# Smoking cessation: population and clinical approaches

## Programme of work April 2007-March 2012

## Version 1: 25 January 2007

## a) Summary

The aim of the programme is to produce findings that increase the rate at which smokers are motivated to try to stop and succeed in doing so, with the ultimate goal of reducing the harm caused by tobacco use. There are three themes to the proposed programme which are linked to seven groups of studies. The themes are: 1) collecting timely and accurate information on the national smoking cessation picture, 2) improving understanding of the process of smoking cessation, and 3) developing and evaluating new interventions.

The seven groups of studies are:

1) *Smoking Toolkit Study (STS)* A rolling programme of household surveys and associated follow-ups to provide vital national statistics on rates of attempts to stop smoking, use of aids in those attempts, triggers of those attempts, 6-month continuous abstinence rates following those attempts and contextual information such as degree of cigarette addiction. This programme will also provide a basis for drawing panels of smokers to take part in more detailed studies on the process of stopping and piloting interventions to promote and aid cessation.

2) *Analysis of existing and ongoing data sets* Analyses will be undertaken from eight data sets examining a range of issues including effectiveness of nicotine nasal spray without behavioural support, patterning of quit attempts, success rates of quit attempts as a function of past quit attempts, and short- and medium-term changes in physical and mental health and healthcare utilisation after stopping smoking.

3) *The stop smoking clinic research network* We have developed a collaboration with a network of 11 high quality stop smoking clinics with a combined annual throughput of more than 7000 clients as a resource for establishing best practice in smoking cessation treatment. The focus here is on implementation issues which appear to play a major role in effectiveness and reach. Comparisons will be made, for example, between behavioural support programmes undertaken according to a range of different models (e.g. rolling groups, drop-in centres, nurse clinics) and involving a range of different providers (e.g. pharmacists, practice nurses, full-time specialists).

4) *Evaluation of the nicotine cannon* We have undertaken preliminary development work on a novel nicotine delivery device that offers the prospect of providing smokers wanting to stop with a means of obtaining relatively rapid nicotine intake in a form that is flexible and convenient. A series of studies is proposed to continue development of this device including a pharmacokinetic investigation and a study comparing the effect of this device versus other NRT products on ad lib smoking and on urges to smoke during abstinence.

5) *Evaluation of Tabex (cytisine) for smoking cessation* The National Prevention Research Initiative is funding the running costs of a placebo-controlled randomised trial of this medication which offers the promise of an extremely low-cost treatment that could be of benefit to millions of smokers that could not afford other medications. This application seeks funding for staff time to supervise the new trial and a collaborative programme of research whose running costs will be externally funded.

6) *The process of change studies* This is a series of studies involving an interview-based study, a postal survey with follow-up and a series of experimental studies to test hypotheses from the PRIME Theory of motivation, to develop and improve the theory and provide a better understanding of the process of behaviour change that can feed in the development of clinical and population-level interventions.

7) *Activating emotional processes to motivate smoking cessation* Funds are being sought externally for running costs of a trial to evaluate a promising intervention that involves exposing smokers to ultrasound images of their carotid arteries.

In addition to the research studies, a major component of the programme involves specific communication activities and policy development. This includes continued guideline development, advice and support to national and international agencies involved in tobacco control and smoking cessation and undertaking major systematic reviews.

## b) The research proposal

### b) 1. Background

The overall aim of the programme is to produce research findings that will contribute to a reduction in tobacco-related harm through smoking cessation, first and foremost in the UK but also worldwide. The choice of topics and methods is designed to: 1) capitalise on the strengths and experience of the research team including members who are currently funded for specific projects, 2) build research capacity for the future, 3) complement research that is already underway in the UK and overseas, 4) inform policy decisions, population level interventions and clinical practice over three timescales: the short term (within 5 years), medium term (5-10 years) and the long term (beyond 10 years), 5) be informed by, and contribute to, theoretical advances, 6) create synergy within the tobacco programme and within the Health Behaviour Research Centre as a whole

Cigarette smoking prevalence in the UK was officially estimated at 25% of adults in 2004 (1), and appears to be falling at a rate of approximately 0.4% per year (2). Although the Health Survey for England (HSE) in 2004 estimated prevalence at 23% (3), this differed from the General Household Survey (GHS) estimate given above and also from a large national survey we conducted in April-May 2005 which gave a figure identical to the HSE (4). We repeated this survey with 2000 adults in May 2006 and also obtained a prevalence estimate of 25% (unpublished data) which confirms that the decline in smoking prevalence is very slow. On current projections smoking will kill 90,000 people in the UK in 2006 falling to approximately 70,000 in 2020 when the decline will flatten off (5).

Some countries such as the US have achieved lower smoking prevalence figures than the UK but worldwide the problem appears to be growing with the current estimated death toll of 4.9 million premature deaths per year estimated to rise to 10 million per year by 2020 (6). Therefore, tobacco smoking presents a worldwide public health problem of massive proportions.

A reduction in prevalence in the UK of 1% per year for 10 years would probably prevent 69,000 premature deaths in the same period (7). This is a challenging but potentially reachable target. Other things being equal, to achieve a 1% reduction per year would require more than a doubling of the current rate at which smokers stop permanently from an estimated 2.5% (5) to more than 5%.

Smoking prevalence could also be reduced by reducing take-up of smoking (8). There is clearly a need for research into how to reduce the rate at which young people take up smoking (9) but the priority for the present programme is increasing the rate of smoking cessation. This is because that is where the main health gains in the next 40 years will be achieved and where we feel that the team can best complement the research already taking place internationally. There is also a need for research into the uptake, use and cessation of other tobacco products (e.g. smokeless tobacco) (10, 11), but for similar reasons as given above this is not a priority for this current programme.

Some subpopulations merit greater attention than others. Low income smokers deserve attention because they have greater difficulty in stopping smoking, smoke at a higher rate, experience more economic hardship because of smoking and have other risk factors that combine with smoking to cause death and disability (see 12). Some ethnic minority groups deserve special attention because of high rates of smoking and barriers to accessing information and services that would promote and aid cessation (3). Pregnant smokers are of particular concern because of the immediate damage to the fetus and the long-term effects on the offspring and the mother (13-15). Smokers with a smoking-related disease whose progression can be halted, such as chronic obstructive pulmonary disease, or are partly reversible such as atherosclerosis, have a more urgent need to stop than other smokers (see e.g. 16). Middle-aged smokers should also be a high priority because they have reached the point where continuing to smoke is leading to a rapidly escalating risk and stopping immediately can add the most number of healthy life years (17).

