NETSCC, HTA

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A Randomised Controlled Trial of Self-help Materials for the Prevention of Smoking Relapse

(Protocol)

1. Research objectives

This proposed trial aims to evaluate the effectiveness and cost-effectiveness of a set of self-help educational materials for the prevention of smoking relapse in the NHS Stop Smoking Service.

NHS Stop Smoking services are effective to help smokers stop smoking. However, smoking relapse is common among short-term quitters. No specific interventions for relapse prevention have been recommended in the current smoking cessation guidelines. Evidence from trials in other countries indicated that self-help educational materials specially designed for relapse prevention may reduce smoking relapse in those who were able to quit for at least one week. The objective of the proposed trial is to investigate the effectiveness and cost-effectiveness of self-help materials for the prevention of smoking relapse in 4-week quitters who have used NHS Stop Smoking Services. By the end of the proposed trial, we will know whether short-term quitters who have used self-help material (Forever Free booklets) for relapse prevention have a lower rate of smoking relapse at 12 months, as compared with short-term quitters in the control group.

2. Existing research/background

Behavioural support and pharmacotherapy are effective to help smokers who are motivated to quit for smoking cessation to do so.[2-6] However, relapse rates following these interventions are high.[7] According to data from English Stop Smoking services, about 50% of smokers who set a quit date stopped smoking at 4 weeks,[8] but 75% of the 4-week quitters go back to regular smoking between 4 and 52 weeks.[9] The long-term success rates still make these interventions highly cost-effective a life-saving intervention but there is a need to find effective interventions to reduce relapse rates after the initial treatment episode. A Cochrane systematic review of trials of interventions for smoking relapse prevention[10 11] concluded that "there is insufficient evidence to support the use of any specific intervention for helping smokers who have successfully quit for a short time to avoid relapse".[10] Therefore, the current smoking cessation guidelines do not recommend any specific interventions for smoking relapse prevention.[12 13] A survey of Stop Smoking

professionals found that the uncertain evidence base about effectiveness was an important barrier to the use of relapse prevention interventions.[14]

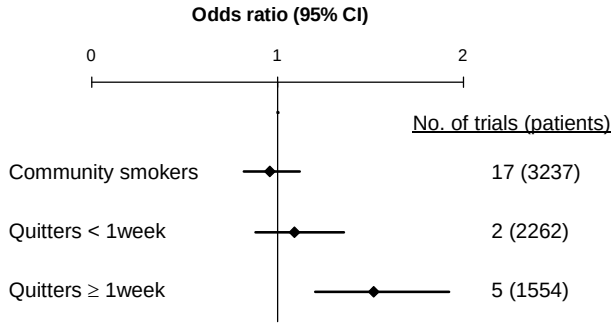
2.1 Findings from an exploratory meta-analysis

Psycho-educational interventions for smoking relapse prevention are complex healthcare interventions that usually contain several interacting components and involve changes of people's behaviours.[15 16] The new MRC guidance on development and evaluation of complex interventions in health stresses that 'a good theoretical understanding is needed of how the intervention causes change'.[16] Pawson et al recommended a method of "realist review", which emphasises the explicit consideration of theories underlying complex interventions.[17] We recently conducted a theory-guided research synthesis of 49 trials on psycho-educational interventions for smoking relapse prevention in an updated systematic review.[1 18] Most interventions in the trials included were at least partly based on the cognitive-behavioural approach to coping skills training.[19]

With coping skills training, participants are trained to identify situations with high risks of smoking relapse (such as going out with friends or feeling frustrated), and to develop and practice skills to cope with such situations. Therefore, the effectiveness of coping skills training for relapse prevention will depend on (1) the delivery and receipt of interventions, (2) the acquirement of coping skills by quitters, and (3) the use of such skills in high risk situations. This delineation of the mechanisms whereby coping skills training interventions work suggests that the following mediating process are likely to be important: acquisition of skills to identify and cope with high-risk situations, and the actual use of coping skills when required. However, only a few trials have reported on these processes.[1] For example, only two trials reported the actual use of coping skills by participants. They showed that those participants in skills training and abstainers may be more likely to have used their newly acquired coping skills than those who relapsed.[20 21]

The effectiveness of coping skills training differs between population subgroups. Our meta-analysis found that coping skills training for smoking relapse prevention was ineffective for pregnant or postpartum quitters, hospitalised ex-smokers, forced short-term quitters, and smokers with mental health illnesses or drug abusers. For community volunteers, coping skills training interventions were not effective for current smokers who were motivated to quit (OR=0.96, 95% CI 0.82 to 1.12) or for those who had quitted smoking for less than one week (OR=1.09, 95% CI 0.88 to 1.36).[1] However, coping skills training interventions significantly reduced smoking relapse in community quitters who, at baseline, had been able to quit for at least one week at baseline (OR=1.44, 95% CI 1.14 to 1.81) (see Figure below). (Note: results here for community ≥1 wk quitters is slightly different from that reported in the meta-analysis paper, due to the use of a more conservative method for data analysis in a trial [26])

Results of meta-analysis of trials of coping skills training in community volunteers, according to smoking status or length of abstinence at baseline



These findings show that the timing of relapse prevention is important and that coping skills training seems effective in secured quitters who are highly motivated to remain abstinent. Clearly, the acquisition of coping skills alone is not sufficient, and only those who use these skills really benefit.[22] This evidence can be interpreted in terms of the theoretical mechanisms of coping skills training for relapse prevention.

