. You will be expected to attempt to quit one week later. You will be asked to provide another saliva sample and carbon monoxide reading, and to fill in a short questionnaire. NRT will be provided for the following week.

Session 3
This will be on the day before you quit smoking. Your advisor will talk to you about your progress and provide advice and support. NRT will be given for the following week. Individuals in the abrupt quit group will be provided with another type of NRT as well as patches, such as gum or lozenges, depending on what is preferred. We will obtain a saliva sample, carbon monoxide reading and ask you to fill in a short questionnaire.

Sessions 4-6
At weekly intervals there will be three more sessions with the nurse. The main aim of these sessions is to support you in your attempt to stop smoking. You will be able to discuss your progress, your treatment, and also to ask questions about the research. At each session you will be asked to provide a carbon monoxide reading and to complete some short questionnaires. At session 4 you will also be asked to provide a saliva sample.

Session 7
This session will be the last of the weekly sessions, and will be four weeks after you quit smoking. You will be able to discuss with the advisor how your quit attempt is going so far and how to continue with it, as well as providing a saliva sample, carbon monoxide reading, and filling in a short questionnaire. You will be provided with enough NRT to last until 8 week follow-up.

Telephone Interview
If you stated at the consent stage that you were happy to be interviewed, then a researcher will call you at a convenient time for you, between session 7 and session 8. The interview should take no more than half an hour and will be about your experience and opinion of the method you used to quit. The interview will be digitally recorded and then transcribed by the interviewer. Both the digital recording and the transcription will be anonymised. The contents of the interviews – including yours – will be analysed during the course of the research. The findings will be written-up into a report and may also be used in published works, such as academic journal articles. This written work may include quotations from some of the interviews, including yours. Neither your own name nor any of your other personal details that would identify you will ever be associated with these quotations.

Session 8 (8 weeks after quitting)
You will be able to discuss your progress with your advisor and will be asked to provide a carbon monoxide reading and fill in a short questionnaire. NRT use will be discussed and treatment will be given to last for the next 4 weeks.

6 month telephone call
We will contact you again by telephone call six months after quit day to see how the quit attempt and use of NRT has progressed. If you have stopped smoking for 7 days or more at this point you will be asked to attend a final session where a carbon monoxide reading will be taken.

Do I have to take part?
It is up to you to decide whether or not you want to take part. If you decide to take part, you will be asked to sign a copy of the consent form, while keeping a copy for yourself. This will take place during your first meeting with the stop smoking advisor working on the study. At this stage you will be given the opportunity to opt out of the telephone interview if you are not happy to take part in that part of the study. If you decide to take part in the study, you are free to withdraw at any time and without giving a reason. If you withdraw from the study, you may ask for any data that you have provided to be destroyed or removed from the study. If you do not take part, or withdraw from the study, this will not affect the care you receive.

What are the possible benefits of taking part?
By using NHS stop smoking services, you have a very good chance of stopping smoking, with all the health benefits this brings. Participating in the study could increase these chances of stopping even more if using NRT treatment before quitting is effective, as suggested by past research.

What are the possible disadvantages or risks of taking part?
NRT is a widely used very safe form of treatment and we do not expect there to be any adverse effects, however any side effects while using this treatment will be monitored by an advisor. Taking part in the study and filling in the daily diary before quit day will take up some of your time, however we hope this will be outweighed by the help you will receive to give up smoking.

What if something goes wrong?
If you are harmed due to someone's negligence then you may have grounds for legal action but you will have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms will be available to you.

Confidentiality
All the information we obtain will be strictly confidential. Only study investigators will have access to the data stored within encrypted, password protected databases within a locked office. Information about you is bound by the regulations of medical confidentiality and will not be made available to outside organisations or insurance companies. Because we ask you to complete a series of questionnaires, we will need some way of linking your responses. All participants will be given an individual code number and this number will be used to link all data provided by that individual. No participant will be identifiable from their responses and the linking information will be stored in a locked cabinet, accessible only to the research team. The use of some types of personal information is safeguarded by the Data Protection Act 1998 (DPA). The DPA places an obligation on those who record or use personal information, but also gives rights to people about whom information is held. If you have any questions about data protection, contact the University of Birmingham Data Protection officer on 0121 415 8659.

What happens to my saliva samples after the study?
As explained earlier, you will be asked to provide samples of your saliva. These will be kept locked within the Primary Care Clinical Sciences Department of the University of Birmingham until the end of the study, when they will be analysed to check nicotine levels before destroying in accordance with the Human Tissue Act 2004.

What will happen to the results of the research?
We hope to finish the study in 2011. A copy of the results will be sent to you at the address you have provided to the study team.

Who is funding and organising the research?

This study is funded by the British Heart Foundation. It is organised through a team of researchers and doctors based at the University of Birmingham and University College London.

Who has reviewed this study?
This study has been reviewed and approved by the NHS Research Ethics Committee (Reference Number: 08/H0408/213), Birmingham and the Black Country Comprehensive Local Research Network (Reference Number: 10840), West Midlands (South) Comprehensive Local Research Network (Reference Number: 10840), and the Medicines and Healthcare products Regulatory Agency (Reference Number: 21761/0222/001-0001).

Contact for further information
If you would like any more information about this study please contact:

- Mike Healy (Trial manager)
  Address: Primary Care Clinical Sciences, University of Birmingham, Edgbaston, Birmingham, B15 2TT
  Tel: 0774 776 3729 or 0121 414 6422
  Email: m.healy@bham.ac.uk

- Paul Aveyard (Primary Investigator)
  Address: Primary Care Clinical Sciences, University of Birmingham, Edgbaston, Birmingham, B15 2TT
  Tel: 0121 414 8529
  Email: p.n.aveyard@bham.ac.uk

- Nicola Lindson (Research Associate)
  Address: Primary Care Clinical Sciences, University of Birmingham, Edgbaston, Birmingham, B15 2TT
  Email: nll839@bham.ac.uk

Thank you for taking the time to consider taking part in this research

APPENDIX 6: RRT CONSENT FORM

Participant ID:.....

UNIVERSITY OF BIRMINGHAM

Consent Form

There are three copies of this form: one for you to keep, one for the study records and one for your patient records

Title of Study Rapid Reduction Study

Principal Researcher Dr Paul Aveyard

		Please initial box
1	I confirm that I have read and understand the information sheet for this study (version 4, 13 January 2010) and have had the opportunity to ask questions.	
2	I agree to give saliva samples for research in this study. I understand how the samples will be collected, that giving samples for this research is voluntary and that I am free to withdraw my approval for use of the samples at any time without giving a reason, and without my medical care or legal rights being affected.	
3	I agree that the anonymised information gathered about me can be stored by the Department of Primary Care Clinical Sciences, University of Birmingham for possible use in future projects. I understand that some of these projects may be conducted by researchers other than the team who ran this study.	
4	I give consent for my General Practitioner (G.P.) to be notified of my participation in the study.	
5	I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. I agree to take part in the above study.	
6	I understand that identifiable personal information, such as my name and telephone number, will be collected by the research team at the University of Birmingham as part of the research and that they may need to contact me directly during the study. I understand they will keep this confidential within the research team.	
7	I understand that relevant sections of my research notes may be looked at by responsible individuals from the Research and Development Department of the NHS Trust, Ethics Department and the MHRA to make sure that the research is being conducted properly. I give permission for these people to have access to my research records.	

		Please tick one box	
		Yes	*No*
8	I agree to take part in a telephone interview as part of the above research study. I understand that the interview will be digitally recorded and transcribed, and that this recording and transcription will be anonymous. I understand that the anonymous quotations from the interview may be used in the write-up of the above study and therefore may be included in published works, such as journal articles.		

Name of Patient	Date	Signature
Name of Person taking consent (if different to researcher)	Date	Signature

THANK YOU FOR PARTICIPATING IN THIS RESEARCH

APPENDIX 7: RRT CASE REPORT FORM

CASE REPORT FORM

Participant ID number : ☐☐☐☐☐ **Trial Arm:** Rapid Reduction ☐ Abrupt Quitting ☐

If Rapid Reduction – which technique? HR ☐ (HR-D ☐ or HR-E ☐) SFP ☐ SR ☐

If Rapid Reduction – did they choose themselves or where they randomised? Chose themselves ☐ Randomised ☐

If Randomised – Method Randomisation Number: ☐☐☐☐☐

Session	Date	Attended	Questionnaire completed	Diary completed	Data Entry – Initials & Date
- 2 wk		◯	◯		
- 1 wk		◯	◯	◯	
Quit		◯	◯	◯	
+ 1 wk		◯	◯	◯	
+ 2 wk		◯	◯		
+ 3 wk		◯	◯		
+ 4 wk		◯	◯		
+ 8 wk		◯	◯		
Extra Visit 1 if applicable		◯	◯	◯	
Extra Visit 2 if applicable		◯	◯	◯	

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Summary Sheet

Q.No.	Event	Date Commenced	Date Stopped	Yes=1 No=2	Researcher initials
SS3	Quit smoking at week +4 (NHS) (see below)		N/A		
SS4	Quit smoking at week +4 (RRT) (see below)		N/A		
SS5	Abandoned this quit attempt	N/A			
SS6	Quit smoking at week +8 (RRT) (see below)		N/A		
SS7	Withdrawn from study	N/A			
SS8	Moderate/Severe Adverse Event(s) *(graded 3 or above for "caused by study medication" on adverse events form)*				
SS9	Serious Adverse Event(s)				
SS10	Quit smoking at 6 months (RRT) (see below)		N/A		
SS11	Lost to follow-up at 6 months	N/A			
SS12	Made a new quit attempt		N/A		
SS13	Quit smoking at week +4 (NHS) (see below) not verified by CO				
SS14	Quit smoking at week +4 (RRT) (see below) not verified by CO				
SS15	Quit smoking at week +8 (RRT) (see below) not verified by CO				

Definitions of quit

Time of quit	Definition
+ 4 week (NHS)	No cigarettes at all (not even 1 puff) since week +2 verified by CO of <10
+ 4 week (RRT)	No more than 5 cigarettes since week +2 verified by CO of <10
+ 8 week (RRT)	No more than 5 cigarettes since week +2 verified by CO of <10
6 month (RRT)	No more than 5 cigarettes since week +2 verified by CO of <10
NB: since week +2 means at the end of the second week post quit date – verify by using data collected at weeks +3 onwards visits and NOT DATA FROM THE WEEK +2 VISIT	

Definitions

Severe acute or chronic psychiatric or medical condition	Any unstable or terminal existing condition that may either make it unsafe for one to one appointments for the member of staff or put the participant in a compromising position.
Severe adverse reaction to NRT	a) any reaction that has made them feel very unwell to the extent they wouldn't be prepared to use it again, or/and b) patches only – sore, open and blistering skin, or/and localised swelling of tissues
Severe cardiac arrhythmias	a) any cardioversion in past medical history not associated with acute MI or/and b) taking any antiarrhythmic medication other than digoxin and beta blockers, except where beta blockers are taken for arrhythmia.
Severe extensive dermatitis/eczema	Odd blemishes alright but if skin is so badly affected that they would not be able to wear the NRT patches then we can't offer them the programme knowing they wouldn't be compliant with study protocol.
Severe hepatic impairment	liver damage to the extent that GP is having to reduce their normal medications due to toxicity.
Drugs affected by smoking cessation	Caffeine Chlorpromazine Clozapine Haloperidol Olanzapine Theophylline/Aminophylline Insulin Fluvoxamine Propranolol Flecainide Benzodiazepines Duloxetine Warfarin

Research Phase

Assessment form to decide eligibility for Rapid Reduction Trial

Rapid Reduction trial checklist inclusion criteria

Section 1 Please complete for all subjects

Is the participant

18 years of age or older	Yes ☐	No ☐
Willing to attempt to quit smoking completely in two weeks	Yes ☐	No ☐
Willing and able to comply with all study procedures	Yes ☐	No ☐

Does the participant

Smoke an average of 15 or more cigarettes or 12.5g or more of loose tobacco (in roll your own cigarettes) a day? OR blows greater than or equal to 15 on CO monitor	Yes ☐	No ☐

If **NO** is the answer to **any** of the above questions the participant is unable to participate in this study.

Section 2 Please complete for all female subjects

Is the participant currently pregnant or breast-feeding?	Yes ☐	No ☐
Is the participant intending to get pregnant in the next 3 months?	Yes ☐	No ☐

If **YES** is the answer to **any** of the above questions **in section 2** the participant is unable to participate in this study.

Rapid Reduction trial checklist exclusion criteria

Section 3 Please complete for all subjects

Does the participant have a history of:

Severe cardiac arrhythmia?	Yes ☐	No ☐
Severe adverse reactions to NRT? (this includes patches and oral NRT)	Yes ☐	No ☐

In the past three weeks, has the participant experienced:

Myocardial infarction/unstable angina/acute coronary syndrome?	Yes ☐	No ☐
Cerebrovascular accident?	Yes ☐	No ☐

Does the participant have:

Severe extensive dermatitis/eczema?	Yes ☐	No ☐
Currently uncontrolled hyperthyroidism?	Yes ☐	No ☐
Severe renal impairment (i.e. GFR ≤ 29mls/min)?	Yes ☐	No ☐
Severe hepatic impairment?	Yes ☐	No ☐
Active phaeocromocytoma?	Yes ☐	No ☐
A severe acute or chronic psychiatric or medical condition? (see definition for this criteria)	Yes ☐	No ☐

Is the participant currently using:

NRT?	Yes ☐	No ☐
Bupropion, nortriptyline, mecamylamine, reserpine, or varenicline?	Yes ☐	No ☐
Undergoing any other treatment for tobacco dependence e.g hypnosis?	Yes ☐	No ☐

Has the participant :

Taken part in any other medicinal trials within the last 3 months?	Yes ☐	No ☐

Do you suspect:

That the participant is abusing drugs and/or alcohol?	Yes ☐	No ☐

Research Phase

If **YES** is the answer to **any** of the questions in section 3 the participant is unable to participate in this study.

If **you are unsure on any of the inclusion / exclusion criteria** you must discuss with the trial doctor or trial manager whether the person can participate in this study.

Name of person spoken to (if applicable) .....

Medical History Form/Elective admissions

Medical History: Write none here if nil to report_____

Number	Diagnosis	Current Status: 1= Past, 2= Controlled, 3= Active	Date Informed (dd/mm/yyyy)	Initials of researcher taking history
MH1				
MH2				
MH3				
MH4				
MH5				
MH6				
MH7				
MH8				
MH9				
MH10				

Number	Elective hospital admissions (for next 7 months).	Approximate dates	Date Informed (dd/mm/yyyy)	Initials of researcher taking history
EA 1				
EA 2				

Concomitant Medication

No	Trade or generic name Write none here if nil to report_____	Reason for use (must match diagnosis on medical history or adverse events form)	Start date (dd/mm/yy)	Stop date (if stopped by final visit) (dd/mm/yy)	Ongoing at final visit 1=Yes 2=No
1					
2					
3					
4					
5					
6					
7					
8					
9					
10					
11					
12					

Form completed by (initials) _____

Are any of these drugs on medication list affected by smoking cessation (see page 3): Yes/No?
If yes, send GP2 letter at visit 4 (when smoking has stopped/greatly reduced).

Research Phase

Have you completed medical history/elective admissions? Yes ☐ No ☐

Have you completed concomitant medication? Yes ☐ No ☐

Is the person able to enter the trial? Yes ☐ No ☐

Name of assessor _____ Date of assessment _____ Signature _____

Summary note

Copy of consent to GP Yes ☐ No ☐ Date sent _____

Copy of consent to patient Yes ☐ No ☐ Date given _____

GP letter sent informing of trial entry Yes ☐ No ☐ Date sent _____

Response from GP Yes ☐ No ☐ Date received _____

GP withdrawn from trial Yes ☐ No ☐

Research Phase

Visit 1: Preparation week 1 - 2 weeks pre-research quit attempt

V1a	Advisor name	
V1b	Date of session	day / month / Year: 2 0
V1c	Time of visit (24 hr clock)	
~	Does the participant meet the inclusion criteria as stated on the pre-screening form?	Yes ☐ No ☐
~	Has the participant signed the consent form?	Yes ☐ No ☐
~	Has the Patient Information Form been completed?	Yes ☐ No ☐
~	Has the participant completed baseline questionnaire?	Yes ☐ No ☐
~	Has the Participant GP letter been completed?	Yes ☐ No ☐
V1d	How many manufactured cigarettes does the participant smoke per day? Please provide a specific no. (remember: must be at least 15/day to be eligible for the study)	_____
V1e	How many rolled cigarettes does the participant smoke per day? Please provide a specific no. (remember: must be at least 12.5g loose tobacco/day to be eligible for the study)	_____
V1f	Exhaled Carbon Monoxide reading (ppm)	_____
V1g	Has saliva sample S1 been taken?	Yes ☐ No ☐
~	Has a quit date been agreed (2 weeks time)?	Yes ☐ No ☐
V1h	Write in date	_____
~	Participant trial arm preference	_____

Randomise Participant

Research Phase

NRT

~ Have you given the participant their NRT patches? Yes ☐ No ☐

~ Has the participant chosen their preferred type of acute NRT Yes ☐ No ☐

V1i Preferred extra NRT chosen: _____

In rapid reduction arm only:

~ Have you given the participant their weekly reduction regime Yes ☐ No ☐

~ Has the acute NRT been given to participant? Yes ☐ No ☐

V1k Have you given the participant their weekly diary? Yes ___ No ___

V1l How long did you spend on this appointment? Hours_____ Minutes _____

V1l Any additional notes/comments from this session?

Date_____ Initials_____

Research Phase

Visit 2: Preparation week 2 **- 1 week pre-research quit attempt**

V2a	Advisor name	
V2b	Did participant attend appointment?	Yes ☐ No ☐
V2c	Date	day ☐☐ month ☐☐ Year 2 0 ☐☐
V2d	Time of visit (24 hr clock)	☐☐☐☐
~	Does participant still meet inclusion criteria?	Yes ☐ No ☐
~	Confirm consent	Yes ☐ No ☐
~	Has the participant completed the -1wk questionnaire?	Yes ☐ No ☐
V2e	Exhaled Carbon Monoxide reading (ppm)	_____
V2f	Has saliva sample S2 been taken?	Yes ☐ No ☐
~	Have you talked about preparing to quit?	Yes ☐ No ☐
V2g	Reconfirm the planned quit date (was planned last week). Write in:	_____

NRT

V2h	When after 1st visit did participant start wearing their patch?	Next day	☐	Other (provide date) _____	☐
V2i	Is the participant wearing their patch?			Yes ☐ No ☐	
V2j	If no, date stopped wearing patch	day ☐☐ month ☐☐ Year 2 0 ☐☐			
V2k	Has the participant experienced any significant side effects/adverse events (e.g. vomiting) (If Yes fill in Adverse Event Form on page 28)			Yes ☐ No ☐	

Research Phase

V2l Complete nicotine overdose symptom checklist Yes ☐ No ☐

If symptoms present, what action taken?
- continue with prescribed dose? ☐
- direct participant to reduced dose? ☐
- other (please give details below) ☐

~ Have you given the participant their NRT patches for next week? Yes ☐ No ☐

In rapid reduction arm only:

~ Have you given the participant their weekly reduction regime Yes ☐ No ☐

~ Has the acute NRT for next week been given to participant? Yes ☐ No ☐

V2m Has the participant been taking their extra NRT? Yes ☐ No ☐

V2n If no, date stopped taking extra NRT Day ____ Month ____ Year 2 0 ____

V2o

		No. of cigarettes smoked							
Day	No. of hours patch worn	Manufactured	Roll-ups	Gum, lozenge or Microtab 2mg strength	No. used	Gum or lozenge 4mg strength	No. used	Inhalator cartridge	Sprays from nasal spray
1									
2									
3									
4									
5									
6									
7									
8									
9									
10									
Total									

~ Have you checked concomitant medication? Yes ☐ No ☐

~ Have you given the participant their weekly diary? Yes ☐ No ☐

Research Phase

V2p Time spent on appointment **hours _____ minutes _____**

V2q Any additional notes/comments from this session?