This programme, in addition to considering the smoking population as a whole, will focus on low-income smokers and smokers in middle age. There are three themes to the programme that are designed to meet the objectives set out on the previous page:
1. Providing key quantitative data at a national level on smoking cessation patterns with a view to providing essential information for the future development and targeting of national and international policies.

2. Obtaining a more detailed and accurate understanding of the process of stopping smoking to feed into the development of more effective population-level and clinical interventions.
3. Developing and evaluating improved clinical interventions.

### b) 1.1. Theme 1: The national smoking cessation picture

For any country, a national strategy to reduce smoking prevalence by increasing smoking cessation must be informed by reliable and up-to-date data on key indicators. Figure 1 maps out these indicators and the need for better information on them is outlined in subsequent paragraphs.

In Figure 1a) (i) refers to smoking prevalence at a given time point, T1, (ii) refers to the mean number of quit attempts per smoker over a subsequent period, e.g. 12 months, (iii) refers to the proportion of long-term (e.g. >6 month) successes per quit attempt made in that period, (iv) refers to the proportion of the smokers at T1 that achieve long-term abstinence as defined. In Figure 1b) individual rates are specified for quit attempts using different aids (v). Because a single quit attempt can use more than one aid, the rates are not mutually exclusive. This delineation of use of different aids is fundamental to monitoring tobacco control interventions because a key goal is to maximise the use of the most effective aids. It is also crucial to asses the success rates (vi) associated with use of these different aids to quantify their role in creating long-term ex-smokers. Figure 1c) goes one step further and attempts to delineate the specific triggers (vii) and how far they generate quit attempts involving different aids (viii). For example, how far GP advice triggers quit attempts that involve use of medications or the NHS Stop Smoking Services. Currently we do not have these critical pieces of information for the population as a whole or for priority subpopulations.

If accurate and up-to-date figures can be entered into such a model, it will be possible to monitor the effects of clinical, legislative and other interventions and to predict the effects of possible future interventions. The following paragraphs explain the inadequacies of the current data and the figures that the proposed research programme will seek to provide. Each paragraph is labelled according to the corresponding indicators (i to viii) in the figure.

**(i) Smoking prevalence**: By comparing self-reported smoking status with evidence of smoking using saliva cotinine concentrations, we have found that the headline figure for smoking prevalence probably underestimates the true figure in the UK by approximately 3% (18). This figure may seem small, but in the context of an aspiration to increase the current estimated 0.4% annual prevalence reduction to a 1% reduction its significance is clear. Given that smoking prevalence is the single most important target indicator of progress in tobacco control the accuracy of assessment of prevalence needs to be urgently addressed with an improved sustainable methodology. A possible approach is to examine the use of 12-month, 3-month and 1-month 'incidence' of tobacco smoking as the headline figure, with correction for misreporting based on saliva cotinine concentrations in a sample.

**(ii) Rates of attempts to stop smoking**: Our headline estimates of the rate at which smokers attempt to stop are based on retrospective reports from cross sectional surveys with relatively small samples and recall over a 12 month period, most notably the ONS omnibus surveys in October and November of each year (19). Data from the Smoking Toolkit Pilot (STP) have revealed that this methodology produces misleading estimates (4). Previous researchers have recognised that failed quit attempts are often forgotten (20). However, the STP shows that they are forgotten after as little as one week. Using a more sensitive methodology suggests that the patterning of quit attempts is very different from what had been thought with multiple quit attempts within a year being the norm for those that try to stop. This makes it necessary to examine both the proportion of smokers that make at least one quit attempt a year and the rate at which quit attempts are made.

*Figure b) 1.1.1: A population model of smoking cessation (see text for explanation)*