Furthermore, interventions of using self-help materials seem as effective as interventions based on individual or group counselling. Five trials of coping skills training in community quitters who stopped smoking for at least one week were further separated into two subgroups: trials of self-help material and trials of counselling. The pooled odds ratio of coping skills training is 1.46 (95% CI: 1.05 to 2.05) for self-help material trials, and 1.41 (95% CI: 1.02 to 1.94) for counselling trials.[1]

2.2 Important public health implications

About 50% of smokers who used NHS stop smoking services are abstinent at 4 weeks but this declined to 12.5% at 12 months without relapse prevention. The coping skills training for quitters at 4 weeks may reduce the relapse rate in 12 months from 75% to 67.6% (based on an odds ratio of 1.44). That is, for every 1000 smokers who used the NHS Stop Smoking Service, there will be on average 37 more long-term quitters by providing coping skills training for 500 short-term quitters. It can be estimated that the number of 4-week quitters needed to treat (NNT) for one additional long-term quitter is 14.

Over one year, from April 2008 to March 2009, of 671,259 smokers who used NHS Stop Smoking Services (at all settings) in England, 337,054 successfully quit at 4 weeks.[23] However 75% of these short-term quitters will relapse and only 25% (n=84,263) remained smoke free at 12 months. The trial evidence suggests that coping skills training for smoking relapse prevention could increase the number of quitters at 12 months by a third, from 84,263 to 109,205, and would result in 24,942 additional long-term quitters per year in England. According to a previous cost-effectiveness analysis, 3.59 life-years would be saved on average by one life-long quitter.[24] Assuming that only 25% of the 24,942 quitters at 12 months never

smoked again, 22,385 life-years would be saved by providing smoking relapse prevention interventions to 337,054 short-term quitters, a number needed to treat of just 15 per life year gained. In addition, the self-help educational material for smoking relapse prevention may be a cost-saving intervention by reducing repeat use of NHS Stop Smoking services, and by reducing use of healthcare services for smoking related illness. The prevention of smoking relapse in 4-week quitters will contribute greatly to a reduction in adult smoking rates from 21% in 2008 to 10% or less by 2020, a target set out in the new Tobacco Control Strategy for England.[25]

2.3 Forever free booklets

Self-guided educational materials for skills training seem as effective as, but cheaper than, more expensive face-to-face counselling sessions, and so seem likely to be highly cost-effective. Brandon et al have developed a series of 8 booklets to be used as self-help materials for smoking relapse prevention.[26 27] Forever free booklets for smoking relapse prevention have been evaluated by Brandon et al in two randomised controlled trials in the United States.[26 27] Unaided quitters from the community were recruited by advertisement and public announcement. It was found that participants who received all 8 booklets had a lower rate of smoking relapse than participants who received only a single booklet (the introduction booklet). The odds ratio of abstinence was 1.53 (95% CI 0.81 to 2.89) and 1.44 (95% CI: 0.97 to 2.13) respectively in the two trials. The more recent trial suggested that repeated mailing (high contact) was no more effective than massed mailing (low contact) of the 8 booklets.[27] Brandon et al suggested that their two studies may have under-estimated the true effectiveness of Forever Free booklets, because participants in the control group received the introduction booklet that provided a summary of all relevant skills. The use of the Forever Free booklets for smoking relapse prevention was found to be highly cost-effective (US $83 - $160 per QALY gained).[27]

2.4 Further research required

Existing trials on coping skills training for smoking relapse prevention in community quitters were mostly conducted in the United States, and recruited participants mainly by advertisement in newspapers. It is uncertain whether the results of our meta-analysis[1] and individual trials by Brandon et al[26 27] are generalisable to 4-week quitters who used the NHS stop smoking services. Therefore, we propose a randomised controlled trial to evaluate the effectiveness and cost-effectiveness of self-help materials (Forever Free booklets) for the prevention of smoking relapse in 4-week quitters who have used NHS stop smoking services.

3. Research methods

3.1 Design

The proposed study design is a randomised controlled trial, to evaluate the effectiveness of self-help educational material (Forever Free booklets) for the prevention of smoking relapse, compared to a smoking cessation booklet used currently. Appendix 1 shows the **flow diagram** for the proposed trial.