Date_____ Initials_____

Research Phase

STOP

Before starting to fill in their Visit 3 sheet is this their true and planned quit appointment?

IF not then:

If delaying their quit attempt by 1 week then fill in Extra Visit 1 instead, confirm new quit date and book a new Visit 3 appointment for next week.

If delaying their quit attempt by 2 weeks then fill in Extra Visit 1 instead, confirm new quit date and book an Extra Visit 2 appointment for next week.

If wanting to delay their quit attempt by more than 2 weeks then cease treatment and give them the local stop smoking services number for when they are ready to set a new quit date.

Extra Visit 1(Appendix 1) and Extra Visit 2 (Appendix 2) sheets are only to be used for delayed quit appointments as applicable – all true quit week appointments are to be completed on the Visit 3 sheets and no-one can delay for more than 2 weeks.

Visit 3: One day before quit day	Research Phase 0 WK

V3a Advisor name

V3b Did participant attend appointment — Yes ☐ No ☐

V3c Date — day ☐☐ month ☐☐ Year 2 0 ☐☐

V3d Time of visit (24 hr clock) ☐☐☐☐

~ Has 0wk questionnaire been completed? — Yes ☐ No ☐

V3e Exhaled Carbon Monoxide reading (ppm) _____

V3f Has saliva sample S3 been taken? — Yes ☐ No ☐

V3g Confirm the planned quit date: _____

NRT

V3h Is the participant wearing their patch? — Yes ☐ No ☐

V3i If no, date stopped wearing patch — day ☐☐ month ☐☐ year 2 0 ☐☐

V3j Has the participant experienced any significant side effects/adverse events (e.g. vomiting) (If Yes fill in Adverse Event Form on page 28) — Yes ☐ No ☐

V3k Complete nicotine overdose symptom checklist — Yes ☐ No ☐
If symptoms present, what action taken?
- continue with prescribed dose? ☐
- direct participant to reduced dose? ☐
- other (please give details below) ☐

~ Have you given the participant their NRT patches? — Yes ☐ No ☐
(to begin taking either after the session or tomorrow morning)
Has the participant been given their extra NRT? — Yes ☐ No ☐

Research Phase

	In rapid reduction arm only:			
V3l	Has the participant been taking their extra NRT?	Yes	No	
V3m	If no, date topped taking extra NRT	Day	Month	Year 2 0

V3n

Day	No. of hours patch worn	No. of cigarettes smoked: Manufactured	No. of cigarettes smoked: Roll-ups	Gum, lozenge or Microtab 2mg strength	No. used	Gum or lozenge 4mg strength	No. used	Inhalator cartridge	Sprays from nasal spray
1									
2									
3									
4									
5									
6									
7									
8									
9									
10									
Total									

~ Have you checked concomitant medication? Yes ☐ No ☐

~ Have you given the participant their weekly diary? Yes ☐ No ☐

~ Time spent on appointment hours _____ minutes _____

V3o Any additional notes/comments from this session?

Date_____ Initials_____

Research Phase

Visit 4: 1 week post quit day **+ 1 WK**

V4a Advisor name

V4b Did participant attend appointment Yes ☐ No ☐

		Day	Month	Year
V4c	**Date**			2 0

V4d Time of visit (24 hr clock)

~ Has +1 wk questionnaire been completed? Yes ☐ No ☐

V4e Confirm when the participant began their quit attempt _____

V4f Has the participant smoked since their quit date? Yes ☐ No ☐

V4g Has the participant continued with their quit attempt? Yes ☐ No ☐

V4h Exhaled Carbon Monoxide reading (ppm) _____

V4i Has saliva sample S4 been taken? Yes ☐ No ☐

NRT

V4j Is the participant wearing their patch? Yes ☐ No ☐

V4k Is the participant taking their extra NRT? Yes ☐ No ☐

		day	month	Year
V4l	If no, date stopped wearing patch			2 0
V4m	if no, date stopped taking extra NRT			2 0

V4n Has the participant experienced any significant side effects/adverse events (e.g. vomiting) (If Yes fill in Adverse Event Form on page 28) Yes ☐ No ☐

V4o Complete nicotine overdose symptom checklist Yes ☐ No ☐

If symptoms present, what action taken?

- continue with prescribed dose? ☐
- direct participant to reduced dose? ☐
- other (please give details below) ☐

Research Phase

~ Have you given out the next weekly pack of NRT patches Yes ☐ No ☐

~ Have you given out a week's supply of extra NRT Yes ☐ No ☐

~ Participant's trial arm preference _____

V4p

Day	No. of hours patch worn	No. of cigarettes smoked: Manufactured	No. of cigarettes smoked: Roll-ups	Gum, lozenge or Microtab 2mg strength	No. used	Gum or lozenge 4mg strength	No. used	Inhalator cartridge	Sprays from nasal spray
1									
2									
3									
4									
5									
6									
7									
8									
9									
10									
Total									

~ Have you checked concomitant medication? Yes ☐ No ☐
Does GP2 letter need to be sent? See Medication List pages 3 & 6.

V4q Time spent on appointment hours _____ minutes _____

V4r Any additional notes/comments from this session?

Date_____ Initials_____

Research Phase

Visit 5: 2 weeks post quit day **+ 2 WK**

V5a **Advisor name**

V5b **Did participant attend appointment?** **Yes** **No**

		day	month	Year
V5c	**Date of Visit**			2 0

V5d **Time of visit** **(24 hr clock)**

~ **Has +2 wk questionnaire been completed?** **Yes** **No**

V5e **Has the participant smoked since their last visit?** **Yes** **No**

V5f **Has the participant continued with their quit attempt?** **Yes** **No**

V5g **Number of manufactured cigarettes smoked since last visit?** _____

V5h **Number of roll-ups smoked since last visit?** _____

V5i **Exhaled Carbon Monoxide reading (ppm)** _____

NRT

V5j **Is the participant wearing their patch?** **Yes** **No**

V5k **Is the participant taking their extra NRT?** **Yes** **No**

		day	month	Year
V5l	**If no, date stopped wearing patch**			2 0
V5m	**if no, date stopped taking extra NRT**			2 0

V5n **Has the participant experienced any significant side effects/adverse events (e.g. vomiting)** **Yes** **No**
(If Yes fill in Adverse Event Form on page 28)

Research Phase

V5o **Complete nicotine overdose symptom checklist** **Yes** ☐ **No** ☐

If symptoms present, what action taken?

- continue with prescribed dose? ☐

- direct participant to reduced dose? ☐

- other (please give details below) ☐

~ **Have you given out the next weekly pack of NRT patches** **Yes** ☐ **No** ☐

~ **Have you given out the next week's supply of extra NRT** **Yes** ☐ **No** ☐

~ **Have you checked concomitant medication?** **Yes** ☐ **No** ☐

V5p **Time spent on appointment** **hours** _____ **minutes** _____

V5q **Any additional notes/comments from this session?**

Date_____ **Initials**_____

Research Phase

Visit 6: 3 weeks post quit day **+ 3 WK**

V6a Advisor name

V6b Did participant attend appointment? Yes ☐ No ☐

		day	month	year
V6c	Date			2 0

V6d Time of visit (24 hr clock)

~ Has +3 wk questionnaire been completed? Yes ☐ No ☐

V6e Has the participant smoked since their last visit? Yes ☐ No ☐

V6f Has the participant continued with their quit attempt? Yes ☐ No ☐

V6g Number of manufactured cigarettes smoked since last visit? _____

V6h Number of roll-ups smoked since last visit? _____

V6i Exhaled Carbon Monoxide reading (ppm) _____

NRT

V6j Is the participant wearing their patch? Yes ☐ No ☐

V6k Is the participant taking their NRT? Yes ☐ No ☐

		day	month	year
V6l	If no, date stopped wearing patch			2 0
V6m	if no, date stopped taking NRT			2 0

V6n Has the participant experienced any significant side effects/adverse events (e.g. vomiting) (If Yes fill in Adverse Event Form on page 28) Yes ☐ No ☐

V6o Complete nicotine overdose symptom checklist Yes ☐ No ☐

If symptoms present, what action taken?

- continue with prescribed dose? ☐
- direct participant to reduced dose? ☐
- other (please give details below) ☐

Research Phase

~ Have you given out the next weekly pack of NRT patches Yes ☐ No ☐

~ Have you given out the next week's supply of extra NRT Yes ☐ No ☐

~ Have you checked concomitant medication? Yes ☐ No ☐

V6p Time spent on appointment Hours _____ Minutes _____

V6q Any additional notes/comments from this session?

Date_____ Initials_____

Research Phase

Visit 7: 4 weeks post quit day **+ 4WK**

V7a Advisor name

V7b Did participant attend appointment? Yes ☐ No ☐

		day	month	Year
V7c	Date			2 0

V7d Time of visit (24 hr clock)

~ Has + 4 wk questionnaire completed? Yes ☐ No ☐

V7e Has the participant smoked since their last visit? Yes ☐ No ☐

V7f Has the participant continued with their quit attempt? Yes ☐ No ☐

V7g Number of manufactured cigarettes smoked since last visit? _____

V7h Number of roll-ups smoked since last visit? _____

V7i Exhaled Carbon Monoxide reading (ppm) _____

NRT

V7j Is the participant wearing their patch? Yes ☐ No ☐

V7k Is the participant taking their NRT? Yes ☐ No ☐

		day	month	Year
V7l	If no, date stopped wearing patch?			2 0
V7m	if no, date stopped taking NRT?			2 0

V7n Has the participant experienced any significant side effects/adverse events (e.g. vomiting) (If Yes fill in Adverse Event Form on page 28) Yes ☐ No ☐

V7o Complete nicotine overdose symptom checklist Yes ☐ No ☐

If symptoms present, what action taken?

- continue with prescribed dose? ☐
- direct participant to reduced dose? ☐
- other (please give details below) ☐

Research Phase

V7p Future treatment plan

Negotiate with participant how their treatment will be reduced **Agreed actions:**

~ **Have you given out the next supply of NRT patches** **Yes** ☐ **No** ☐
~ **Have you given out the next supply of extra NRT** **Yes** ☐ **No** ☐

~ **Have you checked concomitant medication?** **Yes** ☐ **No** ☐

V7q Time spent on appointment **hours** _____ **minutes** _____

V7r Any additional notes/comments from this session?

Date_____ **Initials**_____

Visit 8: 8 weeks post quit day — *Research Phase* +8wk

V8a Advisor name

V8b Did participant attend appointment? Yes ☐ No ☐

V8c Date — day ☐☐ month ☐☐ Year 2 0 ☐☐

V8d Time of visit (24 hr clock) ☐☐☐☐

~ Has + 8 wk questionnaire completed? Yes ☐ No ☐

V8e Has the participant smoked since their last visit? Yes ☐ No ☐

If yes:

V8f Date participant last smoked _____

V8g Has participant smoked more than 5 cigarettes since week +2 Yes ☐ No ☐

V8h Has the participant continued with their quit attempt? Yes ☐ No ☐

V8i Exhaled Carbon Monoxide reading (ppm) _____

NRT

V8j Is the participant wearing their patch? Yes ☐ No ☐

V8k Is the participant taking their extra NRT? Yes ☐ No ☐

V8l If no, date stopped wearing patch? — day ☐☐ month ☐☐ Year 2 0 ☐☐

V8m if no, date stopped taking NRT? — day ☐☐ month ☐☐ Year 2 0 ☐☐

V8n Has the participant experienced any significant side effects/adverse events (e.g. vomiting) (If Yes fill in Adverse Event Form on page 28) Yes ☐ No ☐

V8o Complete nicotine overdose symptom checklist Yes ☐ No ☐

If symptoms present, what action taken?

- continue with prescribed dose? ☐
- direct participant to reduced dose? ☐
- other (please give details below) ☐

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Research Phase

~ **Have you given out NRT patches** **Yes** ☐ **No** ☐
~ **Have you given out extra NRT** **Yes** ☐ **No** ☐

~ **Have you checked concomitant medication?** **Yes** ☐ **No** ☐

V8p Time spent on appointment **hours** _____ **minutes** _____

V8q Any additional notes/comments from this session?

Date_____ **Initials**_____

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6 Month: Follow-up phone call

+6ma Advisor name

+6mb Date of follow-up — day / month / Year (2 0 __ __)

+6mc Has the participant smoked since their last visit? Yes ☐ No ☐

If yes:
+6md Date participant last smoked _____
+6me How many smoking now?

+6mf Has participant smoked more than 5 cigarettes since week +2 Yes ☐ No ☐

+6mg Has the participant continued with their quit attempt? Yes ☐ No ☐
+6mh How many does the participant smoke currently if still smoking? Yes ☐ No ☐

+6mi Write start date of any new quit attempt __ __/ __ __/ 20 __ __

+6mj Is the participant still using a patch? Yes ☐ No ☐

+6mk Is the participant still using oral/nasal NRT? Yes ☐ No ☐

NRT

+6ml If no, date stopped wearing patches? (best approximate date possible) — day / month / Year (2 0 __ __)

+6mm if no, date stopped using oral/nasal NRT? (2 0 __ __)

+6mn Has the participant experienced any significant side effects/adverse events (e.g. vomiting) (If Yes fill in Adverse Event Form on page 28) Yes ☐ No ☐

+6mo If no longer abstinent how long was participant abstinent for? (best approximate date possible) _____

+6mp Does participant need a 6 month validation visit, i.e. not smoked in past 7 days or not smoked more than 5 cigarettes since week +2. Yes ☐ No ☐

+6mq If no, Completed +6m questionnaire (questions 2, 3, 6 & 7) over phone? Yes ☐ No ☐

+6mr If needed, when has validation visit been arranged for?

Date_____ Time_____

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Research Phase

+6ms Any additional notes/comments from this session?

Date_____ **Initials**_____

Research Phase

Visit 9: 6 month validation visit **+ 6mths**

+6mt **Advisor name**

+6mu **Did participant attend appointment?** **Yes** ☐ **No** ☐

+6mv **Has participant completed +6m questionnaire?** **Yes** ☐ **No** ☐

		day	month	Year
+6mw	**Date**			2 0

+6mx **Time of visit** **(24 hr clock)**

+6my **Exhaled Carbon Monoxide reading (ppm)** _____

+6mz **Any additional notes/comments from this session?**

Date_____ **Initials**_____

Adverse Event Form

No.	Diagnosis/Syndrome/Symptom	Start Date (dd/mm/yy)	Stop Date (dd/mm/yy)	Intensity 1=Mild 2=Moderate 3=Severe	Serious 1=Yes 2=No	Caused by Study med 1=No 2= Unlikely 3=Possibly 4=Probably 5=Yes	Action taken with study med 1=None 2=Dose reduced 3=Medication discontinued	Outcome at last session 1=Recovered 2=Recovered with sequelae 3=Continuing 4=Death 5=Unknown
1								
2								
3								
4								
5								
6								
7								
8								
9								
10								
11								
12								
13								

Form completed by (initials) _____

Research Phase

Appendix 1:
Extra Visit 1: Preparation week 3 **- 1 week pre-research quit attempt**

EV1a **Advisor name**

EV1b **Did participant attend appointment?** **Yes** **No**

EV1c **Date** Day month Year 2 0

EV1d **Time of visit** **(24 hr clock)**

~ **Does participant still meet inclusion criteria?** **Yes** **No**

~ **Confirm consent** **Yes** **No**

~ **Has the participant completed the extra visit questionnaire?** **Yes** **No**

EV1e **Exhaled Carbon Monoxide reading (ppm)**

~ **Have you talked more about preparing to quit?** **Yes** **No**

EV1f **When is the new planned quit date. Write in:**

NRT

EV1g **Is the participant wearing their patch?** **Yes** **No**

EV1h **If no, date stopped wearing patch** day month year 2 0

EV1i **Has the participant experienced any significant side effects/adverse events (e.g. vomiting)**
(If Yes fill in Adverse Event Form on page 28) **Yes** **No**

EV1j **Complete nicotine overdose symptom checklist** **Yes** **No**
If symptoms present, what action taken?
- continue with prescribed dose?
- direct participant to reduced dose?
- other (please give details below)

30

CRF«id»

Research Phase

~ Have you given the participant their NRT patches for next week? Yes ☐ No ☐

In rapid reduction arm only:

~ Has the acute NRT for next week been given to participant? Yes ☐ No ☐

EV1k Has the participant been taking their extra NRT? Yes ☐ No ☐

EV1l If no, date stopped taking extra NRT Day ☐☐ Month ☐☐ Year 2 0 ☐☐

EV1m

Day	No. of hours patch worn	No. of cigarettes smoked: Manufactured	No. of cigarettes smoked: Roll-ups	Gum, Mictrotab or lozenge 2mg strength	No. used	Gum or lozenge 4mg strength	No. used	Inhalator cartridge	Sprays from nasal spray
1									
2									
3									
4									
5									
6									
7									
8									
9									
10									
Total									

~ Have you checked concomitant medication? Yes ☐ No ☐

~ Have you given the participant their weekly diary? Yes ☐ No ☐

EV1n Time spent on appointment hours _____ minutes _____

EV1o Any additional notes/comments from this session?

Date_____ Initials_____

Research Phase

Appendix 2:
Extra Visit 2: Preparation week 4 **- 1 week pre-research quit attempt**

EV2a **Advisor name**

EV2b **Did participant attend appointment?** **Yes** **No**

EV2c **Date** day month Year 2 0

EV2d **Time of visit** **(24 hr clock)**

~ **Does participant still meet inclusion criteria?** **Yes** **No**

~ **Confirm consent** **Yes** **No**

~ **Has the participant completed the extra visit questionnaire?** **Yes** **No**

EV2e **Exhaled Carbon Monoxide reading (ppm)**

~ **Have you talked more about preparing to quit?** **Yes** **No**

EV2f **When is the new planned quit date. Write in:**

NRT

EV2g **Is the participant wearing their patch?** **Yes** **No**

EV2h **If no, date stopped wearing patch** day month year 2 0

EV2i **Has the participant experienced any significant side effects/adverse events (e.g. vomiting)**
(If Yes fill in Adverse Event Form on page 28) **Yes** **No**

EV2j **Complete nicotine overdose symptom checklist** **Yes** **No**
If symptoms present, what action taken?
- continue with prescribed dose?
- direct participant to reduced dose?
- other (please give details below)

32

CRF«id»

Research Phase

~ Have you given the participant their NRT patches for next week? Yes ☐ No ☐

In rapid reduction arm only:

~ Has the acute NRT for next week been given to participant? Yes ☐ No ☐

EV2k Has the participant been taking their extra NRT? Yes ☐ No ☐

EV2l If no, date stopped taking extra NRT Day ☐☐ Month ☐☐ Year 2 0 ☐☐

EV2m

Day	No. of hours patch worn	No. of cigarettes smoked: Manufactured	No. of cigarettes smoked: Roll-ups	Gum, Microtab or lozenge 2mg strength	No. used	Gum or lozenge 4mg strength	No. used	Inhalator cartridge	Sprays from nasal spray
1									
2									
3									
4									
5									
6									
7									
8									
9									
10									
Total									

~ Have you checked concomitant medication? Yes ☐ No ☐

~ Have you given the participant their weekly diary? Yes ☐ No ☐

EV2n Time spent on appointment hours _____ minutes _____

EV2o Any additional notes/comments from this session?