*a) Model for all quit attempts*
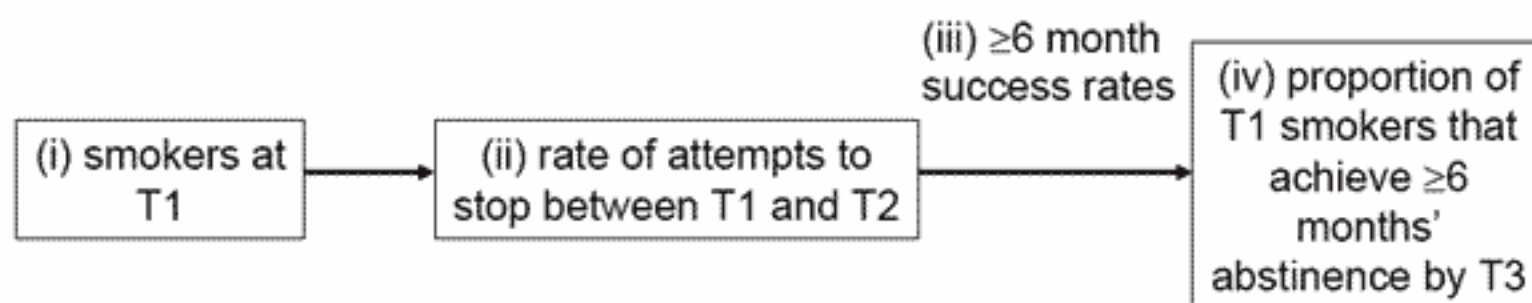


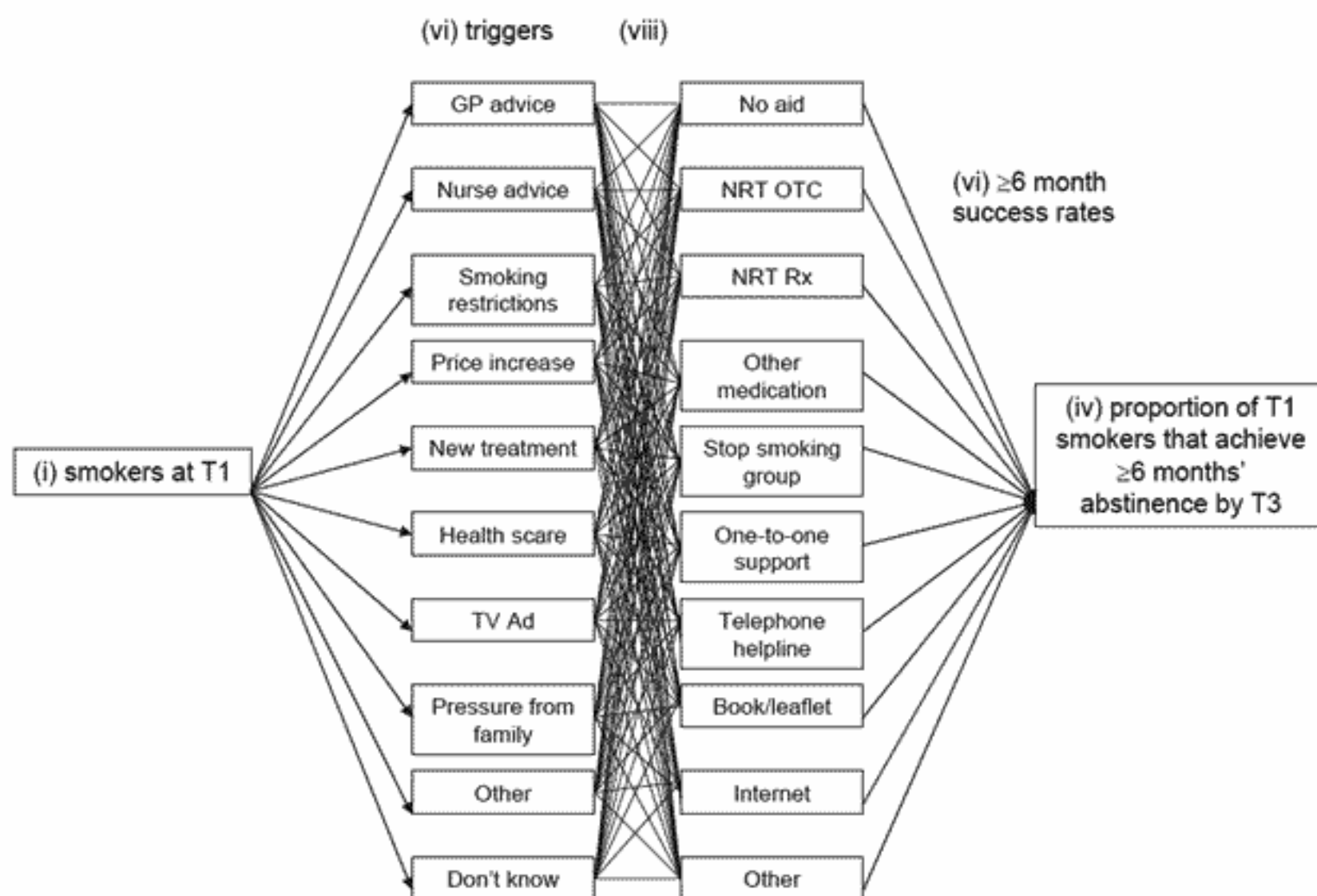*b) Model showing use of aids to quit attempts*
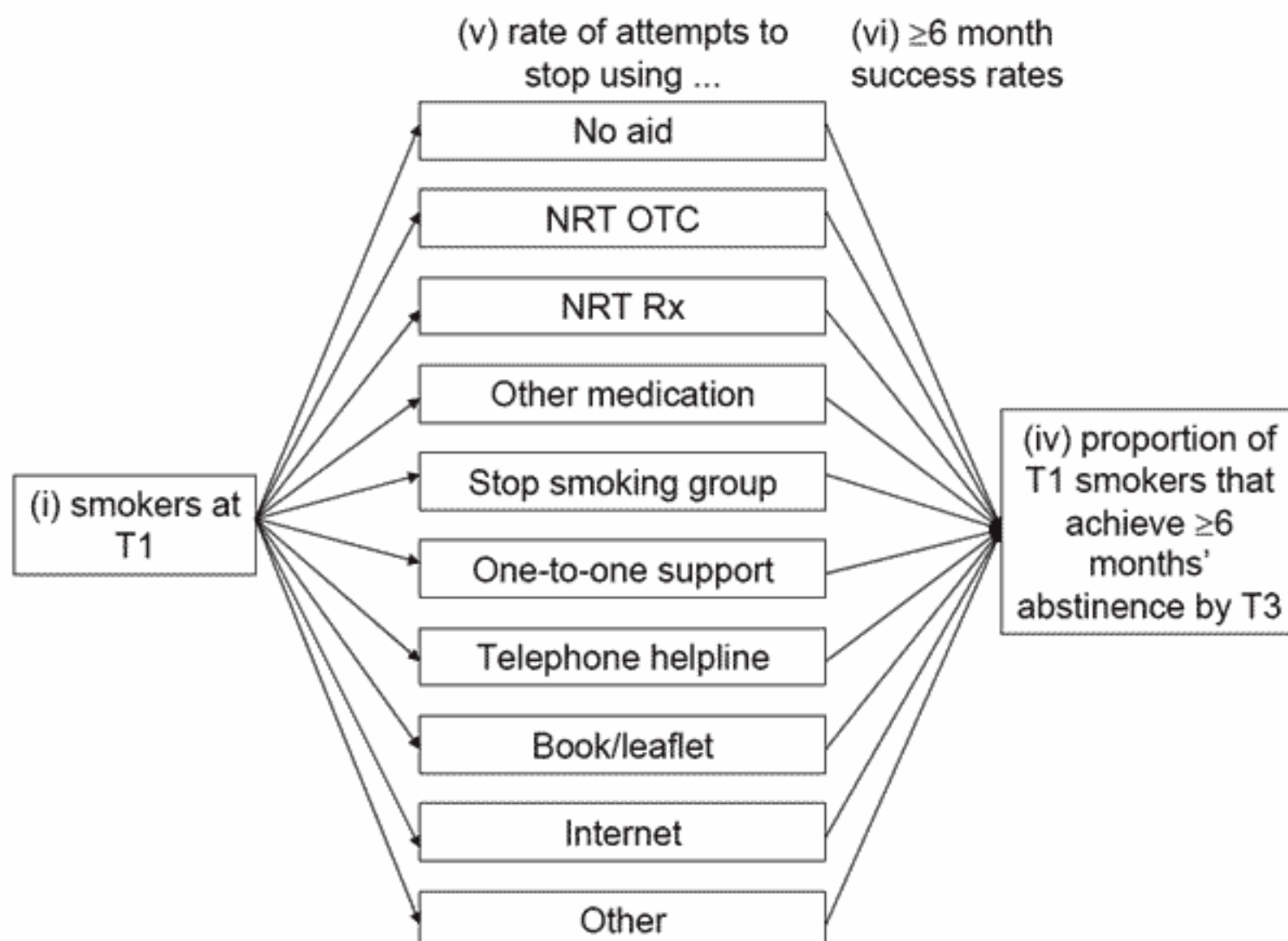
*c) Model showing triggers and aids to quit attempts*



(iii) **Success rates of attempts to stop smoking and (iv) prevalence of long-term successes**: There are surprisingly few data on the success rates of quit attempts outside of clinical trials. The figure that is widely used of success of unaided quit attempts is about 4% lasting 6 months but this is based on relatively small convenience samples and there are no published data of this kind for the UK (21). Because quit attempts that fail are often very quickly forgotten, using cross-sectional surveys looking back over 12 months to make estimates is not appropriate.