3.2 Setting

We will recruit 4-week quitters in NHS Stop Smoking clinics. The investigated self-help educational material will be sent to trial participants for their use at home. At the final follow-up (12 months), we will invite those who are still not smoking to have a breath carbon monoxide (CO) test to confirm the self reported status of non-smoking. The test will be carried out by a researcher from UEA. People may come to a clinic at UEA or we can visit them at home for this test.

3.3 Participant recruitment and randomisation

Current smokers are referred to the NHS Stop Smoking Clinics from various sources (eg, GP, self-referral, etc). Clients who contact the Stop Smoking Service are given an appointment for assessment with a Stop Smoking advisor, either individually or in group sessions. Following assessment, the client typically receives weekly behavioural support, focused on withdrawal orientated therapy, with medication to reduce craving and withdrawal. The total contact time for each client is at least 1.5 hours from pre-quit preparation to four weeks after quitting. About 50% of clients who set a quit date are successful at 4 weeks but most (75%) of them relapse by 12 months.[9] Interventions for smoking relapse or maintenance of abstinence are not provided, although Stop Smoking services will support renewed quit attempts for relapsed smokers.

The target population of the proposed trial is 4-week quitters treated in the NHS Stop Smoking clinics. Stop smoking advisors will give an invitation letter containing information on the relapse prevention trial (Appendix 2) to all expected quitters at week 2 or 3 following the quit date. At the final follow-up session (4 week post-quit) in the Stop Smoking clinic, the advisor will again explain the nature of the trial, to CO-verified quitters only, answer questions from them, and invite them to participate in the trial by signing the consent form (Appendix 3). Clients who have failed to quit are not part of the study and will not be included.

After eligible quitters have signed the consent form, stop smoking advisors will complete the baseline questionnaire and send it to the trial coordinator at UEA. The trial coordinator will randomly allocate participants to two groups (the control group and the relapse prevention group), and send them the corresponding self-help material by post. Quitters in the control group will receive a letter and the currently used booklet about smoking cessation, Stop Smoking Start Living (if the quitter has not had one). Quitters in

the intervention group will receive a letter and all 8 Forever Free booklets (please see section **Planned interventions** for more details on these booklets).

The random allocation of participants into the two arms will be carried out by using a computerised allocation system provided by the Norwich Clinical Research and Trial Unit (CRTU). This allocation of trial participants is 'concealed' because the recruitment of quitters occurs before the random allocation.

This will be an open trial, without attempts to blind investigators and patients after randomisation. Because the outcome assessor and trial participants know the allocated intervention, bias may be introduced in results. However, evidence suggested that the risk of bias may be much reduced in trials with objectively assessed outcomes.[28] In this proposed trial, the primary outcome will be biochemically verified abstinence at 12 months, which can be considered as an objectively assessed outcome.

It is necessary to avoid possible information contamination across the trial arms and "non-independence" between members of the same family. We will include only one member from the same family in the analysis. Where couples of the same family are recruited at the same time, we will randomly select only one of them into the trial. If the members of the same family use the NHS Stop Smoking Service at different times during the trial recruitment period, we will include only the first family member. To carry out exploratory analysis, we will record information on whether there are other family members who are excluded for this reason.

We will prevent the multiple entries of the same people who make repeat attempts to quit during the trial period. Before recruiting a new short-term quitter, Stop Smoking advisors will check whether the quitter has already been included in the trial. In addition, the trial coordinator will also check to make sure no multiple entries by same quitters.

4. Planned interventions

The experimental intervention tested in the proposed trial is the full pack of 8 Forever Free booklets. Findings from an exploratory meta-analysis suggested that coping skills training may be effective for smoking relapse prevention in motivated quitters.[1] Results of two clinical trials in the United States suggested that a cheap intervention using Forever Free booklets developed by Brandon et al[26 27] may be as effective as more expensive counselling for coping skills training. Forever Free booklets include a series of 8 booklets. Booklet 1 (with 17 pages) is a brief summary of all relevant issues, including an introduction of nicotine dependence, the stages of smoking cessation, situations that are high risk for relapse, ways of coping with urges to smoke, the abstinence violation effect, and ways to handle an initial slip.[27] The remaining 7 booklets provide more extensive information on important issues for relapse prevention, entitled *Smoking Urges; Smoking and Weight; What if You Have a Cigarette?; Your Health; Smoking, Stress, and Mood; Lifestyle Balance;* and *Life Without Cigarettes*.[27] The booklets can be understood by

people with a reading level of 5th to 6th grade in the United States (expected reading level for children of 10-12 years old).

The original Forever Free Booklets are prepared for users in the United States. We will revise and update the booklets in places where judged necessary or helpful, to make the material more suitable to British users and the UK NHS (Anglicisation). We have obtained permission from the copyright holders (H. Lee Moffitt Cancer Center and Research Institute, Tampa, FL), and obtained price quotations for revision and printing of the revised booklets. Members of the trial steering committee, project team, and three lay representatives will review and comment on the revised booklets.