Date_____ Initials_____

33

CRF«id»

APPENDIX 8: EXAMPLE DAY OF RRT ABRUPT ARM PRE-QUIT DIARY

Rapid Reduction Study

Abrupt Cessation Group

(Weeks -2, -1 and Extra Visits)

Diary

Participant ID: _____

Week commencing: _____

UNIVERSITY OF BIRMINGHAM

British Heart Foundation

Rapid Reduction Study: Participant Diary

How to use this diary

This diary is for you to keep a daily record of your smoking, during the time between your weekly clinic sessions.

We ask you:

- whether you have used a nicotine patch today,
- Have you smoked any cigarettes today. If so how many.
- the answer to 2 questions about your cravings for cigarettes during the day

Finally, there is space for you to write any other comments about NRT or how you are feeling about your quit attempt. Do use additional paper if you want to. There is contact information at the back of this diary if you have any problems or concerns about using your NRT.

Day 1. Date:_____

We would like to know :

1. **Have you used a nicotine patch today? (please circle)** YES NO

2. **How many hours did you wear the patch for?** ☐

3. **Have you smoked any cigarettes today? (please circle)** YES NO

4. **If YES, how many?:** Manufactured ☐ Roll-ups ☐

5. **How strong have the urges to smoke been *(Circle one number below)***

No urges	Slight	Moderate	Strong	Very strong	Extremely strong
0	1	2	3	4	5

6. **How much of the time have you felt the urge to smoke in the past 24 hours? *(Circle one number below)***

Not at all	A little of the time	Some of the time	A lot of the time	Almost all the time	All the time
0	1	2	3	4	5

7. **If you have any comments please write them here:**

Contact for further information

If you have any problems or concerns about using your NRT, you can contact:

Monday – Friday, 9 am – 5 pm:

Mike Healy 0121 414 6422 / 07747 763729

Tel: 0774 776 3729

E-mail: m.healy@bham.ac.uk

Everyday, 7 am - 11 pm

The NHS Smoking Helpline

Tel: 0800 022 4 332

At all other times:

NHS Direct on 0845 46 47

APPENDIX 9: EXAMPLE COMPLETED WEEK 1 SR REDUCTION SCHEDULE

Participant Name: Patricia Smith Participant number: 00145

You currently average 35 minutes in between each cigarette

By next week we want you to be smoking I cigarette every 70 minutes.

To achieve this what we want you to do is:

Tomorrow smoke one cigarette every	0	hours	40	minutes	on	Tues day
Next Day smoke one cigarette every	0	hours	45	minutes	on	Wednes day
Next Day smoke one cigarette every	0	hours	50	minutes	on	Thurs day
Next Day smoke one cigarette every	0	hours	55	minutes	on	Fri day
Next Day smoke one cigarette every	1	hours	0	minutes	on	Satur day
Next Day smoke one cigarette every	1	hours	5	minutes	on	Sun day
Next Day smoke one cigarette every	1	hours	10	minutes	on	Mon day

Do not exceed the daily target number of cigarettes that is written in your diary

To achieve this what we want you to do is:

Today if week 1 - smoke as normal

Today if week 2 carry on with todays regime you started with this morning

APPENDIX 10: EXAMPLE COMPLETED WEEK 1 HR-E REDUCTION SCHEDULE

Participant Name: Albert Brown

Participant number: 00456

Cigarettes identified as habitual: **Give up on:**

	Fri day	Sat day	Sun day	Mon day	Tues day	Wed day	Thurs day
Driving to work	X						
Afternoon break (around 15.00)							X
First after getting home			X				
Through the evening					X		
Through the evening						X	
Through the evening		X					
Through the evening							X
Through the evening				X			

Cigarettes identified as particularly rewarding: **Give up on:**

	Fri day	Sat day	Sun day	Mon day	Tues day	Wed day	Thurs day
First in the morning							
with breakefast							
Mid morning break (around 10.30 am)							
After Lunch							
Driving home							
Driving home							
After Dinner							
Last one before bed							

APPENDIX 11: EXAMPLE COMPLETED WEEK 1 SFP REDUCTION SCHEDULE

Participant Name: Sarah Brown Participant number: 00200

	Today Wed day	Day 1 Thurs day	Day 2 Fri day	Day 3 Sat day	Day 4 Sun day	Day 5 Mon day	Day 6 Tues day	Day 7 Wed day
0.00								
0.30								
1.00								
1.30								
2.00								
2.30								
3.00								
3.30								
4.00								
4.30								
5.00								
5.30								
6.00								
6.30								
7.00								
7.30								
8.00								
8.30								
9.00								
9.30								
10.00								
10.30								
11.00								
11.30								
12.00								
12.30								
13.00								
13.30								
14.00								
14.30								
15.00								
15.30								
16.00								
16.30								
17.00								
17.30								
18.00								
18.30								
19.00								
19.30								
20.00								
20.30								
21.00								
21.30								
22.00								
22.30								
23.00								
23.30								
No. of sfp	20	18	17	15	13	12	11	10

APPENDIX 12: EXAMPLE DAY OF RRT REDUCTION ARM PRE-QUIT/QUIT DAY DIARY

Rapid Reduction Study

Rapid Reduction Group

(Weeks -2, -1, 0 and Extra Visits)

Diary

Participant ID: _____

Week commencing: _____

Type of extra NRT (fill in the circle which corresponds to the extra NRT you are using)			
	2mg	4mg	Other
Lozenge	O	O	
Gum	O	O	
Microtab	O		
Inhalator			O
Nasal Spray			O

UNIVERSITY OF BIRMINGHAM

British Heart Foundation

Rapid Reduction Study: Participant Diary

How to use this diary

This diary is for you to keep a daily record of your NRT use and your smoking, during the time between your weekly clinic sessions. We suggest that you keep the diary close to your supply of NRT.

In the morning

Every morning we would like you to:

1. Write down the number of gums/lozenges/microtabs/cartridges in the box in the space provided. If you are using a nasal spray you do not need to do this however you may wish to keep a tally of the number of sprays you use throughout the day in the space provided.

In the evening

At the end of every day, there are two things that we would like you to do:

1. Write down the number of gums/lozenges/microtabs/cartridges in the box. Not necessary for nasal spray.
2. Write how many gums/lozenges/microtabs/cartridges/sprays of the nasal spray you have used during that day. This number should equal the number of NRT in the morning – the number in the evening.

For example, if you had 10 gums in the box in the morning and there are 4 in the box in the evening, you should have used 6 gums:

$$10 - 4 = 6.$$

We then ask you:

- whether you have used a nicotine patch today,
- whether you have smoked any cigarettes during the day. If you have, please write down how many you smoked,
- and the answer to 2 questions about your cravings for cigarettes during the day

Finally, there is space for you to write any other comments about NRT or how you are feeling about your quit attempt. Do use additional paper if you want to. There is contact information at the back of this diary if you have any problems or concerns about using your NRT.

Day 1. Date:_____

We would like to know :

1) Either:

The number of gums/lozenges/microtabs/inhalator cartridges in box first thing in the morning ☐

The number of gums/lozenges/microtabs/inhalator cartridges in box at the end of the day

Number of gums/lozenges/microtabs/inhalator cartridges used today ☐

(number of NRT in box in the morning – number of NRT in the box at the end of the day)

Or

The number of sprays (from nasal spray) used today. You can use the space below to keep a tally of these throughout the day if it helps ☐

2. **Have you used a nicotine patch today? (please circle)** YES NO

3. **How many hours did you wear the patch for?** ☐

4. **Have you smoked any cigarettes today? (please circle)** YES NO

5. **If YES, how many?:** Manufactured ☐ Roll-ups ☐

6. **How much of the time have you felt the urge to smoke in the past 24 hours? *(Circle one number below)***

Not at all	A little of the time	Some of the time	A lot of the time	Almost all the time	All the time
0	1	2	3	4	5

7. **How strong have the urges to smoke been *(Circle one number below)***

No urges	Slight	Moderate	Strong	Very strong	Extremely strong
0	1	2	3	4	5

8. **If you have any comments please write them here:**

Contact for further information

If you have any problems or concerns about using your NRT, you can contact:

Monday – Friday, 9 am – 5 pm:

Mike Healy

Tel: 0774 776 3729

E-mail: m.healy@bham.ac.uk

Everyday, 7 am - 11 pm

The NHS Smoking Helpline

Tel: 0800 022 4 332

At all other times:

NHS Direct on 0845 46 47

APPENDIX 13: RRT SEMI-STRUCTURED INTERVIEW SCHEDULE

- Which quit method did you use?
- **(Reduction only)** Did you choose method? If so why?
- **(Hierarchical reduction only)** Why did you choose to eliminate the easier/harder cigarettes first as opposed to the harder/easier ones?
- What were your first impressions of the quit method?
- How easy did you find the instructions to understand and follow? Why?
- How easy was the method to carry out?
- **(Smoke-free periods only)** Did you end up reducing your cigarettes per day as well as smoking periods over the two week reduction?
- Were there any times when it was easier or harder?
- **(Hierarchical (easy) reduction only)** Considering that you eliminated the hardest cigarettes last do you think this made reduction harder as you went on?
- **(Hierarchical (difficult) reduction only)** Considering that you eliminated the hardest cigarettes first do you think this made reduction easier toward the end of the reduction period?
- Did you manage to stick to the pre-quit instructions? Why?
- Were there any good points to the method?
- Were there any problems or bad points with the method?
- Did it fit in with your lifestyle? Why was that?
- Would you make any changes to the method?
- What did you think to the materials that you used (schedules/diaries)?
- What are your feelings about the nurse support that you received?
- What did you think to how the nicotine replacement therapy was used as part of the method?
- Were there any personal strategies or techniques that you used to help you along?

- How did you feel when you reached your quit day?
- Did your feelings about quitting change at all in the 2 weeks between your first appointment and your quit day?
- Are you pleased with method you used or not?
- Why do you think it worked or didn't work for you?
- How do you think people quit smoking? With this in mind do you think this method could help people to quit?
- When people have made their minds up and try to quit smoking, are there things that they do that can reduce their chances of making it successfully? With this in mind do you think this method could prevent people from quitting?
- Would you choose this method if you quit again?
- Would you recommend this method to someone else?
- Had you attempted to quit before this study? If so which method of quitting did you use? How did that method compare to the method you used this time?
- Before the study if you had been given the choice how would you have quit?
- Following the study how would you choose to quit? Why?
- Has your opinion changed pre to post study? Why?
- **(If still smoking)** Has the trial changed your smoking behaviour at all or are you smoking the same as before the trial?
- Any other comments?

APPENDIX 14: PARTICIPANT NOTES SHEET FOR THE RRT INTERVIEW STUDY

Interview Notes

Thank you for agreeing to take part in a telephone interview about the method of quitting you used during the Rapid Reduction Trial. You will be contacted by a researcher roughly 5 weeks after your quit day. They will ask you about your experiences of quitting and for your opinions about the method of quitting you used. The following is a list of some of the questions you may be asked. Please look through these regularly during your quit attempt and feel free to make notes as you go along, in as much detail as possible. When you are interviewed you will be able to use these notes to jog your memory.

When preparing to stop smoking, were you asked to smoke as normal for two weeks, or to reduce the amount you smoked before quitting?
If you were <u>reducing</u>, how did you reduce? Increasing the amount of time between cigarettes, cutting out either your favourite cigarettes or your habitual cigarettes one at a time or having periods of time when you weren't allowed to smoke which were increased over the two week period? Did you choose this method yourself? If so, why?
What were your first impressions of the way you were asked to quit?
Did you find the method easy to follow? Why?
Was the method easy to carry out?
What were the good points?

Were there any problems or bad points?
Did you manage to stick to the pre-quit instructions? Why?
Did it fit in with your lifestyle?
Would you make any changes to the method?
Are you pleased with the method?
Why do you think it worked/didn't work for you?
How do you think people quit smoking? With this in mind do you think this method could help people to quit?
What can prevent people from quitting? With this in mind do you think this method could prevent people from quitting?

Would you choose this method if you quit again?
Would you recommend this method to someone else?
Had you attempted to quit before this study? If so which method of quitting did you use? How did that method compare to the method you used this time?
Before the study if you had been given the choice how would you have quit?
Following the study how would you choose to quit?
Has your opinion changed pre to post study?
Any other comments?

APPENDIX 15: RRT ADVERSE EVENT REPORTING

Definitions

Adverse event

An adverse event (AE) is any untoward medical occurrence in a clinical investigation subject administered a product or medical device; the event need not necessarily have a causal relationship with the treatment or usage. Examples of AEs include but are not limited to:

- abnormal test findings,
- clinically significant symptoms and signs,
- changes in physical examination findings,
- hypersensitivity, and
- progression/worsening of underlying disease.

Additionally, they may include the signs or symptoms resulting from:

- drug overdose,
- drug withdrawal,
- drug abuse,
- drug misuse,
- drug interactions,
- drug dependency,
- exposure in utero.

Failure of expected pharmacological action or therapeutic benefit alone (i.e. lack of efficacy) is not necessarily an AE.

Definition of serious adverse event (SAE)

A serious adverse event or serious adverse drug reaction is any untoward medical occurrence at any dose that: results in death, is life-threatening (immediate risk of death), requires inpatient hospitalisation or prolongation of existing hospitalisation, results in persistent or significant disability/incapacity, and/or results in congenital anomaly/birth defect. An important medical event may not be immediately life-threatening and/or result in death or hospitalisation. However, if it is determined that the event may jeopardise the subject and may require intervention to prevent one of the other outcomes listed in the definition above, the important medical event should be reported as serious. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse.

Definition of adverse reaction (AR)

Means any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

Definition of suspected serious adverse reaction (SSAR)

Means an adverse reaction that is classed as serious and which is consistent with the information about the medicinal product in question set out

a) in the case of a licensed product, in the summary of product characteristics (SmPC) for that product, or

b) in the case of any other investigational medicinal product, in the Investigator's Brochure (IB) relating to the trial in question

Definition of suspected unexpected serious adverse reaction (SUSAR)

Means an adverse reaction that is classed as serious and which is not consistent with the information about the medicinal product in question set out

a) in the case of a licensed product, in the summary of product characteristics (SmPC) for that product

b) in the case of any other investigational medicinal product, in the Investigator's Brochure relating to the trial in question

Monitoring and reporting adverse events

All observed or volunteered adverse events regardless of treatment group or suspected causal relationship to any of the nicotine replacement therapies will be reported as described in the following sections. For all adverse events, the investigator will pursue and obtain information adequate both to determine the outcome of the adverse event and to assess whether it meets the criteria for classification as a serious adverse event requiring immediate notification to the sponsor, the UK National Health Service (NHS) Research and Development (R&D) office, and the Research Ethics Committee (REC). The investigator will assess causality. For adverse events follow-up by the investigator is required until the event or its sequela resolve or stabilise.

Severity Assessment

If required on the adverse event case report forms, the investigator will use the adjectives mild, moderate, or severe to describe the maximum intensity of the adverse event. For purposes of consistency, these intensity grades are defined as follows:

- Mild- Does not interfere with subject's usual function.
- Moderate- Interferes to some extent with subject's usual function.

- Severe- Interferes significantly with subject's usual function.

Note the distinction between the severity and the seriousness of an adverse event. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with subject's usual function) but would not be classified as serious unless it met one of the criteria for serious adverse events, listed above.

Causality Assessment

The investigator's assessment of causality must be provided for all adverse events (serious and non-serious). An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the investigational product caused or contributed to an adverse event. If the investigator's final determination of causality is unknown and the investigator does not know whether or not investigational product caused the event, then the event will be handled as "related to investigational product" for reporting purposes. If the investigator's causality assessment is "unknown but not related to investigational product", this should be clearly documented on trial records. In addition, if the investigator determines a serious adverse event is associated with trial procedures, the investigator must record this causal relationship, as appropriate, and report such an assessment in accordance with the serious adverse event reporting requirements, if applicable.

Exposure In Utero

The license for nicotine replacement therapy (NRT) does not exclude use in pregnancy and the National Institute for Health and Clinical Excellence (NICE) guidelines allow such use. We will exclude pregnant or breast feeding women because the dose and format of NRT advised for pregnant women is different from that used in our protocol. Consequently, we will adjust the dose of NRT should a woman become pregnant during treatment.

The CI/PI's responsibilities and processes for evaluating AEs

Each AE will be evaluated for seriousness, causality, expectedness and severity. The responsibility for this will lie with Dr Paul Aveyard, the Principle Investigator (PI), and then reported to the Sponsor. The study team will be taught and have access to documents explaining how to assess AEs and SAEs and decide whether any event requires further expedited reporting by the Sponsor.

The CI/PI's responsibilities, definitions and criteria for the evaluation of SAEs

If the AE is assessed as serious Dr Aveyard will report the event to the sponsor immediately or within 24 hours of being made aware of the event. An initial verbal report can be made but will be followed promptly with a detailed written report on the trial SAE form.

Evaluation of AEs for Causality

- Not Related. Onset of the event as relative to administration of the product is not reasonable; or, another cause itself can explain the occurrence of the event
- Unlikely to be related. Onset of the event as relative to administration of the product is possible but another cause itself can explain the occurrence of the event, or there are no reasonable grounds for suspecting that the product could have caused the event.
- Possibly related. Onset of the event as relative to administration of the product is reasonable; however the event could have been due to another, equally likely, cause
- Probably related. Onset of the event as relative to administration of the product is reasonable and is more likely explained by the drug than by any other cause.
- Definitely related. Onset of the event as relative to administration of the product is reasonable and there is no other cause to explain the event; or a re-challenge (if feasible) is positive.

Recording of AEs

Dr Aveyard will record all AEs on to the appropriate Trial Recording Form and copies filed in the subject's notes.

Sponsor's responsibilities for AE recording and reporting

The sponsor will obtain all AE records and perform an evaluation with respect to seriousness, causality and expectedness. Expedited reporting will be required where the AE has a possible causal relationship to the trial intervention, and/or is unexpected.

What the Sponsor will do following receipt of SAE report from Chief Investigator/Principal Investigator

On receipt of each and every SAE form the sponsor will provide an evaluation of 'expectedness'. All SAEs related to the medication that are both unexpected and serious, are subjected to expedited reporting. Other safety issues also qualify for expedited reporting, where they might alter the current risk-benefit assessment of the investigational medicinal product (IMP); or where the issue may be sufficient to consider changes in the IMP administration or overall conduct of the trial, i.e. new events that relate to the conduct of the trial or the development of the IMP likely to affect the safety of subjects ie: lack of efficacy of an IMP in the treatment of a life threatening disease, single case reporting of an expected SAE, but with an unexpected outcome, an increase in the rate of occurrence, or severity of an expected SAE, judged to be clinically important post study SUSARs that occur after the subject has completed a trial.

Timeframes in which the Sponsor will submit expedited reports to the Research Ethics Committee (REC) and to the Medicines and Healthcare Products Regulatory Agency (MHRA)

Fatal/life threatening SUSARs

The sponsor will inform the REC of the above as soon as possible, but no later than 7 calendar days after he has first knowledge of the minimum criteria for expedited reporting.

Non-fatal and non-life threatening SUSARs

The sponsor will report all other SUSARs and safety issues to the REC as soon as possible but no later than 15 calendar days after he has first knowledge of the minimum criteria for expedited reporting.