Related to (iii) we currently have no adequate population-level data on the proportion of people who were smokers in a given year that achieve long-term abstinence. This is demonstrated by findings from cross sectional surveys such as the California smokers survey which appeared to show that 20% of smokers making an unaided quit attempt were abstinent for at least 6 months (22), and data from the STP baseline survey which suggested that some 40% of quit attempts made at least 6 months ago lasted at least 6 months (23). This is clearly at variance with findings from prospective studies and wholly unrealistic.

(v) **The use of aids to smoking cessation and (vi) success rates associated with different cessation methods**: Current national estimates of use of aids to cessation are based on retrospective reports which assume that smokers make just one attempt a year and can accurately recall their quit attempts over the past 12 months (19). The real-world effectiveness of aids such as NRT has been called into question but this has been based on cross sectional surveys (22). We have analysed data from the ATTEMPT cohort indicating that use of NRT without additional behavioural support was associated with an approximate doubling of 6-month continuous abstinence rate, in line with expectations from clinical trials (18). However, this study was too small to enable analysis of other aids such as NHS stop smoking services or medications such as bupropion and the cohort is now terminated.

(vii) **Triggers of smoking attempts and (viii) rate of use of different aids resulting from quit attempts arising from different triggers**: We could find no published figures on triggers to stopping smoking in nationally representative samples. Indeed, there is very little research on

*c) Model showing triggers and aids to quit attempts*
events that prompt quit attempts. Surveys ask about reasons for stopping smoking which is not the same thing (19). From a policy perspective it is important to be able to link quit attempts with particular triggers to determine whether and how far policy initiatives are having an impact. The STP sought to investigate triggers and the results suggest that studying triggers is feasible. It is also useful to be able to link triggers with the use of different aids to quitting and ultimately success rates. It is important to know, for example, whether quit attempts promoted by GP advice are more likely to involve use of NRT or NHS Stop Smoking Services and whether they are more or less likely to be successful, other things being equal.

**Social and personal factors influencing the success of attempts to stop smoking:** Interpreting the above figures requires an understanding of the personal and social factors that contribute to smokers using different methods to stop and their likelihood of success in stopping. For example, if smokers that are more nicotine dependent use behavioural support or NRT and are less likely to be able to stop, this may lead to underestimation of the contribution that use of these methods makes to success of quit attempts (24). It is therefore essential to collect such data (see 25).

**Ongoing studies relevant to these issues:** The International Tobacco Control (ITC) cohort study (26) includes assessment of quit attempts and success rates but does not take account of multiple quit attempts in a 12-month period and the follow-ups are too infrequent to overcome issues of recall bias when it comes to accurately assessing success rates. In addition the UK sample is too small for reliable parameters estimation. The ATTEMPT study, mentioned earlier, involved following up a multinational cohort of smokers every 3 months for 2.5 years (27). The use of quarterly follow-up goes a long way to addressing problems of recall bias but the UK sample is too small for reliable parameter estimation and the sample is restricted to middle-aged smokers of 5+ cigarettes per day who at baseline said that they intended to stop smoking in the next 3 months.

There are a number of studies overseas that seek to address this topic, most notably in California (22, 28, 29). However, none of them address the issues directly in a way that takes account of multiple quit attempts per year and the high rate of forgetting of quit attempts.

### b) 1.2. Theme 2: Understanding the process of stopping smoking

Surprisingly little is known about the process of stopping smoking. Probably the dominant model for practitioners is the Transtheoretical Model (TTM) of behaviour change (30). This model has been heavily criticised and empirical evidence has not supported the existence of 'stages' in any meaningful sense (see 31, 32). Other accounts have arguably provided greater insights, including prediction of smoking cessation through analysis of 'intrinsic' and 'extrinsic' motivation (33), and detailed analysis of temptations to smoke and lapses (34-39).There is good evidence that factors that predict quit attempts differ from those that predict the success of those attempts (25, 40).

RW has proposed a model of behaviour changes based on a general theory of motivation (called PRIME Theory after the five putative layers of motivation: plans, reflexes, impulses, motives and evaluations) (41). This theory attempts to draw together insights from common observation as well as diverse existing theories of motivation covering such concepts as choice and decision making as well as habit learning, drives, self-control, and basic psychobiological processes (see www.primetheory.com). The ultimate focus is on the balance between impulses and inhibitory forces in the moment-to-moment control of behaviour and how this is influenced directly and indirectly by elements at different levels of complexity within the 'motivational system'. For example, it hypothesises that beliefs about what is good and bad, right and wrong etc. can exert an influence only through what it calls motives (wants and needs) operating at the time. It describes how and when plans are formed and the path that links these to responses. PRIME Theory proposes that the dynamics of the motivational system are 'chaotic (in the sense of chaos theory). It also notes the pivotal role of 'identity' (mental representations of the self and associated emotions and wants and needs) as the foundation of self-control, and self-control as central to generation of wants and needs relating to new behaviour patterns that can compete with and override impulses, wants and needs to engage in the previous behaviour.

Many individual elements of the PRIME model have direct or indirect supporting evidence, as would be expected given that it brings together existing models and evidence. With regard to the role of identity for example, there is a large literature but mostly on adolescent smokers and gender identity and smoking (42-46). However, there are reports that measures of a 'smoker' identity are predictive of resistance to anti-smoking campaigns (47) and failure of attempts to stop stopping (48). The fact that future plans regarding stopping smoking have only moderate stability (49) also fits with the theory. Evidence on which the theory is based is described in more detail in West (41).

The theory makes a number of specific predictions about the process of change and the likely success or otherwise of interventions to promote it. Four of these have begun to be explored.

It has been observed that a large proportion of 'quit attempts' are put into effect as soon as the decision to quit is made and retrospective reports suggests that, other things being equal, these unplanned quits are more likely to result in lasting change than those that are planned in advance (23). PRIME Theory would predict that the advantage of unplanned quits will become manifest to a greater extent in relation to long-term rather than short-term success. This is because the benefit of unplanned attempts arises from a more complete transformation in identity (a kind of epiphany) which requires immediate action rather than delay. In the early stages of the quit attempt, pharmacological dependence on nicotine resulting in powerful cravings would be expected to play more of a role but after a period of abstinence cravings are less importance and commitment to a new identity as a non-smoker would be expected to play a greater role.

It has been found in an analysis of data from the ATTEMPT cohort study that approximately 50% of smokers attempting to stop who have succeeded for one week label themselves as non-smokers (manuscript in preparation). It was found that these are more likely to maintain abstinence for at least 6 months than those who label themselves as 'smokers'. This suggests the importance of self-labelling in achieving prolonged abstinence. PRIME Theory predicts that the self-labelling is important and that this association will be maintained once other potential confounding factors have been controlled for.