During their Anglicisation, we will ensure the acceptability/understanding of the booklets to as wide a range of users as possible. For the proposed trial, the revised booklets will be available in English language only because of considerable cost implications to translate the booklets to other languages. If proved effective, the booklets can be translated into other languages or different media formats (for example, DVD video) for people who have difficulty in English reading. Currently over 90% of users of stop smoking services in Norfolk are White British. For participant recruitment, stop smoking advisors will find out whether English is the first language for a client, and if not, whether the client is able to read and understand English.

After randomisation, we will send a letter and the full pack of 8 revised Forever Free booklets to participants in the intervention group, and a smoking cessation booklet (Stop Smoking Start Living) to participants in the control group. Stop Smoking Start Living booklet focuses on smoking cessation, which may be considered as a 'no-relapse-prevention' control.

5. Planned inclusion/exclusion criteria

The target population of the proposed trial is 4-week quitters treated in the NHS Stop Smoking clinics. The biochemically verified 4-week quitter is defined as a treated smoker who self-report continuous abstinence from day 14 post-quit date to the 4-week follow-up point (or within 25 to 42 days of the quit date) and who blows an exhaled carbon monoxide (CO) reading of less than 10ppm.[29] The inclusion and exclusion criteria are described below.

5.1 Inclusion criteria:

- CO-verified quitters at 4 weeks in the NHS stop smoking clinic who can read English and sign the consent form to participate in the trial.

5.2 Exclusion criteria:

- Pregnant quitters will be excluded. According to the available research evidence,[1] smoking relapse prevention intervention by coping skills training is ineffective for women who have stopped smoking during pregnancy.
- We will exclude quitters who are not able to read the educational material in English, because the revised booklets are currently available in English language only.
- Quitters from families in which one member has already been included in the trial.

6. Ethical arrangements

Tobacco smoking caused more than 80,000 premature deaths in England in 2008.[25] The self-help educational booklets for the prevention of smoking relapse investigated by the proposed research have important public health implications. If their effectiveness is proven, the prevention of smoking relapse could result in about 25,000 additional long-term quitters (which could be translated into about 22,000 life-years saved) each year in England. The prevention of smoking relapse in 4-week quitters may contribute greatly to a reduction in adult smoking rates to 10% or less by 2020, a target set out in the Tobacco Control Strategy for England.[25]

The trial proposal has been peer reviewed by six independent reviewers selected by the HTA programme, and by members of the NIHR HTACET board. The proposal has been satisfactorily revised according to comments from peer reviewers and the HTACET board. The trial team consists of investigators with essential multidisciplinary skills and experience, and is well placed to carry out the proposed research.

No adverse effects or harm on target population or society could be expected from the intervention.

We will provide sufficient information for 4-week quitters to consider whether they would like to participate in the trial, and recruit only those who sign the consent form. We will not use patient information from any existing databases. Data on individual participants will remain strictly confidential, and only researchers directly involved in the trial will have access to original data. The study protocol will be submitted to an NHS Research Ethics Committee for approval.

Completed questionnaires will be kept in the locked cabinet at the University of East Anglia. Electronic database with personal data (name, sex, age, address, telephone number) will be stored in University password protected computer system (managed by the Norwich Clinical Research and Trial Unit).

Data on individual participants will remain strictly confidential. Only investigators within the trial team will have access to the original data. For data analysis, we will use participant code to replace personal details (name, address, telephone number). Trial coordinator at UEA will need to access participants' name,

telephone number and home address to conduct follow up telephone interviews. Only researchers directly involved in the trial will have access to participants' personal data during the study.

7. Proposed sample size

The abstinence rate of 4-week quitters at 12 months is estimated to be 25.0% in the control and 32.4% in the intervention group (based on an odds ratio of 1.44). Assuming alpha=0.05 and 1-beta=0.8, and a dropout rate of 15%, about 1,400 patients will be required in total (700 in each arm).[30]

During April 2008 and March 2009, the number of successful short-term quitters in Norfolk was 1,986 from Stop Smoking clinics and 1,867 from primary care settings (Jacqueline Bryony, Norfolk Stop Smoking Service Manager, personal communication). The Norfolk Stop Smoking clinics currently have 12 core professional advisors (8 FTE) and three non-professional advisors, while other providers in primary care setting are diverse and widely dispersed. To simplify the project management, we will recruit participants mainly from the core Stop Smoking clinics. The number of CO-verified 4-week quitters from the core service was 1774 in year 2008/9. Based on an estimate that the proportion of quitters from the same family is 12% (personal communication, Dr Paul Aveyard), we will be able to recruit enough participants even if only 48% of the eligible 4-week quitters agree to participate over 21 months. All professional advisors in the Norfolk Stop Smoking clinics will be invited to a meeting before the start of the trial to discuss issues related to the recruitment of short-term quitters.