Reporting other safety issues

A letter entitled Safety Report will be sent to the REC where other safety issues also qualify for expedited reporting by the sponsor. The first page will contain the EudraCT number, title of the trial and the trial protocol code number.

The Co-ordinator of the main REC will acknowledge receipt of safety reports within 30 days.

APPENDIX 16: COCHRANE REVIEW SEARCH STRATEGIES

a) MEDLINE search strategy

1. cold turkey.mp [mp=title, abstract, heading word, table of contents, key concepts]

2. (schedul* adj3 smok*).mp

3. (cut* down or cut-down).mp

4. (({Gradual* or abrupt*}) adj3 (reduction or reduce* or quit* or stop* or abstin* or abstain* or cessat*)).mp

5. fading.mp

6. taper*.mp

7. controlled smoking.mp

8. 1 or 2 or 3 or 4 or 5 or 6 or 7

9. RANDOMIZED-CONTROLLED-TRIAL.pt

10. CONTROLLED-CLINICAL-TRIAL.pt

11. CLINICAL-TRIAL.pt

12. Meta analysis.pt

13. exp Clinical Trial/

14. Random-Allocation/

15. randomized-controlled trials/

16. double-blind-method/

17. single-blind-method/

18. placebos/

19. Research-Design/

20. ((clin$ adj5 trial$) or placebo$ or random$).ti,ab.

21. ((singl$ or doubl$ or trebl$ or tripl$) adj5 (blind$ or mask$)).ti,ab.

22. (volunteer$ or prospectiv$).ti,ab.

23. exp Follow-Up-Studies/

24. exp Retrospective-Studies/

25. exp Prospective-Studies/

26. exp Evaluation-Studies/ or Program-Evaluation.mp.

27. exp Cross-Sectional-Studies/

28. exp Behavior-therapy/

29. exp Health-Promotion/

30. exp Community-Health-Services/

31. exp Health-Education/

32. exp Health-Behavior/

33. 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 or 22 or 23 or 24

or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32

34. smoking cessation.mp. or exp Smoking Cessation/

35. “Tobacco-Use-Cessation”/

36. “Tobacco-Use-Disorder”/

37. Tobacco-Smokeless/

38. exp Tobacco-Smoke-Pollution/

39. exp Tobacco-/

40. exp Nicotine-/

41. ((quit$ or stop$ or ceas$ or giv$) adj5 smoking).ti,ab.

42. exp Smoking/pc, th

43. 34 or 35 or 36 or 37 or 38 or 39 or 40 or 41 or 42

44. 9 or 10 or 11 45. 33 and 43

46. (animals not humans).sh.

47. (44 or REVIEW.pt.) and 43

48. 47 not 46

49. 45 not 47

50. 45 not 47 not 46

51. exp Smoking/

52. 33 and 51

53. 52 not 45

54. 53 and 44

55. (53 and 44) not 46

56. 53 not 54

57. 53 not 54 not 46

58. 57

59. 55

60. 50

61. 48

62. 59 or 61

63. 8 and 62

64. 60 or 58

65. 8 and 64

66. 63 or 65

b) PsycINFO search strategy

1. cold turkey.mp

2. (schedul* adj3 smok*).mp

3. (cut* down or cut-down).mp

4. (({Gradual* or abrupt*}) adj3 (reduction or reduce* or quit* or stop* or abstin* or abstain* or cessat*)).mp

5. fading.mp

6. taper*.mp

7. controlled smoking.mp

8. smoking cessation.mp. or exp Smoking Cessation/

9. (antismoking or anti-smoking).mp.

10. (quit$ or cessat$).mp

11. (abstin$ or abstain$).mp

12. (control adj smok$).mp

13. exp behavior modification/

14. 9 or 10 or 11 or 12 or 13

15. tobacco-smoking/

16. (smok$ or cigar$ or tobacco$).mp.

17. Prevention/

18. 15 or 16

19. 14 and 18

20. 17 and 18

21. 8 or 19 or 20

22. 6 or 4 or 1 or 3 or 7 or 2 or 5

23. 22 and 21

c) EMBASE search strategy

1. cold turkey.mp

2. (schedul* adj3 smok*).mp

3. (cut* down or cut-down).mp

4. (({Gradual* or abrupt*}) adj3 (reduction or reduce* or quit* or stop* or abstin* or abstain* or cessat*))

5. fading.mp

6. taper*.mp

7. controlled smoking.mp

8. 1 or 2 or 3 or 4 or 5 or 6 or 7

9. random$.ti,ab

10. factorial$.ti,ab

11. (cross over$ or crossover$ or cross-over$).ti,ab

12. placebo$.ti,ab

13. (double$ adj blind$).ti,ab

14. (single$ adj blind$).ti,ab

15. assign$.ti,ab

16. allocat$.ti,ab

17. volunteer$.ti,ab

18. CROSSOVER PROCEDURE.sh

19. DOUBLE-BLIND PROCEDURE.sh

20. RANDOMIZED CONTROLLED TRIAL.sh

21. SINGLE-BLIND PROCEDURE.sh

22. or/9-21

23. smoking cessation.mp

24. exp smoking cessation/

25. exp smoking-/

26. ((quit$ or stop$ or ceas$ or giv$ or prevent$) adj smok$).mp

27. exp passive smoking/

28. exp smoking habit/

29. exp cigarette smoking/

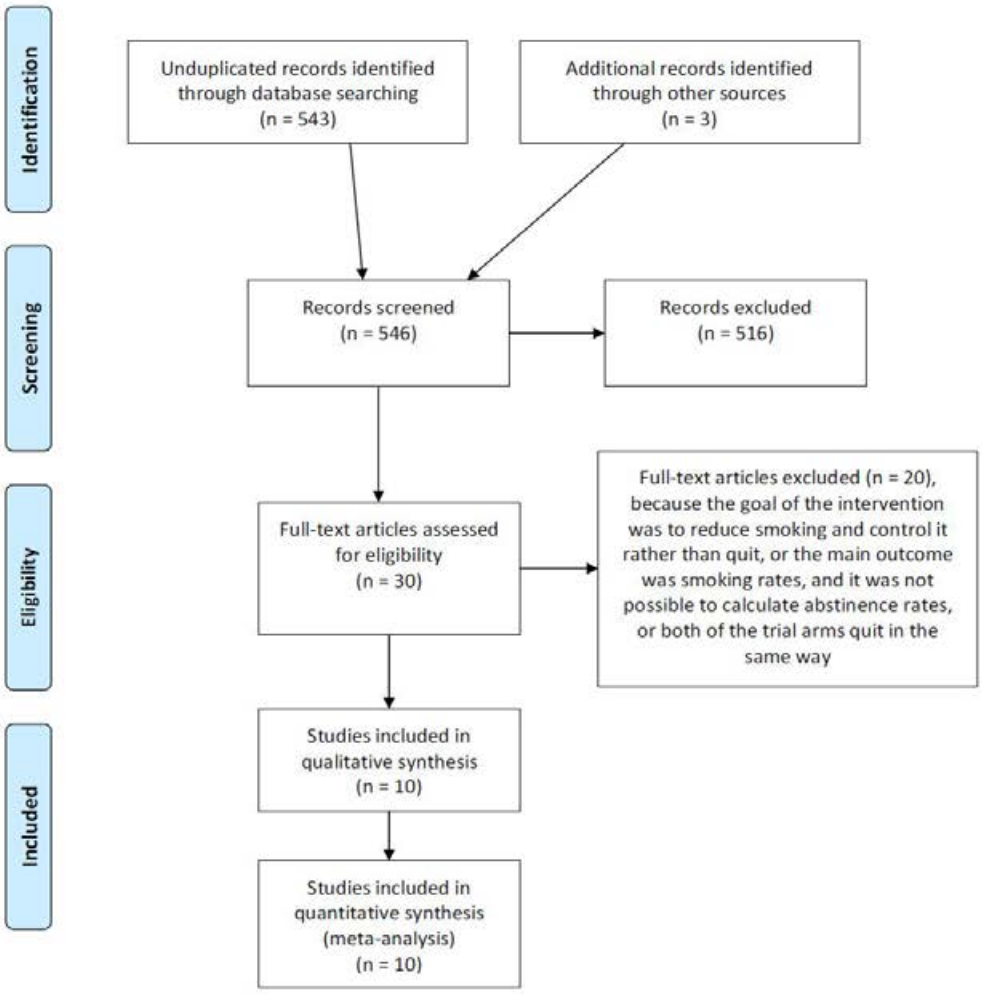
30. or/23-29

31. 22 and 30

32. 8 and 31

APPENDIX 17: COCHRANE REVIEW FLOW DIAGRAM OF STUDY INCLUSION

Template From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. oi:10.1371/journal.pmed1000097



APPENDIX 18: COCHRANE REVIEW CHARACTERISTICS OF INCLUDED STUDIES TABLES

Cinciripini et al. 1995	
Methods	Country: USA Recruitment: Participants recruited from the community, method not stated.
Participants	128 smokers randomised to 4 groups, with at least 3 years smoking history, consumption of 15+ cigarettes per day (CPD), no current cessation treatment, psychiatric disorder or uncontrolled systemic illness. 58% F, av. age 45, av. CPD 24, av. 4 previous quit attempts.
Interventions	1. Scheduled reduced: inter-cigarette interval progressively lengthened, until quit day at week 5. 2. Non-scheduled reduced: CPD reduced using same quota as scheduled group but participants were free to choose when they smoked their cigarettes, until quit day at week 5. 3. Scheduled non-reduced: participants instructed to smoke at regular time intervals but the time intervals were not progressively reduced to quit day at week 5. 4. Non-scheduled, non-reduced: No manipulation of inter-cigarette interval or cigarette frequency, until quit day at week 5. Pharmacotherapy: No pharmacotherapy Type of support: Two-hour weekly group meetings; cognitive behavioural intervention weeks 2-5; relapse prevention weeks 5-9.
Outcomes	Abstinence: Prolonged abstinence (defined as smoking on fewer than 5 days between assessments) at treatment end (week 9) &1, 6 and 12 month post-treatment. (PP at quit week (week 5) also reported). Validation: CO <6ppm at quit week, cotinine <14 mg/ml at treatment end & 1,6 and 12 month follow-up Other outcomes: CPD, coping behaviour, withdrawal score, tension & fatigue mood states, urge frequency, self-efficacy.
Notes	Groups 1 and 2 combined to create reduction group and Groups 3 & 4 combined to create abrupt quitting group.

Risk of bias

ITEM	JUDGEMENT	DESCRIPTION
Adequate sequence generation?	Unclear	Randomised, method not stated.
Allocation concealment?	Unclear	No information given.
Incomplete outcome data addressed? All outcomes	Unclear	Information on attrition/exclusions not given. Those with missing data were counted as non-abstainers.

Cummings et al. 1988	
Methods	Country: USA Recruitment: callers responding to advertisement of stop smoking hotline, who accepted a free stop smoking booklet.
Participants	1895 randomised to 4 experimental groups and 1 control group. 18+ year old current smokers. 65% F, av. age 42, av. CPD 28, av. 3 previous quit attempts.
Interventions	1. Booklet instructing smokers to gradually reduced cigarettes smoked before quitting. Day by day structured guide. 2. Booklet instructing smokers to gradually reduced cigarettes smoked before quitting. No day by day instructions. 3. Booklet instructing smokers to quit abruptly. Day by day guide. 4. Booklet instructing smokers to quit abruptly. No day by day instructions. 5. Control: booklet providing information on the health hazards of smoking and the nature of tobacco addiction, but did not give specific advice on how to stop smoking. Pharmacotherapy: No pharmacotherapy. Type of support: Self-help booklet.
Outcomes	Abstinence: Continuous between 1 month & 6 month follow-up. (1 week PP at 1 & 6 months post-enrolment, 1 month prolonged at 6 months post-enrolment also reported) Validation: surrogate interview conducted with family member or friend. Other outcomes: report of cessation attempt, cigarettes per day, percentage of booklet read, booklet evaluation, actions taken in preparation for quit and after quit, method of quitting.
Notes	Groups 1 and 2 combined to create reduction group and Groups 3 & 4 combined to create abrupt quitting group. Surrogate interview validation data not used as there were problems with allocation of a surrogate - 20% of the quit participants refused to provide a surrogate, and participants were less likely to give a surrogate if they lived alone.

Risk of bias

ITEM	JUDGEMENT	DESCRIPTION
Adequate sequence generation?	Yes	"randomization was done from a pre-randomized list so subjects were randomized as they called into the study and were defined as eligible" (email communication).
Allocation concealment?	Yes	Self-help intervention involving minimal contact with investigators/enrolling clinicians, risk of bias assessed as low.
Incomplete outcome data addressed? All outcomes	Unclear	19.1% of total randomised lost to follow-up, reported not to vary by arm. 18 additional participants missing from report results table, these participants are included in the current analyses and treated as non abstainers, however their allocation to treatment arms is unknown.

Curry et al. 1988		
Methods	Country: USA Recruitment: from the community via radio announcements and newspaper adverts offering stop smoking program.	
Participants	139 cigarette smokers randomised to 4 experimental groups. 51% F, av. age 40.6, av. CPD 28, av. 3.7 previous quit attempts.	
Interventions	1. Reduction (Absolute abstinence)-group based: cigarette tapering and nicotine fading before quit day in week 5. Groups met once a week for two hours, for 8 weeks. 2. Reduction (Absolute abstinence)-self-help: cigarette tapering and nicotine fading before quit day in week 5. Provided with work books with written exercises. 3. Abrupt (Relapse prevention)-group based: quit abruptly at week 3. Groups met once a week for two hours, for 8 weeks. 4. Abrupt (Relapse prevention)-self-help: quit abruptly at week 3. Provided with work books with written exercises. Pharmacotherapy: No pharmacotherapy Type of support: Self-help booklet and group behavioural support.	
Outcomes	Abstinence: Prolonged abstinence from at least month 9 to month 12 at 12 month follow-up (PP at EOT and 3 months post treatment also reported) Validation: saliva thiocyanate test during final week of treatment and at 12 month follow-up. Other outcomes: time to relapse, number of quit attempts, returns to abstinence after lapse.	
Notes	Groups 1 and 2 combined to create reduction group and Groups 3 & 4 combined to create abrupt quitting group for the main analysis. For sub-group analysis this study was split back into 4 groups to look at self-help and behavioural support interventions separately.	
Risk of bias		
ITEM	**JUDGEMENT**	**DESCRIPTION**
Adequate sequence generation?	Yes	"Participants were stratified by availability for day or evening group meetings. Within each stratum a total of 24 participants were picked randomly and were grouped into pairs of 12. A coin toss determined assignment to the RP or AA program."
Allocation concealment?	Unclear	No information given.
Incomplete outcome data addressed? All outcomes	Yes	Significantly more participants assigned to self-help treatment withdrew (64% versus 36% in group condition) before treatment began suggesting assignment to self-help was the overriding contributor to attrition. It is reported that there was no difference in participation rates between the reduction and abrupt quit groups.

Etter et al. 2009	
Methods	Country: Switzerland Recruitment: from the community through advertisements on a smoking cessation web site (http://www.stop-tabac.ch), via newspaper advertisements, and by physicians in private practice
Participants	314 participants randomised to 2 groups, smoking at least 15+ CPD, aged 18+, with a commitment to quit smoking on a target date in the next two months, and to use 10+ pieces of nicotine gum per day. 41.3% F, av. age 43.1, av. CPD 23.7, 42.4% had made a 24hr quit attempt in the past 12 months.
Interventions	Interventions 1. Pre-cessation treatment group: received recommendation to decrease cigarette consumption by half before quitting roughly 2 months after baseline, whilst using nicotine gum. 2. Usual care: received instruction to quit abruptly on a target quit date, roughly 2 months after baseline. Pharmacotherapy: Unflavoured 4 mg nicotine gum. 4 weeks pre-quit in pre-cessation arm and 8 weeks post-quit in pre-cessation and usual care arm. Type of support: Self-help- booklet in the mail and a smoking cessation web site.
Outcomes	Abstinence: 7 day, 4 week, 6 month, and 12 month prolonged abstinence at 12 months post-quit (PP at 3 days post-quit, 7 day , 4 week, 2 month prolonged abstinence at 8 weeks post-quit (EOT) also reported) Validation: CO and saliva cotinine at 12 month follow-up. Other outcomes: self-efficacy, preference for study group, method of quit, gum use, CPD in pre-quit week, cravings, dependence, attitudes toward smoking, appetite, hunger, withdrawal, anxiety and depression, weight gain.
Notes	N/A

Risk of bias

ITEM	JUDGEMENT	DESCRIPTION
Adequate sequence generation?	Yes	"Randomization was based on a list of random numbers generated by a computer."
Allocation concealment?	Yes	Self-help intervention involving minimal contact with investigators/enrolling clinicians, risk of bias assessed as low.
Incomplete outcome data addressed? All outcomes	Yes	Participation rates were similar in both arms at all time points: 11% of reduction group and 12.5% of abrupt group lost to follow-up at 12 months.

Flaxman 1978	
Methods	Country: USA Recruitment: by means of public service announcements of a smoking cessation clinic on television, radio and in local newspapers
Participants	64 cigarette smokers randomised to 4 groups. 50% F, av. age not reported, av. CPD 26, 42.4% av. 3 previous quit attempts.
Interventions	1. Gradual reduction: stimulus hierarchy technique- situations leading to smoking were categorised and rank ordered according to anticipated difficulty of not smoking in each. Participants were instructed to give up in the easiest situation first, progressing to the hardest. Adding one situation every three days. 2. Partially gradual reduction: Same as gradual reduction, however participants quit abruptly when their smoking rates dropped to half of baseline. 3. Target date: a date approximately 2 weeks from the first session was selected for abrupt quitting. 4. Immediate quit: participants were scheduled to quit smoking the next day. Pharmacotherapy: No pharmacotherapy. Type of support: Behavioural. Participants met with experimenters twice a week for 0.5 hour sessions pre-quit and were presented with self-control techniques.
Outcomes	Abstinence: measured at 1 week and 6 months post-treatment. No further definition of abstinence given. Validation: No information given. Other outcomes: mean daily post-treatment smoking rates (weeks1-8 and 6 months), percentage of baseline smoked.
Notes	Groups 1 and 2 combined to create reduction group and Group 3 abrupt quitting group. Group 4 data was not used as this group received a lot less behavioural support than the other groups. Participants in each group were also split into one of two phase 2 post-quit interventions, however there was no difference between these two conditions at 6 month follow-up so this is not taken into account.

Risk of bias

ITEM	JUDGEMENT	DESCRIPTION
Adequate sequence generation?	Unclear	Randomised; "Sixty-four subjects were blocked by sex and number of cigarettes smoked per day and randomly assigned to one of the eight treatment cells and to two of the six experimenters", precise method not described.
Allocation concealment?	Unclear	No information given.
Incomplete outcome data addressed? All outcomes	Unclear	No information given.