A further prediction from PRIME Theory concerns quit attempts. There is some evidence that a simple rating of wanting to stop smoking performs better than TTM 'stage' (based on when smokers report intending to stop in the future) in predicting quitting (50). According to PRIME Theory this is because the response to questions about future quitting do not reflect how most smokers actually think about this whereas smokers can readily answer a question about whether they would like to stop. PRIME Theory predicts that while the exact moment when a quit attempt is triggered depends on factors that are difficult to predict, the frequency of feelings of discomfort about current identity as a smoker will make it more likely that on one of these occasions an impulse to act is generated. Thus asking 'how much of the time have you felt that you want to stop smoking' should outperform a simple rating of desire to quit in predicting quit attempts.

A fourth prediction concerns differentiation between 'urges' (feeling an impulse to act) and 'wants' (a feeling of attraction to something). Tiffany (51) has postulated that urges arise from frustration of automated action schemas. PRIME Theory argues that individuals consciously experience urges when they exercise *voluntary* restraint over impulses. Work that is ongoing in the current programme is a first attempt to test this hypothesis (see Section A).

### b) 1.3. Theme 3: Developing and testing better interventions

**Developing improved methods to aid cessation:** The top line conclusions regarding aids to smoking cessation are summed up in Box b) 1.3.1.

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Box b) 1.3.1
1. Randomised controlled trials have found that individual counselling given to smokers seeking help with stopping improves ability to sustain abstinence for at least 6 months by an average 4% when delivered face to face and a similar amount when delivered according to a pre-arranged schedule by telephone – this is compared with minimal support in the form of a brief motivational session or written materials alone (52, 53). There is insufficient information to determine whether one particular approach (e.g. motivational interviewing or cognitive behavioural therapy) is better than another or what are the 'active ingredients'. The evidence suggests that the effect of counselling is broadly additive to the effect of NRT. Evidence from

real-world application of behavioural support methods suggests that the benefits of behavioural support translate from the experimental trials into the routine clinical situation (54).

2. There is no evidence from randomised controlled trials indicating a clear benefit for the range of current behavioural support procedures designed to prevent relapse after the first few weeks of abstinence (55).

3. Randomised controlled trials have found that a course of 8-12 weeks of NRT used by smokers seeking help with stopping improves ability to remain abstinent for at least 6 months by an average 7% compared with placebo (56). There is evidence strongly suggesting that using combinations of different forms of NRT such as patch plus inhaler, and that starting to use NRT for two weeks prior to the quite date improves abstinence rates (56). There is also evidence suggesting that for more dependent smokers, higher dose formulations of NRT products are more effective (56). There is indirect evidence to suggest that for some smokers, a course of NRT longer than 12 weeks may be required (57). There are no published cohort studies on success as a function of NRT use but data from the ATTEMPT cohort show that controlling for smoker characteristics such as degree of cigarette addiction (FTND score), use of NRT without behavioural support is associated with an increase in 6-month continuous abstinence rates similar to what would be expected from clinical trials (18). There is insufficient evidence to determine whether some NRT products are more effective than others either in unselected smokers or in particular types of smoker. Some research has been done which did not find a difference but the power to detect an effect was low (58).

4. Randomised controlled trials have found that a course of 8-12 weeks of sustained release bupropion (Zyban) used by smokers seeking help with stopping improves ability to remain abstinent for at least 6 months by an average 9% compared with placebo (59). Evidence from one randomised controlled trial suggests that bupropion may be more effective than nicotine patch treatment (60) and this is being explored further.

5. Randomised controlled trials of nortriptyline have found that a course of 8 weeks used by smokers seeking help with stopping improves >6 month continuous abstinence rates by an average 9% compared with placebo (61).

6. Randomised controlled trials have found that a course of 12 weeks of the alpha-4, beta-2 nicotinic receptor partial agonist, varenicline used by smokers seeking help with stopping improves >6 month continuous abstinence rates by 15% and that adding a further 12 weeks of treatment to those who are abstinent at the end of 12 weeks improves the >6 month abstinence rates following the end of treatment by a further 7% in that group compared with placebo (unpublished data from Pfizer).

7. Randomised controlled trials have found that a course of 12 weeks of the CB1 antagonist, rimonabant used by smokers seeking help with stopping improves end of treatment success rates by an estimated 5% compared with placebo but the effect on sustained abstinence has not yet been made publicly available. Rimonabant has been found to reduce weight gain associated with smoking cessation and the effect appears to be greater than with NRT though no direct comparison has been made (unpublished data).

Overall, behavioural support and medication together appear to be able to improve >6 month continuous abstinence rates by an average 10-15%. This translates into an increase in the 'permanent remission' rate of approximately 5-8% because there is an approximate 20% loss to relapse between 6 months and one year (data derived from Cochrane reviews) and an approximate 40% of the remainder relapse after that time (62). While this is a small effect, the cost of the treatment and the health benefits make this approach to treatment among the most cost-effective available within any health service (63). The priorities for the future are 1) to improve the success rates, and 2) to widen access to treatment in those that could benefit from it.

### Improved implementation of smoking cessation interventions

There are very wide variations in apparent success rates of different NHS stop smoking services (64). It is apparent that a major element of this arises from differences in methods used to calculate success rates (65). However, there do appear to be real differences in effectiveness across different areas and different parts of the same service. These need to be explored and understood

so that best practice can be established and disseminated. Key areas of enquiry are: use of specialist staff to treat smokers versus practice nurses or pharmacists, group versus one-to-one treatment, use of and type of relapse prevention interventions and use of drop-in clinics versus appoint-based clinics.

*b) 2. Studies*

*Initials in brackets indicate staff allocation to studies. RW: Robert West, EV: Eleni Vangeli, LS: Lion Shahab, JS: John Stapleton, AB: Andrew Bryant, AM: Andy McEwen, JF: Jenny Fidler, ML: Mark Livermore, DB: David Boniface.*

## b) 2.1. Study group 1: The Smoking Toolkit Study (RW, JS, AM, JF, AB, DB)

### Aims and justification

The background to the study is given in section b) 1.1. The primary aim of the study is to provide ongoing, up-to-date national statistics on key parameters relating to smoking cessation to guide policy and clinical practice. It will also provide a unique toolkit for understanding the process of smoking cessation and the role played by triggers such as GP advice, and aids to cessation such as nicotine replacement therapy and behavioural support in the 'real world'. Furthermore, it will provide national data on smokers' attempts at harm reduction, specifically 'cutting down' and the use of aids to cutting down.