8. Baseline and follow up data collection

At the 4-week session following the quit date, Stop Smoking advisors will gather baseline information from participants who have consented to be in the trial. The information collected includes participants' demographic characteristics (e.g., age, gender, and occupation), heaviness of smoking index (i.e., shortened version of the FTND), smoking and quitting history, and level of confidence to remain abstinent (Appendix 4).

The consensus statement of the Society for Research on Nicotine and Tobacco (SRNT) and the Russell Standard both suggest that prolonged abstinence should be the primary outcome of a smoking cessation trial.[31 32] There are several reasons especially relevant here: (1) Smokers may try to stop, fail, and try again within 12 months. Abstinent smokers at 12 months will therefore be a mixture of recent quitters whose relapse was not prevented by the relapse prevention intervention and those whose relapse were. The recent quitters will be random with respect to arm, but this adds noise to the analysis and reduces the chance of detecting an effect. (2) The true outcome from smoking cessation studies is lifetime abstinence, the only

outcome we know with beneficial effects on health. A mixture of recent quitters and one year quitters means that it is impossible to model relapse from 12 months through lifetime and thus impossible to calculate life years gained or QALYs. The consensus statement of the SRNT and the Russell Standard suggest that biochemical verification is necessary in clinic treated patients. These participants have promised an advisor that they will not smoke and feel guilty about having done so. Consequently, we will use prolonged abstinence confirmed by carbon monoxide as our primary outcome measure.

The normal form of prolonged abstinence allows a two week grace period in which lapses do not invalidate abstinence following quit day to assess the outcome of aid to cessation trials. However, a relapse prevention intervention might reasonably prevent lapses (occasional smoking) becoming relapses (fulltime smoking and abandonment of the quit). Therefore we propose a two-month grace period during which lapses to smoking do not count against achieving abstinence. As participants will be four weeks abstinent on enrolment, this equates to the primary outcome being prolonged abstinence from three months after quit day to 12 months follow up. Following the Russell Standard, **the primary outcome** will be prolonged abstinence from months 4-12 with no more than 5 lapses, confirmed by CO<10ppm at 12 month assessment. Participants who decline biochemical verification or who do not respond to follow up will be counted as smokers, but those who have died or genuinely moved away will be disregarded from the numerator and denominator.

The **secondary outcomes** will be point 7-day self-report point prevalence abstinence at 3 months and 7-day biochemically confirmed point prevalence abstinence at 12 months.

For cost-effectiveness analysis (with a health service perspective), we will collect data on resources required for self-help materials (including intellectual property, adaptation, printing, postage) and repeated use of stop smoking services. We will monitor the resource use of other cessation products at the follow-up interviews (Appendix 5). Our hypothesis is that the intervention, if effective, will improve abstinence rates, reduce repeated use of stop smoking services and might reduce use of other health care. Other resources which might be affected by the intervention will also be monitored e.g. pharmacotherapy medications, any related counselling or GP visits. We will measure utility using the EuroQol EQ-5D, as part of the follow-up interviews.

At 2 months after enrolment (3 months after quit day) a researcher from UEA will telephone participants primarily to assess process measures i.e. receipt, liking of, and use of the manuals (in the intervention group), and to assess key skills the manuals try to teach (in both intervention and control groups). This is important, particularly if the intervention is ineffective because it will help us to explain whether the intervention was used but people did not acquire the skills, or whether applying the skills was ineffective in preventing relapse (Appendix 5). This early follow-up contact is important, considering the high risk of relapse during the first few months.

The second and final follow up telephone call (conducted by a researcher from UEA) will take place at 11 months after enrolment (12 months after quit day), primarily to assess the primary and secondary outcomes, although we will once again test for skills acquired. Participants who meet the self-report criteria for at least 7-day abstinence will be invited to attend a local centre to prove this by exhaled CO. These participants will be compensated with £20 for their time and travel expenses. The test will be carried out by a researcher from UEA. People may come to a clinic at UEA or we can visit them at home for this test.

To minimise loss of follow-up, we will include the alternative contact telephone for each trial participants, and ask the most appropriate time for the telephone contact. If necessary, we will make multiple attempts to contact trial participants. We will send the follow-up questionnaire (Appendix 5) with a freepost return envelope by post to those with whom we are not able to contact by telephone at 12 months.

9. Data analysis plan

We will develop a trial database to maintain data from baseline and follow-up questionnaires. Data analyses will be conducted using STATA software. The comparison of smoking abstinence rates (and any other binary outcomes) between the two trial arms will be carried out using odds ratio (and 95% confidence intervals) as the outcome statistic and other related statistical tests.