Gunther et al. 1992	
Methods	Country: Austria Recruitment: patients consulting a hospital based smokers' counselling service between February and December 1988.
Participants	110 participants randomised to 2 groups, examined by a psychiatrist to determine tobacco dependence, value of 6+ on Fagerstrom tolerance questionnaire. Av. CPD 26.4.
Interventions	1. Gradual stopping: From the second hour of counselling the number of cigarettes was reduced, depending on initial consumption the number of cigarettes was reduced by 5-10 cigarettes per week. 2. Sudden stopping: a quit date was set on which participants quit abruptly. Pharmacotherapy: No pharmacotherapy. Type of support: Behavioural - Total of 12 hours of counselling (1 hour per week).
Outcomes	Abstinence: 1 year prolonged (relapse during the 1 year follow-up period= resumption of nicotine use for more than 3 days at follow-up date). Validation: No validation at 1 year follow-up. Other outcomes: response rates, number of CPD at 1 year follow-up, relapse.
Notes	N/A

Risk of bias

ITEM	JUDGEMENT	DESCRIPTION
Adequate sequence generation?	Yes	"computer generated randomized list".
Allocation concealment?	Unclear	No information given.
Incomplete outcome data addressed? All outcomes	Yes	Only the participants initially abstinent were followed to one year (76% sudden, 73% gradual). Of these, loss to follow-up was 36%in the sudden stopping group and 22% in the gradual stopping group (non-statistically significant difference).

Hughes et al. 2010	
Methods	Country: USA Recruitment: respondents to local newspaper and radio advertisements.
Participants	746 daily smokers randomised to 3 groups, smoking at least 15+CPD, with no increase or decrease in CPD by 20%+ in last month. 54% F, av.age 48, av. CPD 23.
Interventions	1. Gradual: participants could choose from three reduction methods to reduce smoking by 25% week 1, 50% week 2, 75% week 3, quit week 4 2. Abrupt: participants advised not to change their CPD prior to set quit day. 3. Brief Advice: praised on decision to quit, not advised how to do so. Pharmacotherapy: NRT (lozenges) used pre-quit in gradual group, participants were advised to substitute one lozenge for each cigarette missed. All participants used lozenges post-quit contingent upon abstinence. Type of support: Behavioural - over the telephone. Both gradual and abrupt groups received 5 calls (90 minutes).
Outcomes	Abstinence: prolonged abstinence from 2 weeks-6 months follow-up (7-day PP at 6 m also reported). Validation: CO at 6 month follow-up. Other outcomes: quit attempts, self-efficacy, severity of dependence, stereotypy, craving, motivation to quit.
Notes	Only the data from the gradual and abrupt groups are of interest to this review as participants in the brief advice group were not advised to quit in any particular way.

Risk of bias

ITEM	**JUDGEMENT**	**DESCRIPTION**
Adequate sequence generation?	Yes	"..our statistician generated a concealed allocation sequence and randomized the participant to the gradual, abrupt or brief advice conditions in a 2:2:1 ratio using blocked randomization (stratified by city and counsellor) based on the SAS procedure PLAN (Cary, NC: SAS Institute, Inc) "
Allocation concealment?	Yes	"..our statistician generated a concealed allocation sequence.."
Incomplete outcome data addressed? All outcomes	Yes	The incidence of adverse events was similar and small across conditions (3% gradual, 5%abrupt, 3%brief intervention), and incidence of discontinuation was lower than 1% in total. Drop-out rates were also similar across groups; loss to follow-up was 20.7% in the abrupt group and 23.6%in the gradual group at 6 months.

Jerome, Behar et al. 1999	
Methods	Country: USA Recruitment: work-sites recruited smokers who wanted to quit to a free work-site self-help smoking cessation program. Recruitment was via posted advertisements and internal memos to employees.
Participants	1025 adult smokers from 61 work-sites randomised to 3 groups. 61.8% F, av. age 37.5, av. CPD 24.
Interventions	1. Computerised, scheduled, gradual reduction (with LifeSign program): Handheld computer used to increase the inter-cigarette interval until quit and record smoking. General advice on coping with urges and maintaining abstinence provided by a manual. 2. American Lung Association (ALA) quit smoking manual provided to participants: 'Freedom From Smoking For You and Your Family'. Includes standard behavioural techniques but not cutting down before quit. 3. General wellness information: printed material provided emphasising the importance of a general program of physical health that included quitting smoking , exercise and sound nutrition. No specific quitting techniques provided. Pharmacotherapy: No pharmacotherapy. Type of support: Self-help materials.
Outcomes	Abstinence: 7-day PP at 12 month follow-up (from treatment initiation) (PP at EOT, & 6 m also reported) Validation: CO at all follow-ups. Other outcomes: program use, ease of use, effectiveness of program.
Notes	Only the data from the gradual reduction and ALA groups are of interest to this review as participants in the general wellness group were not advised to quit in any particular way.

Risk of bias

ITEM	JUDGEMENT	DESCRIPTION
Adequate sequence generation?	Unclear	Cluster randomised: "Work-sites were randomly assigned to one of three treatment conditions," precise method not described.
Allocation concealment?	Yes	Self-help intervention involving minimal contact with investigators/enrolling clinicians, risk of bias assessed as low.
Incomplete outcome data addressed? All outcomes	Yes	Loss to follow-up was comparable in the two arms of interest:13% gradual reduction, 17% ALA at 12 months. Analysis undertaken as intention to treat.

Riley et al. 2005	
Methods	Country: USA Recruitment: Respondents to local television spots who were then screened by phone to determine eligibility.
Participants	423 daily cigarette smokers randomised to 2 groups. Had been smoking for at least 1 year, aged between 18 and 67, smoking 10+ CPD, and not using any other type of tobacco. 44% F, av. age 43.4.
Interventions	1. LifeSign- Nicotine nasal spray (NNS): provided with handheld computer which decreased the use of cigarettes and increased the use of nicotine nasal spray over 10 days. Ps were then expected to quit smoking and use the nasal spray only. After 3 weeks of NNS use the program decreased usage. 2. Nicotine nasal spray only: participants instructed to set a quit date , quit smoking and begin using NNS as instructed on packet. Pharmacotherapy: Nicotine nasal spray was used pre and post quit in LifeSign- NNS arm and only post quit in the NNS only arm. Type of support: Self-help- minimal contact with little/no behavioural support.
Outcomes	Abstinence: 7 day PP at 12 month follow-up (PP at 5 weeks (mid-treatment), 10 weeks (EOT) & 6 m also reported) Validation: CO ≤8 ppm at 10 weeks (EOT), 6 & 12 month follow-ups. Other outcomes: CPD, nasal spray use, reasons for ceasing nasal spray use.
Notes	N/A

Risk of bias

ITEM	JUDGEMENT	DESCRIPTION
Adequate sequence generation?	Unclear	Randomised, method not described.
Allocation concealment?	Yes	Self-help intervention involving minimal contact with investigators/enrolling clinicians, risk of bias assessed as low.
Incomplete outcome data addressed? All outcomes	Unclear	Loss to follow-up was 43% at 6 months, and 57% at 12 months. This data wasn't split by groups so no comparison of loss to follow-up between groups could be carried out. Analysis was carried out as intention to treat.

Roales-Nieto & Fernández Parra 1992	
Methods	Country: Spain Recruitment: students voluntarily responded in answer to announcements made in diverse academic centres of the university and through people who upon learning of the study suggested participation to relatives or friends.
Participants	23 participants took part and chose the goal of abstinence or reduction (controlled smoking), within each goal these participants were then randomised. 14 participants chose abstinence as their goal, and were randomised into 2 groups. Had been smoking for at least 5 years, and smoking 15+ CPD.
Interventions	1. Reduction (with goal of abstinence): received instructions to reduce cigarette consumption over 4 weeks (25% week 1, 50% week 2, 75% week 3, abstinence week 4) 2. Abrupt quitting (with goal of abstinence): received instructions to stop smoking completely on the first day of treatment 3. Reduction (with goal of controlled smoking): participants set reduction goal and received instructions to reduce their consumption to this goal. 4. Abrupt quitting (with goal of controlled smoking): participants set reduction goal and were asked to abruptly drop to this goal consumption Pharmacotherapy: No pharmacotherapy. Type of support: Behavioural.
Outcomes	1 week PP at 1 year follow-up (also reported at EOT, 3 month, 6 month, 9 month and 12 month follow-up). Validation: for some participants a verifier they didn't know about was also asked to report CPD. Participant and verifier ratings corresponded in all cases. Other outcomes: Smoking rates at baseline and follow-ups, treatment compliance.
Notes	Only groups 1 and 2 are of interest and included in this meta-analysis as we are only interested in interventions with a goal to quit.

Risk of bias

ITEM	JUDGEMENT	DESCRIPTION
Adequate sequence generation?	Unclear	Randomised, method not described.
Allocation concealment?	Unclear	No information given.
Incomplete outcome data addressed? All outcomes	Yes	All bar one participant, were followed up for the whole year. Therefore loss to follow- up was 14.3% in the abrupt group and 0% in the reduction group at 12 months. This is a small loss to follow-up, however there were only 14 participants randomised and these were all students at the University where the research took place, and so were potentially easy to follow-up.

CPD - cigarettes per day, EOT - end of treatment, PP - point prevalence abstinence, av. – average, CO – carbon monoxide, ppm – parts per million, F – female, NRT – Nicotine replacement therapy, ALA – American Lung Association, NNS – nicotine nasal spray, mg/ml – milligrams per millilitre.

APPENDIX 19: COCHRANE REVIEW CHARACTERISTICS OF ONGOING STUDIES TABLES

Cinciripini et al. 2006	
Trial name or title	Scheduled smoking with transdermal nicotine.
Methods	Country: USA Recruitment: from the community. Randomisation: method not stated.
Participants	Over 700 daily smokers randomised to 3 groups.
Interventions	1. SSNP: scheduled smoking with concurrent transdermal nicotine replacement. Smoking scheduled using a hand-held computer, which signals smoking at progressively increasing inter-cigarette intervals. 2. SS: scheduled smoking alone plus nicotine replacement therapy post-quit. Smoking scheduled using a hand-held computer, which signals smoking at progressively increasing inter-cigarette intervals. 3. UCC: usual care control, instructed to quit smoking within a few days of study entry and begin using the nicotine patch on their quit day. They are provided with no instructions to reduce and monitor their smoking behaviour using a hand-held computer. Pharmacotherapy: transdermal nicotine patch in all groups. Both pre and post quit in SSNP group and only post-quit in SS and UCC groups. Type of support: Self-help materials
Outcomes	Abstinence: at 4 weeks post quit, long-term quit rates (no further detail known). Validation: Unknown Other outcomes: Unknown
Starting date	01/04/1998
Contact information	Dr Cinciripini, Director Tobacco Treatment Program and Deputy Chair University of Texas MD Anderson Cancer Center Department of Behavioral Science-Unit 1330 PO Box 301439, Houston Texas [pcinciri@mdanderson.org]
Notes	Data analysis is currently being carried out for this study.

Lindson et al. 2009	
Trial name or title	Rapid Reduction Trial (RRT).
Methods	Country: UK Recruitment: General practitioner's practices and NHS Stop Smoking Services write to patients recorded as smokers and offer them treatment. Randomisation: Stata used to accomplish stratified randomisation by therapist with blocking within each stratum. The blocks are randomly ordered blocks of 2, 4, and 6. Each therapist opens sealed numbered envelopes in turn to determine allocation to abrupt cessation or rapid reduction.
Participants	700 participants randomised to two arms. Males and females 18 years+, smoking at least 15 cigarettes or 12.5 grams of loose tobacco daily as roll your own cigarettes, or blows 15 ppm or above on exhaled CO reading, willing to stop smoking completely in two weeks.
Interventions	1. Abrupt cessation arm: participants instructed to smoke as normal for two weeks before quitting abruptly on a designated quit day. 2. Rapid reduction arm: participants instructed to reduce their smoking over two weeks and then quit completely on a designated quit day. Participants choose from one of three reduction methods: 1) Scheduled reduction- the time between cigarettes gradually increased so smoking 50% of baseline end of week 1, and 25% end of week 2. 2) Hierarchical reduction- cigarettes usually smoked identified and eliminated, hardest or easiest first, until smoking 50% of baseline end of week 1, and 25% end of week 2. 3) Smoke-free periods- participants reduce the number of time periods in which they usually smoke by 50% in week 1 and by a further 50% in week 2. Pharmacotherapy: nicotine patches used in both arms pre- and post-quit. Acute NRT (type chosen by participant) used pre- and post-quit in reduction arm and post-quit only in the abrupt arm. Type of support: Behavioural support weekly from 2 weeks pre-quit to 4 weeks post-quit.
Outcomes	Abstinence: PP and prolonged at 4 weeks, 8 weeks and 6 months post quit Validation: Exhaled carbon monoxide Other outcomes: Cotinine levels pre-quit and 1 week post-quit, cigarette reward, urges to smoke, withdrawal, confidence in quitting, smoking stereotypy.
Starting date	01/01/2009
Contact information	Nicola Lindson (nll839@bham.ac.uk), Paul Aveyard (p.n.aveyard@bham.ac.uk) at: Primary Care Clinical Sciences, University of Birmingham, Edgbaston, Birmingham, B15 2TT, UK
Notes	This study is in the participant recruitment and data collection stages and aims to be completed during 2012.

Riley et al. 2001	
Trial name or title	Combining scheduled reduction with nicotine replacement.
Methods	Country: USA Recruitment: through television media advertising. Randomisation: method not stated
Participants	337 smokers desiring to quit randomised to 2 conditions. Aged between 18 and 65, had been smoking over 15 CPD for at least 1 year, no current nicotine product use, no Zyban or other antidepressant use for over 1 month, no medical condition which would preclude the use of the nicotine patch. 44% F, av. age 41, av. CPD 24.4, av. 3.2 previous quit attempts.
Interventions	1. Computerised scheduled gradual reduction + patch: a handheld computer was used to schedule the reduction of smoking rate by increasing the interval between smoking of cigarettes. When smoking rate was down to 10 CPD participants were advised to stop smoking completely and start the use of nicotine patches. 2. Patch only: participants advised to stop smoking abruptly, with no reduction, and then begin using nicotine patch. Pharmacotherapy: nicotine patches were used in both arms post-quit. Type of support: Self-help- minimal contact with little/no behavioural support.
Outcomes	Abstinence: 7 day pp and continuous abstinence at EOT (12 weeks post study entry), unknown at 6 & 12 month follow-up. Validation: CO at EOT, unknown at 6 & 12 month follow-ups. Other outcomes: time to relapse, patch use, satisfaction with patch, computer program use.
Starting date	01/05/1997
Contact information	Dr Riley, NHLBI [William.Riley@nih.gov]
Notes	Data analysis is currently being carried out on 6 & 12 month follow-up data for this study.

SSNP – scheduled smoking with nicotine patch, SS – scheduled smoking, UCC – usual care control, PP – point prevalence abstinence, CPD – cigarettes per day, EOT – end of trial, ppm – parts per million, CO – carbon monoxide.

APPENDIX 20: COCHRANE REVIEW CHARACTERISTICS OF EXCLUDED STUDIES TABLE

Study	**Reason for exclusion**
Bernard & Efran 1972	All study arms reduced- two with a goal of quitting, one with a goal of controlled smoking.
Bolliger 2000- The CEASE trial	Included participants who were all asked to quit in the same way (with nicotine replacement therapy or placebo).
Bolliger 2000- The Rossette study	Included participants who were all asked to reduce with a goal of controlled smoking in the same way (with nicotine replacement therapy or placebo).
Bullen et al. 2010	There was no reduction arm. Both arms were asked to smoke as they wished before quitting.
Cinciripini et al. 1994	The control group was not an abrupt quit intervention. Participants received a complete 'I Quit Kit' (developed by the American Cancer Society), which included a 7-day smoking reduction schedule.
Daughton et al. 1998	All participants quit in the same way, either using nicotine patches or placebo patches.
Glasgow et al. 1989	Reduction occurred in both trial arms. The key difference between arms was post-quit.
Hatsukami et al. 1988	The reduction arm had a goal of reduced controlled smoking rather than quitting smoking.
Herrara et al. 1995	All groups reduced using nicotine gum or placebo gum.
Jerome, Fiero et al. 1999	Reduced scheduling was with regard to nicotine gum use. Both arms quit abruptly before beginning to use the nicotine gum.
Marston & McFall 1971	Main outcome was smoking rates. Abstinence rates were not reported and not possible to calculate from reported results.
Rezaishiraz et al. 2007	Participants were asked to restrict themselves to one pack of reduced nicotine cigarettes per day during the 2 weeks pre-quit. However this instruction was given to both study arms.
Rose et al. 1998	Neither arm was asked to reduce before quitting.
Rose et al. 2006	Neither arm was asked to reduce before quitting.
Rose et al. 2009	Neither arm was asked to reduce before quitting.
Schuurmans et al. 2004	Neither arm was asked to reduce before quitting.
Shiffman et al. 2009	Neither arm quit abruptly. Both study arms reduced before quitting.

APPENDIX 21: PRELOADING REVIEW SEARCH STRATEGIES

a) MEDLINE search strategy

1. (RANDOMIZED-CONTROLLED-TRIAL or CONTROLLED-CLINICAL-TRIAL or CLINICAL-TRIAL).pt.
2. exp Clinical Trial/ or Random-Allocation/ or randomized-controlled trials/
3. 1 or 2
4. smoking cessation.mp. or exp Smoking Cessation/
5. "Tobacco-Use-Cessation"/
6. "Tobacco-Use-Disorder"/
7. exp Tobacco-/
8. exp Nicotine-/
9. ((quit$ or stop$ or ceas$ or giv$) adj5 smoking).ti,ab.
10. exp Smoking/pc, th
11. 4 or 5 or 6 or 7 or 8 or 9 or 10
12. nicotine.mp.
13. NRT.mp.
14. 12 or 13
15. (pre-cessation or precessation or (pre adj cessation)).mp.
16. (pre-loading or preloading or (pre adj loading)).mp.
17. (pre-treatment or pretreatment or (pre adj treatment)).mp.
18. (pre-quit or prequit or (pre adj quit)).mp.
19. ((before adj treat*) or (before adj quit*) or (before adj cessation)).mp.
20. 15 or 16 or 17 or 18 or 19
21. 3 and 11 and 14 and 20

b) PsycINFO search strategy

1. smoking cessation.mp. or exp Smoking Cessation/

2. (control adj smok$).mp.

3. tobacco-smoking/

4. (smok$ or cigar$ or tobacco$).mp.

5. 1 or 2 or 3 or 4

6. (quit$ or cessat$ or abstin$ or abstain$).mp.

7. 5 and 6

8. nicotine.mp.

9. NRT.mp.

10. 8 or 9

11. (pre-cessation or precessation or (pre adj cessation)).mp.

12. (pre-loading or preloading or (pre adj loading)).mp.

13. (pre-treatment or pretreatment or (pre adj treatment)).mp.

14. (pre-quit or prequit or (pre adj quit)).mp.

15. ((before adj treat*) or (before adj quit*) or (before adj cessation)).mp.

16. 11 or 12 or 13 or 14 or 15

17. 7 and 10 and 16

18. from 17 keep 1-70

c) EMBASE search strategy

1. random$.ti,ab.

2. factorial$.ti,ab.

3. (cross over$ or crossover$ or cross-over$).ti,ab.

4. placebo$.ti,ab.

5. (double$ adj blind$).ti,ab.

6. (single$ adj blind$).ti,ab.

7. assign$.ti,ab.

8. allocat$.ti,ab.

9. volunteer$.ti,ab.

10. CROSSOVER PROCEDURE.sh.

11. DOUBLE-BLIND PROCEDURE.sh.

12. RANDOMIZED-CONTROLLED-TRIAL.sh.

13. SINGLE-BLIND PROCEDURE.sh.

14. 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 or 13

15. smoking cessation.mp. or exp smoking cessation/

16. exp smoking-/

17. ((quit$ or stop$ or ceas$ or giv$ or prevent$) adj smok$).mp.

18. exp smoking habit/

19. exp cigarette smoking/

20. 15 or 16 or 17 or 18 or 19

21. (nicotine or NRT).mp.