The unique feature of the study involves recognising that many smokers make multiple quit attempts within a short space of time, and that unsuccessful quit attempts are often rapidly forgotten. This means that surveys need to be carried out frequently and to concentrate on a more limited time period for recall. In addition, the response format needs to be able to cater for multiple quit attempts and the possibility that different quit attempts involve different triggers, use different aids and possibly more than one type of aid.

The STS is also planned to provide a panel from which to draw participants for other studies in the programme, including the process of change studies (see section b) 2.6.).

### Methodology

This study involves repeated cross-sectional household surveys of national samples of smokers and recent ex-smokers for a period of 5 years with each cross-sectional sample followed up after 3 months and 6 months by postal questionnaire.

There will be between 4 and 12 household surveys per year (ideally 12 depending on funding available) for 5 years drawn using an established quota sampling method by the social research company BMRB. To keep the costs to a minimum the baseline surveys will use the BMRB omnibus surveys, their regular series of surveys in which one can 'buy' questions. Figure b) 2.1.1.1 shows the timing of assessments for the smallest feasible study involving quarterly baseline household surveys. The larger alternatives involve bimonthly baseline surveys or ideally monthly baseline surveys.

Each survey will involve 2000 adults of whom an estimated 570 will be people who have smoked in the past year and 500 will be current smokers. It is expected that approximately 250 from each sample will agree to be followed up and complete the 3-month and 6-month postal questionnaires. Half of these will be asked to provide saliva samples and return these by post giving 125 samples to be analysed for cotinine at both the 3-month and 6-month points. Thus it is expected that the annual sample will be between 2200 (for quarterly baseline) and 6600 (for monthly baseline) participants of whom between 1000 and 3000 will be followed up and between 500 and 1500 will provide samples for saliva cotinine analysis.

The inclusion criteria will be: any person aged 16 or above who has agreed to take part in the BMRB household survey. Appendix 2 shows the proposed baseline questionnaire. This has been pilot tested as a postal questionnaire and in May 2006 we commissioned BMRB to test it again as a household questionnaire in an omnibus survey exactly as it would be used in the full study. The key assessments for each participant at each household survey will be: 1) the number of serious quit attempts recalled as having been made within the last 3 months; 2) for each quit attempt made in the past 3 months: a) how long-ago the quit attempts started, b) how long it lasted, c) any aids used (e.g. NRT over-the-counter, telephone helpline), d) what triggered it (e.g. GP advice), e)

whether or not it involved cutting down gradually, f) whether it was planned in advance; 3) current smoking behaviour (or past smoking behaviour in those that have recently stopped); 4) current (or past) nicotine dependence using the Fagerstrom Test for Nicotine Dependence (FTND) (66); 5) demographic characteristics (gender, age, socio-economic group, marital status, employment status, region); 6) whether trying to 'cut down'; 7) NRT use while smoking; 8) in those not currently smoking a) mental state associated with not smoking, and b) perceived vulnerability to resumption of smoking.

In the follow-up postal surveys the key assessments in the household survey will be repeated partly to provide an update and partly to assess re-test reliability. In addition, assessments will be conducted as follows: 8) duration of any quit attempts that were ongoing at the time of the household survey; 9) saliva cotinine concentration.

Saliva samples will be obtained by including a specimen tube and cotton dental roll with the postal questionnaire together with instructions on use (as in the STP).

*Figure b) 2.1.1.1: Timing of assessments (quarterly baseline assessments)*
*a) Years 1 to 3*

| Quarter | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 |
| B1 | W1:3M | W2:6M | | | | | | | | | |
| | B2 | W2:3M | W2:6M | | | | | | | | |
| | | B3 | W3:3M | W3:6M | | | | | | | |
| | | | B4 | W4:3M | W4:6M | | | | | | |
| | | | | B5 | W5:3M | W5:6M | | | | | |
| | | | | | B6 | W6:3M | W6:6M | | | | |
| | | | | | | B7 | W7:3M | W7:6M | | | |
| | | | | | | | B8 | W8:3M | W8:6M | | |
| | | | | | | | | B9 | W9:3M | W9:6M | |
| | | | | | | | | | B10 | W10:3M | W10:6M |
| | | | | | | | | | | B11 | W11:3M |
| | | | | | | | | | | | B12 |

Bx: Baseline household survey; Wx:3M: 3-month postal follow-up survey for baseline survey x; Wx:6M: 6-month postal follow-up survey for baseline survey x.

*b) Years 4 and 5*

| Quarter | | | | | | | |
|---|---|---|---|---|---|---|---|
| 13 | 14 | 15 | 16 | 17 | 18 | 19 | 20 |
| W12:3M | W12:6M | | | | | | |
| B13 | W13:3M | W13:6M | | | | | |
| | B14 | W14:3M | W14:6M | | | | |
| | | B15 | W15:3M | W15:6M | | | |
| | | | B16 | W16:3M | W16:6M | | |
| | | | | B17 | W17:3M | W17:6M | |
| | | | | | B18 | W18:3M | W18:6M |
| | | | | | | B19 | W19:3M |
| | | | | | | | B20 |

The key derived variables for each participant will be: 1) the annualised rate at which quit attempts are made using data from the quit attempts recalled during the past week at each household survey; 2) the proportions of quit attempts that involve cutting down first; 3) the proportions of quit attempts that are planned in advance; 4) the proportions of quit attempts that involve using aids of various kinds; 5) the proportions of quit attempts that last 1 day, 1 week, 1 month, 3 months and 6 months.

The analyses will focus on:

1.  providing accurate up-to-date information on smoking prevalence including all smoked tobacco as well as cigarettes and including the 12-month, 3-month and 1-month 'incidence' of smoking.
2.  providing a series of annual updates of the key cessation parameters (rate of cessation attempts; proportions triggered by key factors such as smoke-free legislation, GP advice etc; proportions using each of the main available aids to cessation, proportions lasting different periods of time (up to and including 6 months) with associated 95% confidence intervals, stratified by socio-economic group, gender and age group; proportions of smokers who stop smoking for at least 6 months
3.  time series analyses to assess changes in each of the above parameters at whatever frequency they are assessed (quarterly, bimonthly or monthly) including seasonal trends, linear trends, and associations with specific events such as changes in the GP contract, major mass media campaigns, introduction of new medication, changes to licensing of existing medications, price changes etc.
4.  random effects logistic regression analyses (to take account of possible multiple quit attempts per smoker) examining the association between specific triggers and quit attempts using different aids (e.g. GP advice and use of NHS stop smoking services)
5.  random effects logistic regression analyses examining the association between use of specific aids and successful abstinence for different periods but primarily focusing on 6 months
6.  random effects logistic regression analyses as in 4. but with adjustment for contextual variables and use of other aids
7.  random effects logistic regression analyses examining the association between planned versus unplanned quit attempts and abrupt versus gradual cessation and successful abstinence for different period but focusing on 6 months, adjusting for potential confounders including use of aids and degree of addiction to cigarettes
8.  construction annually of a full statistical model of the national smoking cessation picture charting the path smokers take through the process of making quit attempts to abstinence (Figure b) 1.1.1) and further modelling of year-on-year changes in that model
9.  providing a series of annual updates on proportions of smokers reporting 'cutting down' the amount they smoke and the proportion of these that report using NRT to help them do so
10. linear regression comparing smokers reporting versus not reporting cutting down, with or without NRT and saliva cotinine concentrations (logged)
11. logistic regression analyses to assess the association between cutting down, with or without NRT, and subsequent quit attempts in the next 6 months adjusting for other predictors of quit attempts; additional logistic regression analyses to assess the association between cutting down, with or without NRT, and odds of 3-month success of quit attempts in the next 6 months adjusting for other predictors of success
12. correlations between quantitative measures of smoking and degree of addiction in continuing smokers at baseline, 3 months and 6 months (cigarettes per day, saliva cotinine - 3 month and 6 month only, FTND)