Exploratory subgroup analyses, including logistic regression analyses with interaction terms, will be conducted to investigate possible effect modifying variables, including age, gender, socio-economic status, level of nicotine dependence, number of prior quit attempts, and use of pharmacological interventions. These exploratory analyses have low statistical power and are also likely to yield false positive findings so the results will need to be interpreted with great caution.

The analysis of mediating variables aims to examine hypothesized mechanisms of the intervention. The intervention using the Forever free booklets is based on the cognitive-behavioural approach to coping skills training. The effectiveness of coping skills training for relapse prevention depends on (1) the adequate delivery and receipt of the booklets, (2) the acquisition of coping skills by quitters, and (3) the application of such skills in high-risk situations. This intervention mechanism suggests certain important process variables that should be investigated in the trial. At the follow-up interviews (see draft questionnaire Appendix 5 in the proposal), we will at first ask trial participants whether they have received the booklets, whether they have read the booklets (and how much time spent, and how many booklets looked at). We will then investigate whether the use of booklets helped the acquisition of coping skills by the participants, in terms of improved capability to identify risky situations and to know more appropriate ways of handling urges to smoke again. Thirdly, we will ask the trial participants whether they have actually applied the skills learnt from the booklets. Finally, we will invite the trial participants to give an overall assessment of the usefulness

of the booklets. We will summarise data collected in tables and plots to examine associations between smoking abstinence and important mediating variables (e.g., level of the use of booklets, actual application of coping skills in high-risk situations). We will also use more complex methods for the exploratory mediation analysis according to MacKinnon and Fairchild.[35] As an example, the Single-Mediator model consists of three equations:

$$(1)\ Y = i1 + c\,X + e1; \quad (2)\ Y = i2 + c'\,X + b\,M + e2; \quad (3)\ M = i3 + a\,X + e3;$$

where Y is the dependent variable (smoking relapse), X is the independent variable (the intervention), and M is the mediating variable (e.g., time spent on reading the booklets, acquisition of coping skills, etc). Then the mediating effect of M could be quantified by a*b (or c'-c). These exploratory mediation analyses will help understand how and why the intervention works or does not work.

Using data on time to the first event of smoking relapse, survival curves of the intervention and control arm will be compared by using Cox regression analysis as secondary analyses. This might reveal patterns indicating relapse is postponed, which could suggest that 'top up interventions' might be helpful.

Using data from the trial and published literature, we will calculate the mean incremental cost for those in the intervention arm (8 forever free booklets), compared to the control arm. Similarly, the incremental effect of the intervention will be equivalent to the difference in the 12 month quit rate between the two arms. Together, the incremental cost and incremental effect will be used to calculate the cost required to have one more long-term quitter with the provision of the Forever Free booklets. The cost-effectiveness analysis will be based on individual level costs and outcome data, with uncertainty expressed as cost effectiveness acceptability curves and if appropriate, confidence intervals for the incremental cost effectiveness ratio. As part of a cost-utility analysis, the incremental QALY gain associated with the intervention will be estimated, based on EQ-5D data collected in the trial and findings from existing studies of relevant economic evaluations.[24 33 34]

10. Project management

A Trial Steering Committee will be established to provide overall supervision for the study on behalf of the NIHR HTA programme. The Trial Steering Committee (TSC) will include two independent experts (nominated names and confirmation required: Dr Andy McEwen, UCL and NHS Centre for Smoking Cessation and Training and Dr Florian Vogt, Kings College London), Clive Slater (NHS Norfolk SSS Commissioning Manager), Debbie Kelly (Community Research Facilitator, Norfolk Community Health and Care NHS Trust), Judy Henwood (Research Facilitator, NHS Norfolk), and Mrs Roberta Aldred (service user, ex-smoker).

The trial will be overseen by a trial management group (TMG), based at UEA, which will meet weekly to monitor and manage the trial. This will consist of the trial coordinator/RA, Fujian Song, Richard Holland and include the secretary. TMG will review an ongoing CONSORT statement (including data on recruitment, intervention and follow-up).

No adverse effects are associated with the educational booklets for smoking relapse prevention. This trial poses no risks to participants and there would be no cause to propose stopping rules for premature closure of the trials. In addition, this trial is open, un-blinded. After a discussion with the NIHR HTA programme, we decide not to have a separate Data Monitoring Committee (DMC). Data monitoring will be carried out by study team members (TMG) and be synchronized with Trial Steering Committee meetings.

Every six months, there will be a full meeting of the team including the members not based in UEA (4 team meetings will be teleconference). The meeting will be arranged according to the project milestones (please see details below). The team will provide a progress report to the trial steering group and NIHR NETSCC, detailing recruitment, intervention provision, follow-up and financial situation. In between these six monthly meetings the investigators will keep in touch by email and work on documents as required.