22. (pre-cessation or precessation or (pre adj cessation)).mp.

23. (pre-loading or preloading or (pre adj loading)).mp.

24. (pre-treatment or pretreatment or (pre adj treatment)).mp.

25. (pre-quit or prequit or (pre adj quit)).mp.

26. ((before adj treat*) or (before adj quit*) or (before adj cessation)).mp.

27. 22 or 23 or 24 or 25 or 26

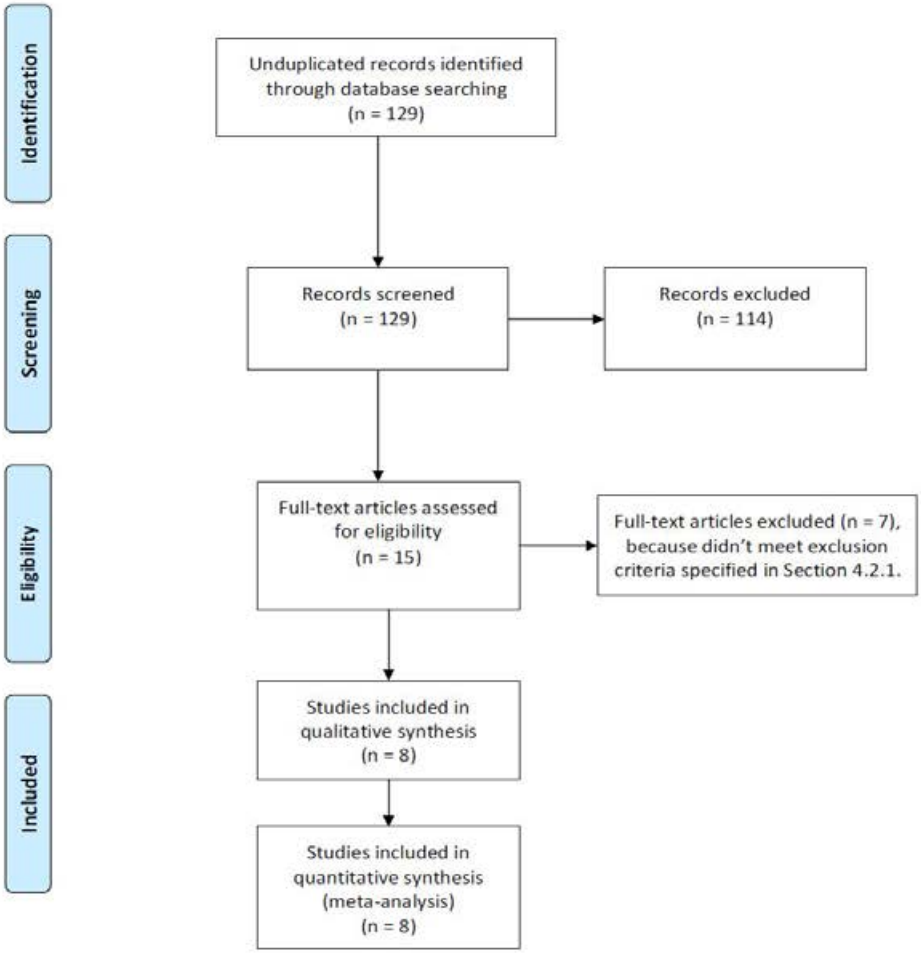
28. 14 and 20 and 21 and 27

APPENDIX 22: PRELOADING REVIEW STUDY ELIGIBILITY FORM

				Comments
1. Is the study an RCT?	Yes ⇩ Go to next question	Unclear ⇩ Go to next question	No ⇩ **Exclude**	
2. Were participant's tobacco cigarette smokers (human study)?	Yes ⇩ Go to next question	Unclear ⇩ Go to next question	No ⇩ **Exclude**	
3. Did participants want to quit smoking?	Yes ⇩ Go to next question	Unclear ⇩ Go to next question	No ⇩ **Exclude**	
4. Did the study include at least 1 group where pre-loading took place? Pre-loading defined as the administration of active nicotine replacement therapy daily for at least a week before the participants' quit day.	Yes ⇩ Go to next question	Unclear ⇩ Go to next question	No ⇩ **Exclude**	
5. Was pre-loading part of a smoking cessation intervention?	Yes ⇩ Go to next question	Unclear ⇩ Go to next question	No ⇩ **Exclude**	
6. Was abstinence reported at at least 6 month follow-up?	Yes ⇩ Go to next question	Unclear ⇩ Go to next question	No ⇩ **Exclude**	
7. Was the nicotine content of cigarettes comparable across relevant conditions pre-quit? (e.g. not denicotinised or low nicotine/tar content vs normal cigarettes)	Yes ⇩ Go to next question	Unclear ⇩ Go to next question	No ⇩ **Exclude**	
8. Was post-quit NRT and behavioural support comparable across relevant conditions post-quit?	Yes ⇩ **Include**, subject to clarification of unclear points	Unclear ⇩	No ⇩ **Exclude**	
Final decision:	**Include**	**Unclear**	**Exclude**	

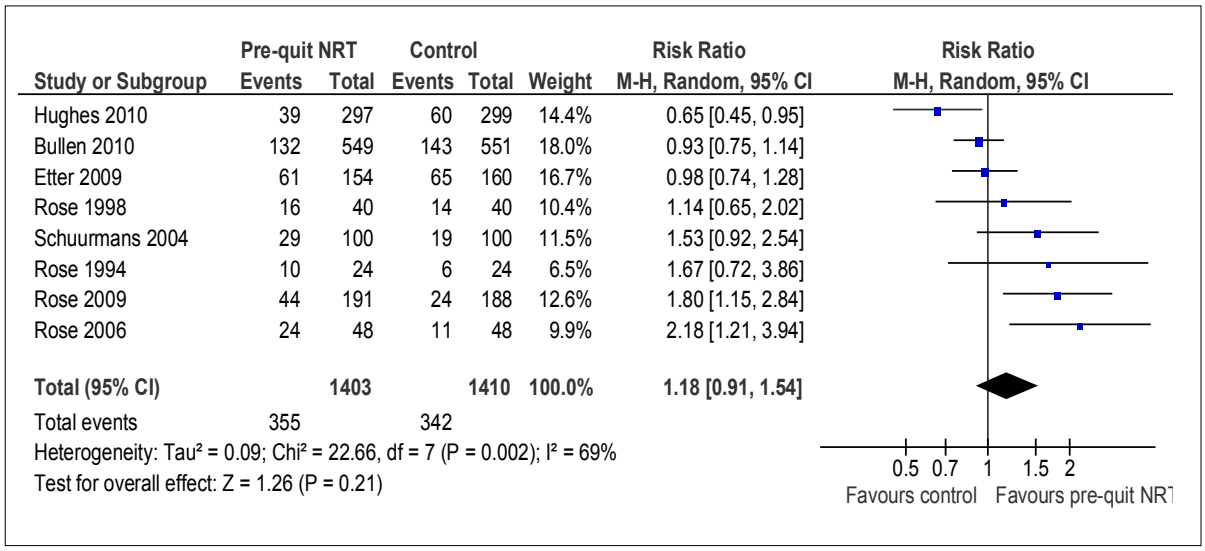
APPENDIX 23: PRELOADING REVIEW FLOW DIAGRAM OF STUDY INCLUSION

Template From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). *P*referred *R*eporting *I*tems for *S*ystematic Reviews and *M*eta-*A*nalyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

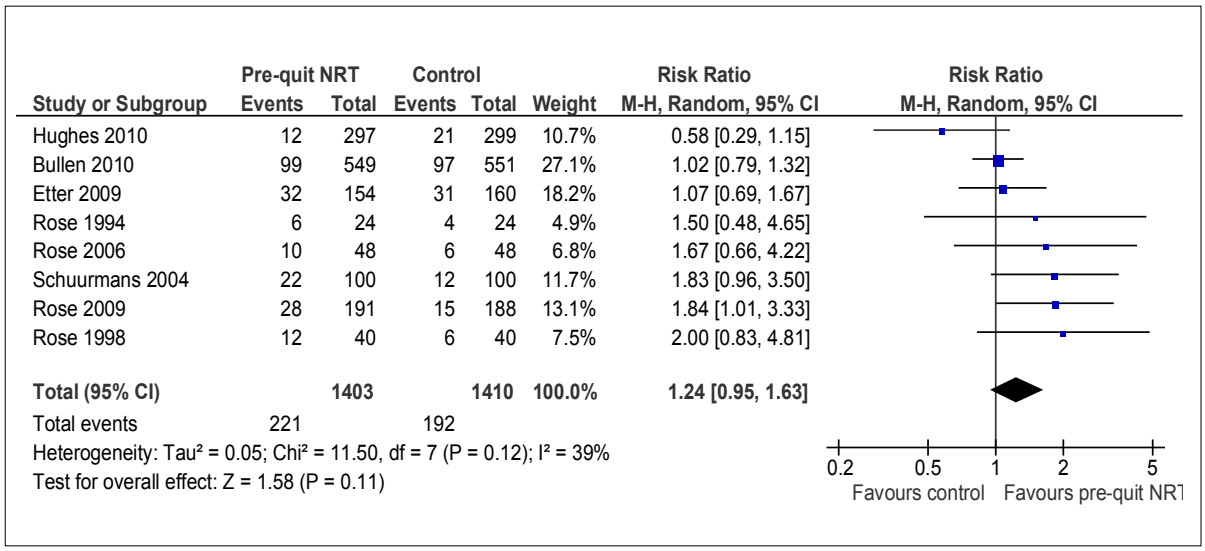


APPENDIX 24: MANTEL-HAENSZEL RANDOM-EFFECTS META-ANALYSES FOR NRT PRELOADING

a) Mantel-Haenszel random-effects meta-analysis for nicotine preloading (short-term abstinence outcome)



b) Mantel-Haenszel random-effects meta-analysis for nicotine preloading (long-term abstinence outcome)



APPENDIX 25: PRELOADING REVIEW RISK OF BIAS TABLES

Bullen 2010	Description	Judgement for low risk of bias (YES/NO/UNCLEAR)
Sequence generation	Randomly allocated using central computerised randomisation, with the randomisation sequence concealed until interventions were assigned. Stratified minimisation used by ethnicity, sex and level of dependence to ensure a balance of characteristics between the study groups.	Yes
Allocation Concealment	Randomisation sequence concealed until interventions were assigned.	Yes
Blinding	All follow-ups and outcome verification procedures made by research assistants blind to treatment allocation. No participant blinding, placebo not used	No
Incomplete outcome data	At 6 month follow-up 26% of each group were lost to follow-up/withdrawn (equal across groups). Analysis was ITT	Yes

Etter 2009	Description	Judgement for low risk of bias (YES/NO/UNCLEAR)
Sequence generation	Randomisation based on a list of computer generated random numbers	Yes
Allocation Concealment	No therapist was involved therefore allocation concealment is irrelevant	Yes
Blinding	No therapist so therapist blinding not necessary. No participant blinding, placebo not used	No
Incomplete outcome data	3 day survey participation (96.5%): 7 lost reduc, 4 abrupt 8 week survey (94.6%): 8 reduc, 9 abrupt 12mth (88.2%): 16 lost, 1 deceased reduction, 18 lost 2 deceased abrupt 12m survey completed by 89.0% of reduction and 87.5% of abrupt (participation rates similar in both arms at all time points). No data appears to be missing from analysis. No SAEs. Analysis ITT	Yes

Hughes 2010	Description	Judgement for low risk of bias (YES/NO/UNCLEAR)
Sequence generation	Statistician generated a concealed allocation sequence and randomised ps to the gradual, abrupt or brief advice conditions in a 2:2:1 ratio using block (stratified by city and counsellor) based on the SAS, procedure PLAN.	YES
Allocation Concealment	Statistician generated a concealed allocation sequence. All post quit day outcomes were collected by research assistants who were blind to study condition and had no role in therapy.	YES
Blinding	No blinding, placebo not used	No
Incomplete outcome data	No data is unaccountably missing based on participant flow diagram. SAEs were rare and similar across conditions (3% gradual, 5% abrupt and 3% brief, and incidence of discontinuation was lower than 1% in total) Withdrawals were similar across groups: Gradual- ITT=297, 290 set quit day, 227 contacted at 6wk, 227 contacted at 6mth. Abrupt- ITT= 299, 286 set quit date, 227 contacted at 6 wk, 237 contacted at 6mth. Analysis ITT However the rate of completion of baseline and pre-quit surveys differed across conditions: 57% completion in preloading, 82% in abrupt so outcomes are based on self-selected sample.	YES for meta-analysis data NO for mediator data

Rose 94	Description	Judgement for low risk of bias (YES/NO/UNCLEAR)
Sequence generation	Simply stated as random allocation, no description of methodology	Unclear
Allocation Concealment	Allocation method not specified	Unclear
Blinding	No blinding in terms of NRT treatment (only blinded for mecamylamine treatment)	No
Incomplete outcome data	Only 3 participants (6%) dropped out. 3 additional ps complained of adverse symptoms but carried on with study. Not specified how these were split across preloading and control however such small numbers can't be large difference. ITT analysis.	Yes

Rose 98	Description	Judgement for low risk of bias (YES/NO/UNCLEAR)
Sequence generation	Simply stated as random allocation, no description of methodology	Unclear
Allocation Concealment	Allocation method not specified	Unclear
Blinding	No blinding in terms of NRT treatment (only blinded for mecamylamine treatment)	No
Incomplete outcome data	6 ps (7.5%) dropped out in 4 week pre-quit period: 5 in preloading, 1 in control. Reasons for drop-out not related to NRT. Loss to follow-up post-quit not reported. ITT analysis	Unclear

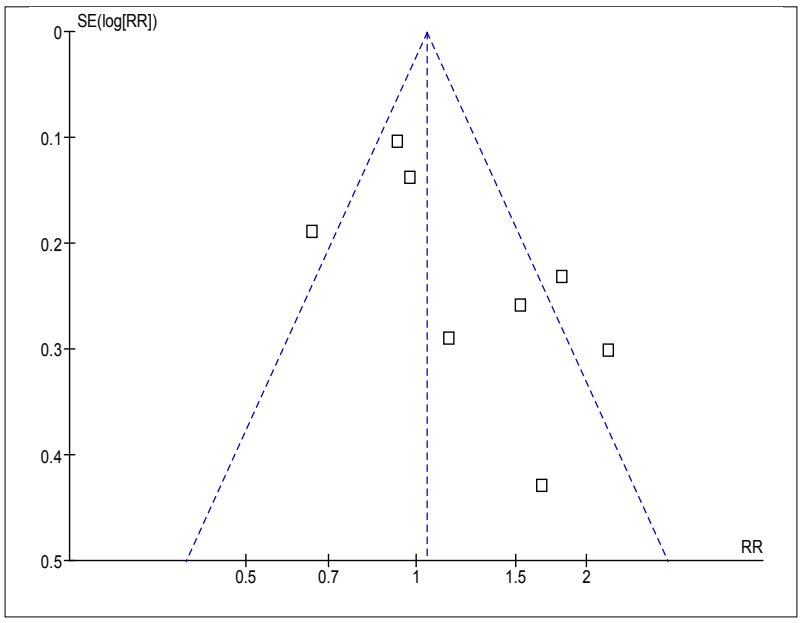
Rose 06	Description	Judgement for low risk of bias (YES/NO/UNCLEAR)
Sequence generation	Simply stated as random allocation, no description of methodology	Unclear
Allocation Concealment	Study described as double-blind so investigators unaware who was in preloading condition, however method of concealment not specified	Unclear
Blinding	Participants and investigators blinded to preloading using placebo patches	Yes
Incomplete outcome data	ITT analysis. 8/96 (8.3%) dropped out before quit day. Loss to follow-up post-quit not reported	Unclear

Rose 09	Description	Judgement for low risk of bias (YES/NO/UNCLEAR)
Sequence generation	Simply stated as random allocation, no description of methodology	Unclear
Allocation Concealment	Study described as double-blind so investigators unaware who was in preloading condition, however method of concealment not specified.	Unclear
Blinding	Participants and investigators blinded to preloading using placebo patches	Yes
Incomplete outcome data	The 10 week study completion rate was 67% and did not differ between groups. Frequency of adverse events did not differ across groups. 210 of 379 participants were contactable at 6 month follow-up, allocation across groups not specified. ITT analysis.	Unclear

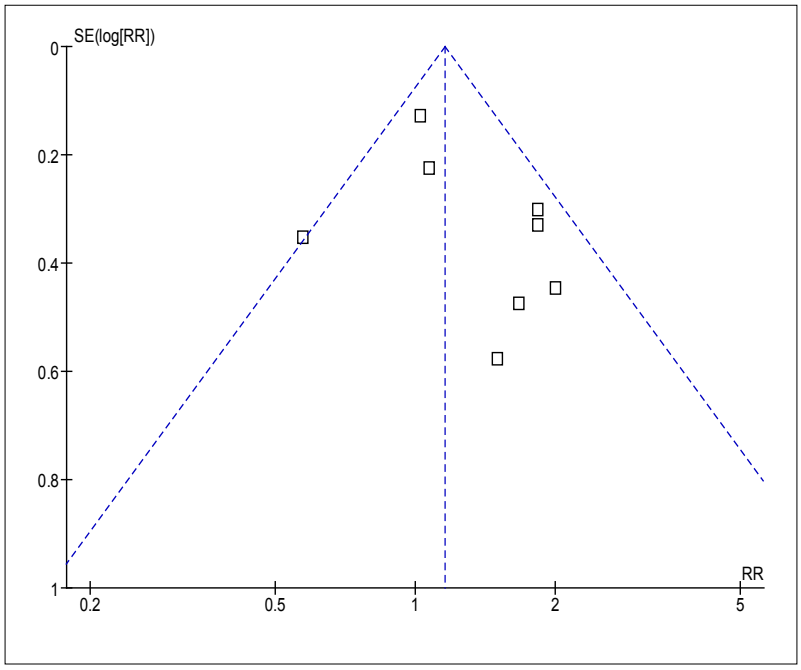
Schuurmans 04	Description	Judgement (YES/NO/UNCLEAR)
Sequence generation	Randomisation was performed with a computer generated list that allocated to placebo or treatment However, it's not clear how they could get exactly 100:100 without some special system which is not described.	unclear
Allocation Concealment	Numbering of identical boxes containing treatment was carried out prior to allocation by someone not involved in study. Treatment code only broken after last follow-up visit and data recorded.	Yes
Blinding	Participants and investigators blinded to preloading using placebo patches	Yes
Incomplete outcome data	ITT analysis. Missing diary cards the same across groups 17/100 preloading, 18/100 control. Adverse events occurred in less than 5% of ps and was the same across groups. There was 1 death in each group unrelated to study. No significant difference in drop out between 2 groups pre-quit (12/100 in placebo, 4/100 in preloading, p= 0.067). No significant difference between drop-out over whole study.	Yes

APPENDIX 26: PRELOADING REVIEW FUNNEL PLOTS FOR MAIN ABSTINENCE OUTCOMES

a) Funnel plot for NRT preloading short-term abstinence outcome



b) Funnel plot for NRT preloading long-term abstinence outcome



APPENDIX 27: RRT INTERVIEW STUDY EXAMPLE THEMATIC CHART

Dislikes thematic chart a)