**Technical feasibility**

This methodology has been pilot tested and there is a high degree of confidence that it will produce the required data.

### b) 2.2. Study group 2: Analysing data from and reporting findings from ongoing and existing datasets

This involves using existing sets and ongoing data-gathering exercises to answer key questions relating to all three of the themes of this programme.

### b) 2.2.1. The ATTEMPT Cohort (JF, RW, LS)
**Aims and methodology**

This data set (see earlier discussion) involved follow-up every 3 months for up to 2.5 years of a sample of smokers drawn from five countries: UK, US, Canada, France and Spain. Data collection completed in late 2005 but with a dataset of this complexity and potential value, it will require a considerable research effort to address the range of key questions about smoking and smoking cessation patterns that the data set can answer. This research effort will continue through the final

period of the existing programme but will need to continue into the first year of the new programme and possibly beyond. The proposed schedule of the first five papers arising from the cohort to be produced under the new programme is: 1) The role of acute and chronic illness in prompting quit attempts and their relationship to success of those attempts; 2) The role of body weight and concern about increases in body weight as a barrier of attempts to stop smoking and to long-term success; 3) The short-term and medium-term benefits to physical and mental health of stopping smoking; 4) Methods used by smokers to help them stop as a function of different smoker characteristics (e.g. low income versus middle and high-income smokers in different countries); 5) Modelling the temporal patterning of quit attempts and their success over a 2-year period.

The detailed methodology for the study is given in an in-press paper (67). This paper reports findings from the initial wave of the study that involved 2009 smokers in the US, Canada, UK and France of whom 52% were followed up successfully for one year. Since then Spain was added to the cohort and the samples from existing surveys were boosted by a further 2500 smokers. The proposed analyses are part of a planned sequence and will be conducted in collaboration with RTI who were contracted to undertake the field work. Accurate estimates of statistical power cannot be made because the analyses involve multivariate analyses with correlated predictors. However, the sample size would be sufficient to detect simple associations equivalent to a correlation of 0.1 with a power of greater than 80% in most cases.

### b) 2.2.2. Randomized placebo-controlled trial nicotine nasal spray in general practice (JS, RW)
**Aims and methodology**

This is a study supervised by JS with 731 smokers randomised to active or placebo spray in general practice with brief behavioural support. The only studies to date involving nicotine nasal spray have been in the context of intensive behavioural support (56) and there is an important issue whether this particular form of NRT is effective when given as a prescription without such support. Doubts have been raised, for example, about whether another acute nicotine system, the inhaler, is effective without behavioural support (68). The primary end-point was 3 months of continuous abstinence, for which the study had 95% power assuming an effect size similar to that found with other NRT products when used in general practice settings. The analyses need to be completed and the study written up.

### b) 2.2.3. The CEASE trial (JS, JF, RW)
**Aims and methodology**

This is a multi-centre double-blind placebo-controlled RCT of the nicotine patch conducted in 17 European countries among 3575 smokers. It is unique in comparing a range of doses and treatment durations for the most popular and well-tolerated smoking cessation aid: the nicotine patch. JS is in charge of the dataset. A high level of follow-up was achieved even with those that resumed smoking. Very detailed measures of psychological health including the General Health Questionnaire (69) were taken at baseline and at follow ups. In addition, several established and new measures of mood-state, tobacco dependence, as well nicotine intake were taken repeatedly throughout the 12-months. The findings of the comparison between treatments have been published (70) but other issues that require examination include: 1) How does mental health change in the short and medium term with smoking cessation? 2) To what extent do predictors of short- and long-term relapse differ? 3) What is the best measure of cigarette addiction in terms of ability to predict relapse? Apart from their clinical significance these issues are fundamental to understanding the process of change in smoking cessation. For example, it will be possible to establish whether late relapse is associated in some individuals with a worsening of mood following the quit attempt that does not remit. The trajectory of mood disturbance following cessation has been found to predict relapse in shorter term studies (71).

### b) 2.2.4. Nicotine patch vs nicotine nasal spray vs combined patch and nasal spray (JS, RW)
**Aims and methodology**

This is randomized placebo-controlled trial in 480 dependent smokers attending the Maudsley

Clinic that has been completed by JS. Subjects were followed up for 12 months. The issue of whether combinations of different forms of NRT are more effective than individual NRT types is of practical and theoretical importance. As noted earlier, data to date suggest that combinations are probably more effective than single forms but this may depend on the forms used. In particular there is very little data in which the combination has been compared with *both* individual forms (56). This study addresses that issue. The trial was also designed to understand better the type of smoker that might respond best to two forms of NRT at opposite ends of the pharmacokinetic spectrum (patch with very slow release versus spray with rapid absorption). Direct comparisons between different forms of NRT in terms of efficacy are extremely rare and indeed to date we know of only two: one involved members of this team (58) and the other compared nasal spray with patch and attempted to identify parameters that could help match smokers to treatments (72). This study would build on those findings. Many smoking characteristics were measured, including plasma nicotine samples before and immediately after smoking a cigarette, and a range of smoking typology and dependence scales. Thus the study offers the opportunity to examine possible differences between smokers in terms of suitability for different forms of NRT.