11. Project timetable and milestones

The proposed trial will last 36 months, including the revising and printing of relapse prevention booklets, patient recruitment, delivery of interventions, follow-up data collection, data analysis, and writing up report and papers (see Figure below). The proposed trial start date is 1st June 2011. We will need two months to revise and print the Forever Free booklets, and to arrange trainings for Stop Smoking advisors who will be involved in the recruitment of 4-week quitters. The recruitment of trial participants will start from August 2011 and last for 21 months until April 2013. This arrangement will cover the **high quitting season** (January and February) in both 2012 and 2013.

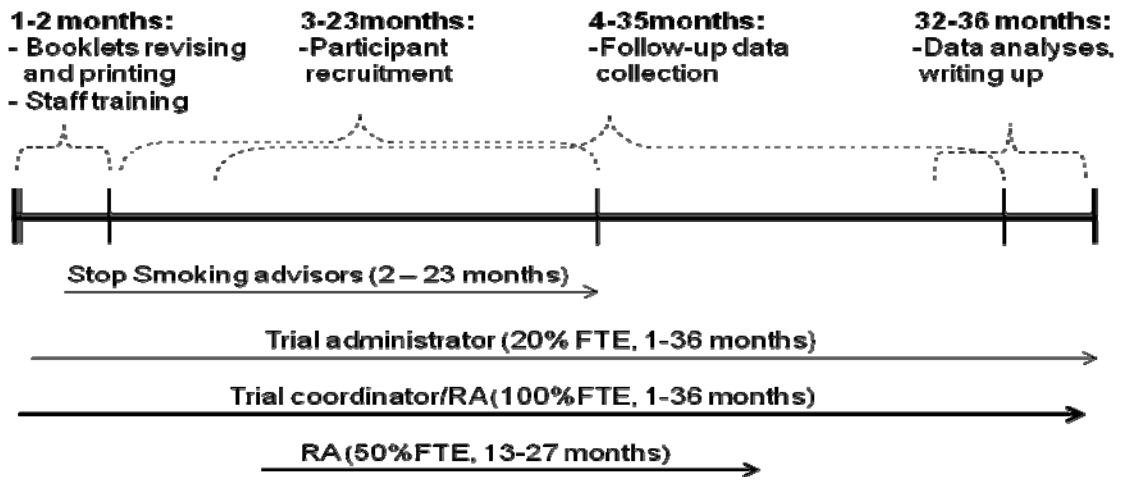


Table below shows major milestones in terms of participant recruitment, follow-up interviews at 3 and 12 months. We can see that the workload will be heavy between August 2012 and July 2013, because of the simultaneous tasks for both 3 and 12 month telephone interviews. Therefore, a half time RA will be employed for 15 months to provide additional support.

Revised quitter recruitment timetable

Start date	End date	Tasks			Milestones
		Recruited	Followed up at 3mon	Followed up at 12mon	
01/06/2011	31/07/2011	**Booklets revising/printing, staff training**			Preparation
01/08/2011	31/10/2011	200	134		
01/11/2011	31/01/2012	**400**	**334**		31/01 2012
01/02/2012	30/04/2012	600	534		
01/05/2012	31/07/2012	800	734		31/07/2012
01/08/2012	31/10/2012	**1000**	**934**	**200**	
01/11/2012	31/01/2013	1200	1134	400	31/01/2013
01/02/2013	30/04/2013	1400	1334	600	
01/05/2013	31/07/2013		1400	800	31/07/2013
01/08/2013	31/10/2013			**1000**	
01/11/2013	31/01/2014			1200	31/01/2014
01/02/2014	30/04/2014			1400	
01/05/2014	**31/05/2014**	**Completing data analysis and report writing up**			Complete

12. Research team/expertise

Our team consists of investigators with essential multi-disciplinary skills and experience, and is well placed to carry out the proposed research. Fujian Song has experience in health technology assessment and research project management. He is the primary author of an exploratory meta-analysis of randomised trials on the prevention of smoking relapse.[1] Based on findings from this meta-analysis, the trial proposal is initiated.

The co-investigators have the requisite mix of research and professional expertise, including public health (Bachman, Holland, and Aveyard), psychology (Sutton, Brandon), primary care (Aveyard), and medical statistics (Leonardi-Bee). The team includes experts who have extensive experience in clinical or smoking cessation trials (Holland, Bachman, Aveyard, Sutton, and Brandon) and cost effectiveness analysis alongside randomised trials (Barton). Brandon is the principal investigator of previous and ongoing smoking relapse prevention trials in the United States who developed and tested the Forever Free booklets in the United States.

NHS Norfolk are very supportive to the proposed research. Norfolk Stop Smoking service Commissioning Manager (Jennifer Pusey), Service Manager (Jacqueline Bryony), and NHS Norfolk Tobacco Control Manager (Clive Slater) have actively contributed to the trial design, and agreed to facilitate the recruitment of 4-week quitters to the proposed trial. NHS Norfolk Public and Patient Involvement in Research (PPIRes) Coordinator (Jacqueline Romero) will support lay persons' involvement in the proposed research. NHS Norfolk research facilitator (Dr Judy Henwood) has contributed to the preparation of research summary and estimation of NHS cost.