	Dislikes			
		A lot to do	Ab- sudden, extreme	Clockwatching
PAR 3. abrupt				
PAR 6. abrupt				
PAR 7. abrupt				
PAR 9. abrupt				
PAR 10. abrupt				
PAR 11. abrupt				
PAR 13. abrupt				
PAR 15. abrupt				
PAR 16. abrupt				
PAR 20. abrupt				
PAR 21. abrupt			2: PAR 21:the abrupt one the horrible one ¶3: INT: Right okay and er ¶4: PAR 21: the cruel nasty mean one INT: Right okay is there any particular reason why you would've preferred to do it gradually ¶10: PAR 21: Er I don't think well I've smoked for 25 years you see and I think ((inaudible)) PAR 21: firstly it would have probably found it a little easier doing the gradual PAR 21: I found the abrupt stopping very hard to do PAR 21: err well yes I it was it was a lot harder I think for me personally, I handled it but it was still hard to do it and as I said I fell off the wagon a couple of times	
PAR 24. abrupt				
PAR 25. abrupt				
PAR 26. abrupt				
PAR 28. abrupt				
PAR 29. abrupt			¶13: INT: so when you were told that was how you were going to quit, what were your first impressions of doing it that way? ¶15: PAR 29: Erm, more chances of pigs flying. ¶31: PAR 29: I think the best way for me to stop is have two patches, one on each side so I can't find them. But other than that, erm, the only way I'm going to do it, is there's no way I'm going to stop abruptly at all, at all. ¶63: PAR 29: I suppose it might be OK for somebody who smokes five, 10 or 15 a day.	

			it might work for them. But if you're a, well, I class myself as a heavy smoker, it just, it's just too difficult for me to go without a cigarette so I'm quite pleased with myself at the minute. I'm still, I'm still smoking but I don't smoke till the evening and I'll probably have maybe five or six which is a lot better than 30 and I think hopefully in a month, two months or even three months hopefully that'll go out of my system as well and I won't bother with any. But abruptly doesn't suit me at all I don't think. PAR 29: I think if I'd have started off on a slow manoeuvre, it may have been a better way for me but abruptly was definitely wrong for me. 115: PAR 29: the only thing I'd say is never, never ask a heavy smoker to stop abruptly and I would suggest they don't – if they are going to continue to smoke at a lower level, buy cigarettes they can't stand, that's going to put them off.	
PAR 30. abrupt			9: INT: so when you were told that was the way that you were going to quit, what were your first impressions of doing it that way? ¶11: PAR 30: I didn't want to do it that way, it was the other way I wanted to do ¶13: INT: Right, OK, was there any particular reason why you would have preferred to do it that way? ¶15: PAR 30: Erm, because I, I knew I wouldn't be able to.	
PAR 32. abrupt				
PAR 33. abrupt				
PAR 41. abrupt			¶5: INT: when you were told that was the way you were going to be quitting what were your first impressions of doing it that way ¶7: PAR 41: Well I was hoping it would be the rapid the erm, sorry, the sort of reduction over a period of time rather than abrupt halt to it ¶9: INT: Yes ok was there any specific reasons why you would have preferred that? ¶11: PAR 41: Well because I was quite a heavy smoker, I mean I have cut down tremendously erm over the last few weeks from where I was, I mean I was smoking er 25 30 plus a day and I've been smoking for 40 years so I just thought it would be erm better for me to sort of reduce gradually rather than abruptly ¶13: INT: Right yes yep ok ¶15: PAR 41: Because of that er you know the time I I've smoked basically I thought it would be too much of a shock to my system just to quit altogether ¶155: PAR 41: I started reducing ¶157: INT: Right yeah okay erm was that because you felt that you just couldn't bring yourself to.. ¶159: PAR 41: Yeah I felt it was too quick. I felt if i'd been able to reduce gradually over say a month. I felt two weeks was too erm short a time, that was all I felt about it really ¶213: INT: is there anything else you'd like to say about the method that you think's	

			important ¶215: PAR 41: Umm I think it works it would work for some people umm but I do think you could slip back quite quickly with the abrupt method, I think it's done over for me too tight a time frame	
PAR 27. Reduc-hier (e)				
PAR 34. Reduc-hier (e)				
PAR 35. Reduc-hier (e)			¶13: INT: when you were told that you were going to be reducing what was your first impressions of quitting that way? ¶15: PAR 35: Happier than I was at being told one of the other ways was cutting out straight away. ¶17: INT: Right, OK and why d'you think you prefer to do it by reducing? ¶19: PAR 35: Well I've been smoking since I was 15 so that was something like 50 years. The very thought of just stopping dead was not appealing.	
PAR 38. Reduc-hier (e)				
PAR 47. Reduc-hier (e)		39: PAR 47: I confess that in the second week when we were y'know when I was wondering whether it was 14 or 13 or 12 or, and I knew that on Saturday it was going to go down to nought. I kind of got fed up of er counting in ones. I smoked less that week. I mean I have reduced, I think maybe and I was around 12, but it was kind of each day rather than 30 in one day and 12 the next day so in spirit I reduced over the period, in practise the detailed scheme of identifying cigarettes didn't work for me. PAR 47: it was a mixture of kind of irritation with it all but as we come to the point where you're not going to smoke any more there was actually a sort of reward which was that you didn't have to do all this stuff anymore counting things up		
PAR 48. Reduc-hier (e)				
PAR 49. Reduc-hier (e)				
PAR 54. Reduc-hier (e)				
PAR 5. Reduc-sched				
PAR 12. Reduc-sched				PAR 12: I found that because I got to go such a long time all I was doing was clock watching
PAR 17. Reduc-sched			¶35: PAR 17: with the method like I say, I didn't feel, when I tried to give up smoking in the past it used to be cold turkey, you know, you were smoking one day and then you had to give it up the next day, it was a sudden shock to your system. With that it was a nice gradual period over two weeks so I didn't feel threatened or too nervous at	¶17: INT: did you manage to stick to the times that you were given to smoke alright? ¶19: PAR 17: Yes, that was fine, yeah I, every day I did a bit of clock watching at the time, you know, but you know, gradually y'know as the times went on you know erm I was, you know, you got

			giving it up really, you know, you had something to look forward to each day. Cos usually when you give up smoking y'know you feel like your life's come to an end especially, when you know, you're dying for a cigarette, you know, you feel like you're, you know, everything's against you and things but doing it like that it didn't feel that bad at all really, you know. ¶87: PAR 17: Well like I say, it's erm if you feel that you had to quit straight away erm, you know, I mean, I tried once before, I mean, Linda had said to you erm that we tried an NHS stop smoking erm thing they had up at Sainsbury's and with that you were smoking the day before and then you had to give it up the very next day and it felt like your life had come to an end almost, you know, it was a shock to the system really but with this way I've, you know, I've found that you had something to look forward to each day even if it was only, you know, your cigarettes were two hours apart or three hours apart, it was something to look forward to every day and then by the time you'd got to the, to the quit day it wasn't so much of a shock to the system, you know, your body really, you know, you were already going only four hours without a cigarette by then anyway. So it wasn't too bad.	into a routine of doing it every day, you know, and I used to write down the times when I could have a cigarette and then I used to tick them off and I found it quite easy doing it that way, yeah.
PAR 31. Reduc-sched			PAR 31: I believe the other way of doing it, you've got to smoke the same amount of cigarettes each day until the last day and then you just cut off and I, I thought, I would have thought that would have been harder to have done that personally because you're still used to smoking your same amount right up to the last minute and then the next minute you've, you've finished smoking and I could imagine that, that would be more difficult. I would have found that more difficult anyway let's put it that way.	
PAR 36. Reduc-sched				
PAR 44. Reduc-sched			¶25: INT: when you were told that you were going to be reducing rather than quitting abruptly what were your first impressions of doing it that way? ¶27: PAR 44: Erm it was sort of like oh yeah that's better. ¶29: INT: Yeah okay why would you have preferred to do it that way do you think? ¶31: PAR 44: It just seemed at the beginning it just seemed the easier option out of the two. ¶33: INT: Yeah. ¶35: PAR 44: The other seemed so sudden.	
PAR 46. Reduc-sched		45: INT: Do you think there's any particular reasons for that or any times when particularly you found it easier or harder? ¶47: PAR 46: I think I just found it difficult cos there was a lot going on in my life it was quite stressful and I thought oh I can't do it all. ¶49: INT: so was it that you found it clashed with anything particularly in your lifestyle or that it was just kind of an extra thing? ¶51: PAR 46: It was just an extra thing and things were happening and oh there was all sorts going on I thought this is ridiculous.		59: PAR 46: This was happening while I was trying to do that and then I couldn't wait for the time to pass to have my next cigarette. ¶61: INT: Right. ¶63: PAR 46: I felt as though I was constantly clock watching. ¶65: INT: so was there anything particularly that you thought was a problem or a bad point about it? Anything that stood out? ¶67: PAR 46: The bad point was waiting I knew I couldn't have another cigarette in so much time that whereas if I'd just stopped it would have been much better cos that would have been it.

		¶53: INT: was there anything actually that you thought was a good point to the method or that you liked about it? ¶55: PAR 46: I did like it but there's just so much going on.		169: INT: do you think your feelings about quitting changed at all over the two weeks when you were reducing do you think you got any more confident or any less confident as time went on. ¶171: PAR 46: I got less confident as time went on. ¶173: INT: Right okay and do you think there is any particular reason for that? ¶175: PAR 46: Because it was reducing it if I'd have done it straight away there and then I think I may have done it. ¶177: INT: Right yeah. ¶179: PAR 46: But because I had to cut down slowly and surely then I wasn't looking really forward to my next one and just watching the clock constantly.
PAR 51. Reduc-sched	¶145: INT: so overall would you say that you were pleased with the method that you used or not so pleased. ¶147: PAR 51: Not pleased, I'd rather have just chosen a day when I was gunna stop like I did last time and then just go for it without still smoking.	¶23: PAR 51: it was just a faff you know so 45 minutes between fags and then 40 minutes and I don't know whether I stuck to it religiously really. ¶57: INT: was there any specifically about the method that you didn't like about it or that you would say was a bad point of doing it that way? ¶59: PAR 51: Well it was just really faffy, this reduced time cos I can't remember what the gap was when I started it was probably about every 35 minutes. If it had been like you know you can have one an hour I kind of could have coped with that a little bit better. ¶61: INT: Right yeah. ¶63: PAR 51: So you know set your mobile phone, set your alarm clock well I couldn't be arsed really so it was really just keeping an eye on the clock so. ¶81: INT: with the scheduled reduction that you did was, I mean anything at all really about it that along the way you thought I would have just changed that a bit or done it different? ¶83: PAR 51: Well I would have simplified it I think. ¶85: INT: Yeah. ¶87: PAR 51: I mean it also didn't take into account the fact that in the daytime retired or not if I'm out in the garden for four or five hours I'm not bothered about having a fag, the danger times are in the evening when you' re settled down and you're relaxing and that's when both of us in fact we probably would have sat down and smoked 7 or 8 fags of an evening. ¶89: INT: Yes. ¶91: PAR 51: So you know sitting there, looking at my watch thinking oh you know it's 7 o'clock I can have one now no I can't have one for 55 minutes or 45 minutes, that was a pain. ¶161: INT: so thinking more generally about how people quit smoking, with that in mind do you think there is anything about this method that could actually help some people to quit smoking? ¶163: PAR 51: Possibly I don't know whether it might be easier for perhaps lighter smokers who say you know you can have a fag erm every three hours say you know that would be easier to manage in some ways but somebody		¶81: INT: with the scheduled reduction that you did was, I mean anything at all really about it that along the way you thought I would have just changed that a bit or done it different? ¶83: PAR 51: Well I would have simplified it I think. ¶85: INT: Yeah. ¶87: PAR 51: I mean it also didn't take into account the fact that in the daytime retired or not if I'm out in the garden for four or five hours I'm not bothered about having a fag, the danger times are in the evening when you' re settled down and you're relaxing and that's when both of us in fact we probably would have sat down and smoked 7 or 8 fags of an evening. ¶89: INT: Yes. ¶91: PAR 51: So you know sitting there, looking at my watch thinking oh you know it's 7 o'clock I can have one now no I can't have one for 55 minutes or 45 minutes, that was a pain.

		who is an even heavier smoker than me cos I was smoking perhaps about 20 day it must be a nightmare, you know you're allowed a fag every 15 minutes well you know. ¶165: INT: Yes yeah. ¶167: PAR 51: I understand how you think oh I can't be bothered you know to do that. ¶169: INT: Yes. ¶171: PAR 51: But it just seems cumbersome and quite hard to do really.		
PAR 52. Reduc-sched		¶53: INT: Do you think it was hard from the perspective that it was hard to cut down or was it just hard to smoke at the specific times, would you have preferred to cut down but smoke them when you wanted to? ¶55: PAR 52: Yes it was definitely difficult to deal with the specific times. ¶97: INT: do you think there's anything particularly that you would have changed about it or as you went along and you thought oh I would have done that a bit differently if it had been done like that it might have worked better was there anything like that? ¶99: PAR 52: Again I can't really remember there probably was erm this thing having to try and stick to the specific timing that was really quite annoying.		
PAR 53. Reduc-sched			¶45: INT: was there any particular reason do you think that you didn't want to do it abruptly or was it just...? ¶47: PAR 53: No just glad I hadn't got to, cos that sounded a bit drastic to me yeah. ¶217: INT: Yeah that's great. OK and do you think you'd recommend doing it this way to other people? ¶219: PAR 53: Yes I think I would I think I would because it's gradual and I think it would probably be too, somebody who smokes as long as I have it would be too much of a shock to the system to just suddenly stop. But if it's gradual and it gets it into your brain I can do this, I can do this. That's my opinion anyway.	
PAR 1. Reduc-sfp				
PAR 2. Reduc-sfp			¶51: INT: bearing in mind how you think people successfully quit smoking, keeping that in mind how do you think this method could help people quit ¶52: PAR 2: Because of uh they can plan their day around their smoking to begin with and it helps them through up to your quit date because you are actually in control of that it's your choice and you know when you want to smoke and when you don't want when you can't smoke which I think is brilliant where other methods are you know like I said before it was you smoke until your quit date and then that's that which is very hard straight away ¶91: INT: before when you came into the study what way would you have liked to quit or how would you have chosen to quit yourself if you'd have been given any choice ¶92: PAR 2: I would have gone for the reduction ¶93: INT: the reduction okay ¶94: PAR 2: definitely, I think the abrupt	

			one kind of frightens people at first thinking ahhh you know ¶95: INT: Yeah ¶96: PAR 2: I get to this day and that's it and I think in some smokers you panic	
PAR 4. Reduc-sfp				
PAR 8. Reduc-sfp				49: INT: do you think there was any problems or bad, bad points to the method? ¶51: PAR 8: Erm, the only thing I would say is as it got bigger spaces, it did make me clock watch a bit and I didn't think at that stage, I didn't think I stood much chance of packing in because in the past when I've done it and cut down, it's like that cutting down and I'd cut down in the past by thinking, right, I'm only going to have five cigarettes today and I'll have one this time and one that time and I used to just sit there waiting for, the clock. So I, I suppose I did find that I did as it got more and more that you had the times when you couldn't smoke, I did watch the clock a bit.
PAR 14. Reduc-sfp			PAR 14: I've tried many a times to pack up cigarettes and doing it abrupt it just didn't work with me. If I stopped straight away, if I said, right I ain't having no more after that one, that was no good for me, none whatsoever.	
PAR 18. Reduc-sfp		¶175: PAR 18: Actually I would have liked to have, er, abruptly really, I was like that one. They said look, this is my quit day, put a patch on, are you using the lozenges and just go like that in the daytime, it was that having cigarettes, you see. ¶177: INT: Why was it that you would have preferred that one do you think? ¶179: PAR 18: Erm, I think it would have been a lot easier, yeah, cos you, as I say, you got to look at your times, you know, on that day.		
PAR 19. Reduc-sfp				
PAR 22. Reduc-sfp				
PAR 23. Reduc-sfp				
PAR 37. Reduc-sfp				¶135: PAR 37: You know, I've still got you know an hour to wait. Yes I was waiting for the time; I did find meself waiting… oh three o'clock I can have a cigarette, d'you know what I mean? ¶137: INT: Yes, sure. ¶139: PAR 37: so yes I was actually looking and waiting for the time.
PAR 39. Reduc-sfp				
PAR 40. Reduc-sfp			5: INT: Yes, yes OK so when you were told that that was the way that you were going to be quitting what were your first impressions of doing it that way? ¶7: PAR 40: I was thankful actually. ¶9: INT: Was you… yeah. ¶11: PAR 40: I was a bit scared of stopping abruptly do you know what I mean?	

			¶13: INT: Yes, yeah. ¶15: PAR 40: Thinking about it, it was the easiest way it really was. 129: INT: So why d'you think doing it in this way works particularly well for you? ¶131: PAR 40: Well it wasn't such a shock to the system as stopping all at once, d'you know what I mean.	
PAR 42. Reduc-sfp			¶29: INT: So why was it that you would rather have reduced than done it abruptly? ¶31: PAR 42: I think when you try and stop abruptly you know it's there and then I think it can be a little bit scary when you've been smoking for so long.	
PAR 43. Reduc-sfp				
PAR 45. Reduc-sfp		31: PAR 45: I found it awkward cos of working cos I had to keep looking up the times and like every day there'd be another half an hour or something taken off you, so I did struggle at times to specifically stay to it you know because obviously with me working and well with me being a carer and that and you know I just found it hard to stick to it really. ¶53: INT: so would you say there was anything particularly that you didn't like about doing it that way? ¶55: PAR 45: The fact of having to look at the chart, find out when I could smoke and when I couldn't smoke and following the times really that was put down for me not to have a cigarette and when to have a cigarette so I found it quite awkward to follow. ¶57: INT: So d'you think that's mainly because of kind of your lifestyle and your job that you know…? ¶59: PAR 45: It was really, yes. ¶61: INT: Yeah yeah OK so d'you think there's anything that you could have changed about the method or that you would have…? ¶63: PAR 45: I would've preferred the first one, I'd rather have gone with that. ¶65: INT: Yeah yeah. ¶67: PAR 45: Because I felt as though I was suffering anyway so I'd rather have just smoked as normal and then quit you know and because I'd have found it just as hard… cos I found it just as hard to give up those cigarettes and not to smoke at certain times and I did if I'd have been told you know it was me quit day and I quit, d'you understand what I'm saying?		¶19: PAR 45: It was the thought of cutting down because I was thinking like it's constantly going to be on your mind when you next have a cigarette d'you know what I mean? ¶21: INT: Right yeah. ¶23: PAR 45: What I… I found it very hard. ¶105: INT: Right OK and would you say that over the time when you were reducing do you think your feelings about quitting changed at all, d'you think you got any more confident or any less confident as time went on? ¶107: PAR 45: Less confident I would say if anything. ¶109: INT: Right d'you think there's any particular reason for that or…? ¶111: PAR 45: Well it was just constantly on me mind when I could have the next cigarette. ¶127: PAR 45: Because like I say I was constantly like thinking about when my next cigarette is. It was like cigarettes ruled me more than ever you know that like in an hour's time I can have another cigarette and you know I was just literally wishing my life away you know for the next cigarette, it was constantly on my mind.
PAR 50. Reduc-sfp			¶13: INT: was there any particular reasons why you would have preferred to do it that way? ¶15: PAR 50: It's a gradual process and I think if I'd done the other one, two weeks of going cold turkey I couldn't do it. ¶17: INT: No right. ¶19: PAR 50: And this one suited me down to the ground it really did.	¶53: INT: how easy did you actually find it to carry out, so how easy did you find it not to smoke in the periods that you were supposed to? ¶55: PAR 50: I found it fairly easy I just couldn't wait for my next time to come up when I could have a cigarette. ¶57: INT: Right okay yeah. ¶59: PAR 50: When I go four hours without a cigarette oh great and my mind is thinking oh it's time to have a cigarette, I shouldn't think like that but I did.

Dislikes thematic chart b)

	Dislikes				
		Couldn't continue reducing	Length of reduction	Scheduled intense for heavy smokers	Sfp- not reduction
PAR 3. abrupt					
PAR 6. abrupt					
PAR 7. abrupt					
PAR 9. abrupt		¶9: when you were told about, that that was the way that you were going to quit, what were your first impressions of, erm, doing it that way? ¶11: PAR 9: I would rather have been chosen to reduce it because I'd already started reducing. ¶13: INT: Right, oh, OK, so how much had you reduced do you think before you came…? ¶15: PAR 9: I'd reduced probably from about 25 down to 18 in two weeks. ¶17: INT: Right, OK. Erm, so how had you done that? Had you just gradually…? ¶19: PAR 9: Erm, no, just by stopping smoking in the house actually and if you want a cigarette, you go in the garage or you go outside. ¶125: INT: Right, OK. So, sorry you said that before the study if you'd been given the choice to quit, did you say you would have quit, you would have reduced first? ¶127: PAR 9: Yes. ¶129: INT: OK, and was that purely just because you'd done that up to then or were there any other reasons why you preferred reducing? ¶131: PAR 9: Erm, no, what we just found it was easiest really and seemed to happen naturally.			
PAR 10. abrupt					
PAR 11. abrupt					
PAR 13. abrupt					
PAR 15. abrupt					
PAR 16. abrupt					
PAR 20. abrupt					
PAR 21. abrupt					
PAR 24. abrupt					
PAR 25.					

abrupt					
PAR 26. abrupt					
PAR 28. abrupt					
PAR 29. abrupt					
PAR 30. abrupt					
PAR 32. abrupt					
PAR 33. abrupt					
PAR 41. abrupt					
PAR 27. Reduc-hier (e)					
PAR 34. Reduc-hier (e)					
PAR 35. Reduc-hier (e)					
PAR 38. Reduc-hier (e)					
PAR 47. Reduc-hier (e)					
PAR 48. Reduc-hier (e)					
PAR 49. Reduc-hier (e)			205: INT: D'you think when you didn't manage to give up on your quit day, d'you think that was anything to do with the method that you were using, d'you think there's anything about this method that made it difficult for you to quit at all? ¶207: PAR 49: I think personally it was extreme for myself. ¶209: INT: Mmmm right. ¶211: PAR 49: Because of the rapid period in two weeks to you know to cut down from more than twenty cigarettes to nothing… ¶213: INT: Right. ¶215: PAR 49: …it was quite a rapid thing for me. ¶217: INT: So would you have preferred that to have been a bit more spread out over a longer period d'you think? ¶219: PAR 49: Yes, yes well having said that anyway that's how it's turned out with me now so I think that would have been the proper method anyway for me. ¶221: INT: How long would you have done it over d'you think if you'd had the choice?		

			¶223: PAR 49: Probably four weeks		
PAR 54. Reduc-hier (e)					
PAR 5. Reduc-sched					
PAR 12. Reduc-sched					
PAR 17. Reduc-sched					
PAR 31. Reduc-sched					
PAR 36. Reduc-sched					
PAR 44. Reduc-sched			163: PAR 44: it's really all said and done even on a reducing there's gunna come a time you know when you're gunna have to pack up completely and you know and that day when you're in the programme doesn't seem you know you're not think it's ever gunna come you know. ¶165: INT: Yes yeah, so when you decided to quit cold turkey, well not cold turkey but abruptly what do you think it was that made you think right I'm gunna do it now? ¶167: PAR 44: It was erm determination and erm it was sort of to say well hold on the way this is going I'll still be smoking in sort of two weeks time almost or whatever it was and erm you know and I really feel like cos I've gone for such long periods without cigarettes you know because I kept missing it and it had gone like a 24 hour period I thought well you know I might as well, it seems daft to have another cigarette now I may as well just go with it and stop.		
PAR 46. Reduc-sched					
PAR 51. Reduc-sched				¶161: PAR 51: so thinking more generally about how people quit smoking, with that in mind do you think there is anything about this method that could actually help some people to quit smoking? ¶163: PAR 51: Possibly I don't know whether it might be easier for perhaps lighter smokers who say you know you can have a fag every three hours say you know that would be easier to manage in some ways but somebody who is an even heavier smoker than me cos I was smoking perhaps about 20 day it must be a nightmare, you	

				know you're allowed a fag every 15 minutes well you know.	
PAR 52. Reduc-sched					
PAR 53. Reduc-sched					
PAR 1. Reduc-sfp					
PAR 2. Reduc-sfp					
PAR 4. Reduc-sfp					51: PAR 4: I know, I said something about tapering down, it didn't sound like I tapered down, what I do I tapered down myself and like I said many years ago, I was smoking a 100 and then I was – it got down since I've been in England, 15 or 20 and then when my pain gets really, really bad, I smoke more so I kind of go back up to 40. But for money's sake and I thought, I can still smoke 40, I mean, you know, you've got three or four hours there where you can smoke, I mean I could probably smoke all 40 of them in that two or three-hour period, you know. So what I did and I cut myself from the day one to limit myself to only 20 cigarettes a day but that was on my part. PAR 4: like I said I, once I started I thought oh, this one's good cos I have done something pretty simple. I think there was one plan that you have to look at the clock all the time, you know, and, erm, so it was simple but after I did it for a while, I thought, yeah, I'm still, I can still smoke the same amount of cigarettes PAR 4: like to me they should cut down on the amount of cigarettes. I mean, it's really not a tapering off, I don't know about the other, you know, the other, the other group could still do the same thing. I believe they were just smoking everything they wanted with, erm, the patches and actually I'm, I'm doing the same thing just, you know, at a different time say between 12 and three. ¶127: PAR 4: Erm, the only personal strategy was my determination, my cutting down the extra 20 cigarettes at the beginning because

					after, yeah, I think about it, I thought, well I could still smoke 40 cigarettes every day and how do they consider that tapering down for two weeks? ¶169: INT: so would you say that you were pleased with the method that you used or not so pleased? ¶171: PAR 4: Erm, not so pleased with the method, no, because, you know, you're not, you're not improving anything for those two weeks, you're still smoking 40 cigarettes just at, at when someone tells you you can. ¶207: PAR 4: And if they read it like I read it, you know, you think oh, well this is good and then you get into it for a couple days and it's like wait a minute, I can still smoke 40, 60, 80 cigarettes a day, I just have a specified time that I can smoke and I think everybody would think the same as I do. As I said I don't know which other, other options were, I just, I remember looking at one and I thought, no, I'm not doing that, I'm not, you know, I think too confusing but I think it might have been all the same. I, I would agree to I guess a tapering off of cigarettes definitely. ¶239: PAR 4: Well, I thought the tapering was a good idea, you know, I did want abruptly but then after she did this I thought maybe this is better, maybe this is better so at the end of the two weeks it won't be as bad so then I was happy with it, erm, until I got into it for a few days and I thought like I said before, oh gosh, I can still smoke 40 or 60. It dawned on me that, you know, it really wasn't tapering off and I figure it would really help a lot of people if that, that programme were changed just slightly, just tweaked a bit. ¶241: INT: Yeah, yeah… ¶243: PAR 4: Because then you get the feeling that you're actually accomplishing something, you know, and you're cutting, you're actually cutting down and then you know when your quit date is so that, you know, it's not a big shock but you're smoking less cigarettes by the time you do quit.
PAR 8.					¶119: PAR 8: I'm one of

Reduc-sfp					these, I don't really, I've never ever been able to do it on a date, you know, like people I know or somebody I work with, you know, like when they say, oh, erm, on New Year's Day, me New Year's resolution, I'm not going to smoke anymore, I can't do it like that. Either I've got to do it right now, I can't think well I'll pack it in four weeks' time so as the time went on plus the fact that I just think I found that in the times when I could smoke although I wasn't smoking as many cos obviously it was impossible to smoke as many, I found that I was probably smoking more in the times that I could smoke, that's what it felt like anyway… ¶121: INT: Right, yeah. ¶123: PAR 8: cos I know like for three or four hours, I wouldn't be able to have one. ¶125: INT: Yeah, yeah, OK. ¶127: PAR 8: So I just thought I can't see how this is going to work.
PAR 14. Reduc-sfp					
PAR 18. Reduc-sfp					
PAR 19. Reduc-sfp					
PAR 22. Reduc-sfp			51: PAR 22: I think probably in the second week when we picked which times I could smoke, I think really it would've been better to have gone over maybe three or four weeks that's just my opinion because I am nearly 60 and I've been smoking for 40 years and it just seemed I know it wasn't the abrupt stop smoking but I thought if it'd gone over for another couple of weeks still being able to smoke and getting less and less. Maybe it was my fault in not smoking the 34 at the beginning. Y'know me perhaps trying to do it a little bit my way. I don't know.		
PAR 23. Reduc-sfp					
PAR 37. Reduc-sfp					
PAR 39. Reduc-sfp					
PAR 40.					¶63: PAR 40: when we initially went on the

Reduc-sfp					reduction plan we did tend to try and cram as many in ((Laughs)) do you know what I mean…? ¶65: INT: Right yeah. ¶67: PAR 40: …at the onset but we soon got out of that habit... well I did actually.
PAR 42. Reduc-sfp					
PAR 43. Reduc-sfp					
PAR 45. Reduc-sfp					
PAR 50. Reduc-sfp					

APPENDIX 28: RRT INTERVIEW STUDY EXAMPLE CASE CHART

Parent nodes	Level 1 child nodes	Level 2 child nodes	Level 3 child nodes	PARTICIPANT 3. Abrupt- Quotes (Age 43, Male, Baseline CO= 34, Baseline FTND=5, Quit @ +4wks?= Yes)
Comparison to previous experience				
	Abrupt preferred to previous reduction			
	Never considered reduction			
	Previous abrupt preferred to reduction			
	Reduction preferred to previous abrupt			
	Unsuccessful unsupported reduction			
Compliance				
	Complied			
	Didn't comply			
		Ab- reduction pre-quit		¶86: PAR 3: after about a week an half I did say to the lady on this stop smoking clinic place I can't remember her name sorry I did say well cos she told me to smoke as nor as normal the amount and I told her I said I've got to tell you the truth I can't smoke that much ¶118: PAR 3: To carry on smoking I really didn't want to do it I said you know I'll try and she said to me I really do want you to smoke as normal but if you can't you can't and I really couldn't I was smoking but it was one or two a day
			Ban in places	
			Increase time to 1st cigarette	
			One cpd	
			Unconscious	
		Didn't follow schedule		
		Excess reduction		
		Hr-scenarios not cigarettes		
		Post-quit smoking		
			Baseline cpd	
			Reduced cpd	
			Premature quit	
Dislikes				
	A lot to do			
	Ab- sudden, extreme			
	Clock watching			
	Couldn't continue reducing			

	Length of reduction			
	Scheduled intense for heavy smokers			
	Sfp- not reduction			
Ease of method				
	Easy			¶41: INT: did you feel that it fit in quite well with your lifestyle or was there anything that it clashed with ¶42: PAR 3: no it was okay it does help with cus you can't smoke like in public places like pubs and stuff it does make it easier when there's no smoking
	Got easier			
	Got harder			
	Hard			
		Change from norm interfered		
		Cue interference with schedule		
		Difficulty identifying cigarettes		
		Task interference with schedule		
Likes				¶43: INT: would you make any changes to the method was there anything that you thought you know it would have been better if it had included that or anything like that ¶44: PAR 3: no not really I thought it was excellent ¶61: INT: would you say that overall your pleased with the method you used or not ¶62: PAR 3: Yes very excellent ¶63: INT: Okay ¶64: PAR 3: Excellent yes
	At will vs when told			
	Clear guidance			
	Decision making			
	Familiarity			
	Post-quit reduction			
	Preparation smoking			¶72: PAR 3: That's what helped me that method by saying you know it's okay carry on smoke as normal ¶116: PAR 3: as I said I did enjoy in the first when you first go on the course they tell you to smoke as normal and they the first week I did I I said to the lady I really really don't enjoy smoking no more but I didn't get to the quit date then I had another week to go
	Reduction encouraged			
	Reduction for hardened smokers			
	Took control			
	'wasn't craving'			
Mechanisms				

	Adaptation			
	Breaks habit			
	Don't spoil hard work			
	Finding you can do it			
	Gets it over with			
	Mindset not the method			
	Monitoring			¶46: PAR 3: the diaries did help cos it just makes you think and like because you've got it all week you have to fill it in by the end of the week you flick through it yourself and you think to yourself oo that's terrible that is smoking that much and just that number yeah it does help yeah ¶114: PAR 3: Education I mean that's what's got me out of smoking you know education i.e talking to people and you know the checks you get the writing you do ¶136: PAR 3: I keep on saying to her oo when you know I go and blow in that thing ¶137: INT: Yeah ¶138: PAR 3: Like I'm gutted when it was like one ¶139: INT: Aaa ¶140: PAR 3: or two I was absolutely gutted I goes aaa and that's the disappointing thing in my eyes cos I'm thinking what's the point what's the point she says well if you're round people or whatever ¶141: INT: Yeah ¶142: PAR 3: it's quite normal you can get up to about 4 or 5 and I'm going ooo no ¶143: INT: Yeah that's even things like traffic and things like that ¶144: PAR 3: Yeah ¶145: INT: If you live in London people who live in London blow very high ¶146: PAR 3: That's what she did explain she cos i said to her oh I've come from town and that something too and I was gutted and she said well that's good those little things help you see
	Schedule frustration			
	Tricky cigarettes			
Method allocation				
	Alternative			
	No preference			
	Preferred			
Opinion change				
	Abrupt-reduction			
	No change			
	No preference-abrupt			
	No preference-reduction			
	Reduction-abrupt			
Preloading				
	Acute preferable to patch			
	'almost like they went			

	together'			
	Beliefs			
		'Happy to believe it'		¶68: PAR 3: with your methods with the method that I've been through now I actually had the patch on and she said go on smoke as normal and then like the first week I was going oo I can't I can't she said no you must ¶69: INT: Yeah ¶70: PAR 3: Yeah it's good
		Helpful		¶53: INT: you mentioned a bit about it but how did you feel about that as part of the method did you like it being included in there ¶54: PAR 3: I did yeah it was very helpful yeah ¶68: PAR 3: and that's not right but with your methods with the method that I've been through now I actually had the patch on and she said go on smoke as normal and then like the first week I was going oo I can't I can't she said no you must ¶69: INT: Yeah ¶70: PAR 3: Yeah it's good ¶122: PAR 3: ya know I would have liked it to be a shorter period of time from when I first seen her to the quit date ¶123: INT: Right okay yeah ¶124: PAR 3: it went on a bit long ¶125: INT: So do you think it would you say it's an important part of the method to have that experience ¶126: PAR 3: Oh I think so yes yeah but not as long as I say because you know I was telling the truth actually trying smoking that many it's not very nice I smell you know I smell and everything ((inaudible)) I won't tell anyone but bear it in mind that
		Not accepted		
		Previous negativity		¶7: INT: when you started the study and you were told that was the way that you were going to quit what were your first impressions of the quit method. ¶8: PAR 3: Well I was quite surprised cus she told me to carry on smoking the amount of cigarettes I was smoking and plus taking the patches ¶9: INT: Right ¶10: PAR 3: I was quite surprised at that but I didn't smoke as many because I just didn't like the, I don't know it give me leg ache and nausea and stuff smoking with the patches on. ¶68: PAR 3: with the method that I've been through now I actually had the patch on and she said go on smoke as normal and then like the first week I was going oo I can't she said no you must ¶69: INT: Yeah ¶70: PAR 3: Yeah it's good PAR 3: when they told me look here's the patches the highest one but carry on smoking the same amount and I was absolutely shocked with that I was shocked
		Previous positivity		
	Effects			
		Lost enjoyment		PAR 3: after about a week an half I did say to the lady on this stop smoking clinic place I can't remember her name sorry I did say well cos she told me to smoke as nor as normal the amount and I told her I said I've got to tell you the truth I can't smoke that much ¶87: INT: Yeah yeah ¶88: PAR 3: I can't it's not very nice I gotta sore throat, it smells and ya know all the things what smoking is ¶116: PAR 3: I did enjoy the in the first when you first go on the course they tell you to smoke as normal and they the first week I did I said to the lady I really really don't enjoy smoking no more but I didn't get to the quit date then I had another week to go
		Nausea		10: PAR 3: I was quite surprised at that but I didn't smoke as many because I just didn't like the, I don't know, it give me leg ache and nausea and stuff smoking with the patches on.
		No effect		

	Mechanism			
		Aversion		¶35: INT: do you think there was any particular good points to the abrupt quitting method that you used ¶36: PAR 3: well the only good thing is like I should imagine is cos I was kept on smoking with the patches on, it got me to a state that I really do dislike cigarettes you know whereas I tried before and like you know first smell of a cigarette you're tempted you're tempted you're very temptable with smoking and the patches on I felt not very nice
		Craving reduction		
	Non-compliance			
	NRT issues			PAR 3: I just didn't like the, I don't know it give me leg ache and nausea and stuff smoking with the patches on.
	Shorten preloading			¶116: PAR 3: as I said I did enjoy when you first go on the course they tell you to smoke as normal and they the first week I did I said to the lady I really really don't enjoy smoking no more but I didn't get to the quit date then I had another week to go ¶117: INT: Right yeah ¶118: PAR 3: To carry on smoking I really didn't want to do it I said you know I'll try and I she said to me I really do want you to smoke as normal but if you can't you can't and I really couldn't I was smoking but it was one or two a day ¶119: INT: Yeah ¶120: PAR 3: and I was thinking to myself what's the point ¶121: INT: Yeah ¶122: PAR 3: ya know I would have liked it to be a shorter period of time from when I first seen her to the quit date ¶123: INT: Right okay yeah ¶124: PAR 3: it went on a bit long ¶125: INT: So do you think it would you say it's an important part of the method to have that experience ¶126: PAR 3: Oh I think so yes yeah but not as long as I say because you know I was telling the truth actually trying smoking that many it's not very nice. I smell, you know, I smell and everything ((inaudible)) I won't tell anyone but bear it in mind that
Quit day feelings				
	Less confident over pre-quit			
	More confident over pre-quit			59: INT: would you say that during the few weeks between when you went to your first appointment and when you went on your quit day did you feel that there were any changes in the way that you felt about quitting ¶60: PAR 3: yes I was more stronger to quit because it wasn't very nice
	Negative feelings on day			
	No change over pre-quit			
	Positive feelings on day			¶25: INT: How easy did you find the instructions to stick to did you find it easy to quit on the quit day or quite difficult ¶26: PAR 3: No I was praying for the quit day to tell you the truth because I didn't like I didn't enjoy smoking with the patches on ¶57: INT: how did you feel when you reached your quit day did you say that you felt.. ¶58: PAR 3: Oh I was glad to quit very glad for it yes yes
Reason for reduction choice				
	Easy cigarettes first			
	Fits around job			
	Harder times first			
	Sounded easiest			

Schedules				
	Awareness needed			
	Clear boundaries			
	Difficulty understanding			
	'Nuisance'			
	Suggestions			
		Chart in each room		
		Clarify sfps		
		List and carry sfps		
		Note and tick times		
		Tick sfps and count		
Suggested changes				
	Baseline period			
	Choice wanted			
	Hr-scenarios not cigarettes			
	Immediate quit			
	Longer reduction			
	Sfp- cpd limit			
	Simplify			

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