Norwich Clinical Research and Trials Unit (Tony Dyer) will be involved in participant randomisation and project database development and maintenance. A number of ongoing trials in Norwich are going to end next year and we know two members of UEA staff (Viv Maskrey, and Annie Blyth) who would be suitable to fulfil the role of Trial Co-ordinator.

13. Service users

A lay person (Mr Brown, current smoker with previous quit attempt) has agreed to be involved. We will also include a female ex-smoker and a suitable person who has played a representative role on a user led charity or pressure group. In addition to the three users in the TSC, we will identify further service users to form a review panel to comment on revised Forever Free booklets. For the user involvement, we will ask advice from the NHS Norfolk PPIRes Coordinator Jacqueline Romero and Professor Linda Bauld (UKCTCS smokers' panel, University of Bath).

14. Justification of support required

14.1 New staff:

- A full time senior trial RA for 36 months to coordinate project activities, enter data from baseline questionnaire, conduct follow-up telephone interviews, and so on.
- A secretary (20% FTE) for 36 months to provide administrative support & arrange meetings.

- A half time junior RA to support follow up interview for 15 months starting from 01/06/2012.
-

14.2 Time by co-applicants

- Dr Fujian Song (Project PI and statistical analysis): 10% FTE 36 months
- Dr Richard Holland (trial expert & public health): 2.5% FTE 36 months
- Dr Garry Barton (health economist): 3% FTE 36 months
- Professor Max Bachman (trial expert and public health): 1% FTE 36 months
- Dr Paul Aveyard (smoking cessation trial expert, Uni of Birmingham) (1 hr/wk for 36 months
- Professor Stephen Sutton (psychologist, smoking cessation trial expert): 1% FTE 36 months
- Dr Jo Leonardi-Bee (medical statistician, University of Nottingham): 1% FTE 36 months
- A lay person for public involvement
-

14.3 Consulting co-investigator:

- Consultancy fees for Professor Thomas Brandon (psychology, smoking relapse prevention trial expert, authors of Forever free booklets. University of South Florida): 10 days in total.

14.4 Norwich Clinical Research and Trial Unit:

- Tony Dyer (Norwich CRTU Database Manager, UEA): To set up the trial database and randomisation system (5 days), plus a total of 36 hours over 3 years for the database maintenance.

14.5 NHS Norfolk collaborators:

- Jacqueline Bryony: Norfolk NHS Stop Smoking Service
- Jennifer Pusey: Commissioning Manager – Stop Smoking service, NHS Norfolk
- Jacqueline Romero, PPIRes Co-ordinator, R&D, NHS Norfolk
- Dr Judy Henwood: Research Facilitator, NHS Norfolk
- Dr Clive Slater: NHS Norfolk Tobacco Control Manager

14.6 Time by NHS Stop Smoking Advisors and other cost:

- Training provided to Norfolk Stop Smoking advisors for the recruitment of 4-week quitters and the completion of baseline questionnaire: 20 x 2 hour = 40 hours (total)

- 10 minutes per 4-week quitter on average to discuss the trial and invite 4-week quitters to participate: 3,400 x 10min = 34,000min = 570 hours
- Additional 5 min per 4-week quitter who agree to participate to complete the baseline questionnaire: 1,600 x 5min = 8,000min = 140 hours
- Cost for sending signed consent form and completed baseline questionnaires to the trial coordinator: £1.24 x 1,600 = £1,984.

14.7 Forever free booklets:

- Copyright fees: £1,800
- Revision of the booklets: £2,400
- Printing/banding of 800 sets of 8 revised booklets: £7,500.

14.8 Other:

- Participant invitation and trial information: 4 x 4,000 = 16,000 pages
- Postal cost for sending booklets to trial participants: £2 x 1,400 = £2,800
- Telephone calls for 6 and 12 months follow up: £2 x 2 x 1,400 = £5,600
- Postal cost for sending questionnaires to those unable to be contacted by telephone: £2 x 100 = £200.
- Carbon monoxide monitor and tubes (250 tubes/box): 2 x £150 + 2x £10 = £320
- Shopping vouchers for self-reported quitters who received CO-test at 12 mon: £20 x500 = £10,000
- Expenses for self-reported quitters at 12 months travel to the Norwich CRTU, and costs for trial staff travelling to some quitters' home for CO validation test: £10 X500 = £5,000
- Other: 6 whole team meetings; TSC and DMEC meetings, user involvement; computing; library service; staff training; conference; publication; ISRCTN.

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Appendix 1.

Flow Diagram – a trial of self-help material for smoking relapse prevention.