### b) 2.2.5. Maudsley Cessation Clinic Research Database (JF, JS, AM, RW)
**Aims and methodology**

The Maudsley database has been maintained by JS since 1987, containing the full pre-treatment, treatment, and outcome records of more than 8000 smokers. As well as allowing large-scale analyses on fundamental areas of importance such as the effect of treatment modality (e.g. one-to-one counselling versus group treatment; comparison of different forms of NRT), the database provides a unique opportunity to study aspects of smoking and smoking cessation for which little is currently known. Of particular practical significance is the prognosis in smokers who return for re-treatment after differing lengths of time. The Maudsley database allows identification of these smokers of whom there are an estimated 1200 to date. It will also be possible to examine the stability of key smoking characteristics in this group, including level of nicotine dependence and severity of withdrawal symptoms during abstinence. There are almost no data on either of these. With regard to the stability of nicotine dependence, we found in the STP that smokers in the population showed a high degree of stability in the FTND (see Appendix 1) but we could find no published data. With regard to the stability of withdrawal symptoms, there is evidence of some degree of stability but in small samples (73). In recent years DNA samples have been collected from those attending the clinic, providing the largest such database where full clinical and smoking history can be related to genetic markers. It is proposed to seek external funding or collaboration to test hypotheses relating particular allelic forms to withdrawal symptoms, urges and short- and long-term abstinence.

### b) 2.2.6. The ZORN trial (JS, EV, RW)
**Aims and methodology**

This is an RCT comparing the effectiveness of nicotine replacement therapy versus bupropion versus a combination of the two as an aid to smoking cessation in the context of behavioural support provided by NHS Stop Smoking Services (see section A b) 1.). Support has been provided by the Department of Health/MRC. The main outcome analysis to assess the relative overall benefit of these treatments will be completed by the end of the current programme but the data set has been designed to answer further questions of fundamental importance in the treatment of nicotine dependence, such as, which smokers are likely to benefit most from being prescribed each treatment and how does their cost-effectiveness compare. Cheek swabs for DNA analysis will have been collected from approximately 700 participants, allowing an ongoing study of the feasibility of pharmacogenetic screening. Pharmacogenetic screening to match smokers to treatments is an active area of study and some important findings are beginning to emerge. For example, it has been found that the the rate of nicotine metabolism, probably related to CYP2A6 functionality, as indicated by pretreatment 3-HC/cotinine ratio derived from cigarette smoking, predicts the effectiveness of transdermal nicotine but not nicotine nasal spray (74). This is an exciting finding that needs following up.

### b) 2.2.7. Health Survey for England (JF, LS, RW, DB)
**Aims and methodology**

The HSE is a rolling survey of a large nationally representative sample in England that involves a household survey of a large sample followed by a nurse visit and detailed assessment of health parameters of a subsample (for the most recent report see 3). Saliva cotinine concentrations are obtained on subsamples. The HSE team, based in our department at UCL, write a report of the top line results each year, but additional manpower is required to analyse data to answer important questions on smoking. A high priority for analyses to be carried out in the first year will be aggregating data from surveys carried out from 1990 onwards to construct a database of more than 100,000 saliva cotinine values to produce definitive parameters of the distribution of cotinines in non-smoking children and adults and smoking adults, stratified by age, socio-economic group, gender, smoking patterns, year of study and exposure to other people's smoke. This will be a landmark study that will provide a point of reference for future studies on nicotine intake from active and passive smoking. It will also provide a starting point for a second paper assessing changes in smoke exposure following introduction of the smoke-free legislation in England.

### b) 2.2.8. International Tobacco Control (ITC) study: (LS, RW)
**Aims and methodology**

The ITC is a large multi-national cohort study of smokers coordinated by Professor Geoff Fong at the University of Waterloo. This ambitious project has reached a stage where it has begun to generate publications at a high rate (40, 75-85). The focus is very much on attitudes and their relationships with policy initiatives but it also examines smoking behaviours and cessation. Dr Ann McNeill, who is a collaborator on the proposed programme is one of the UK leads on the project together with Professor Gerard Hastings at the University of Stirling. The UK cohort consists of 2000 smokers surveyed by telephone approximately annually. CRUK contributes to funding of the UK cohort. LS has formed a collaboration with the team and works with Dr McNeill and others in evaluating whether the UK's national strategy of cessation services and reimbursement of smoking medications results in different attitudes and behaviour among UK smokers than smokers in the USA, Canada and Australia. For the last wave of data, we would also be interested to see whether there is any difference in cutting down to stop as opposed to complete cessation given the UK's recent policy change with regard to NRT.

### b) 2.3. Study group 3: The Stop Smoking Clinic Research Network (AM, ML, JS, EV, DB, RW)
**Aims and justification**

The NHS stop smoking services provide both a resource and a market for information on best ways of implementing effective smoking cessation interventions. AM and RW have been working closely with the services since their instigation providing training, support and advice and close bonds have been established. It is apparent that implementation issues are as important as efficacy when it comes to the effectiveness of the treatment provided. Recent policy initiatives appear to have led to distortions in the implementation of services with reports of some service claiming unrealistic success rates and a general movement away from provision of high quality intensive support to more minimal support in primary care. As this trend develops it will be extremely important to obtain high quality data to establish how far such moves detract from the original objectives of the NHS services which are to provide effective treatment to those that want to use it (86). Such data may be the most important bulwark against deterioration of the services. The monitoring undertaken by the Department of Health (87) cannot fulfil this role because it is apparent that the calculations of success rates used by PCTs are so variable that the figures do not allow comparisons between them (65).

In addition to the need to obtain data to defend high quality services, it is important to be able to make use of the innovation that exists within the services to establish what approaches work better than others in terms of attracting smokers into the services and attaining high quit rates.

We have established a network of clinics that are collecting data of sufficient quality to form a basis for establishing best practice. Currently 11 clinics have signed up with a combined annual throughput of 7000 smokers. This constitutes a unique resource to assess what constitutes best

practice and disseminate it through the channels of communication that we have developed, including the UK national conference. The network will also offer opportunities for the piloting of survey tools and the generation of data for power calculations (necessary for other elements of this programme). The network will also offer access to NHS Stop Smoking Service staff, whose knowledge and attitudes can be evaluated routinely, and in response to specific interventions. Finally, the network will be a major tool for building research capacity within the NHS Stop Smoking Services. The website (www.scsrn.org) provides valuable resources for services wanting to undertake their own audits or research projects and these need to be updated regularly. It also provides a simple system whereby services can upload reports which are catalogued under different headings so that other services can see what has been done.

## Methodology
The website is currently being hosted for free by Exchange Supplies with whom AM has close ties and it is updated by them with input from AM and RW. They also work closely with AM in organising the UK National Smoking Cessation Conference and are happy to continue this relationship. However, the work involved in maintaining and developing the website and working with busy service managers to ensure that they make most effective use of it is more than can be undertaken on present resources. This is a role that will be taken by other members of the research team, the programmer (ML) and the PA and HBRC administrator with supervision by AM.

It is also planned that the network be allotted a regular session at the annual UK conference so that members can report findings and share experiences and resources. Studies proposed for the network include:

1. Comparison of long-term success rates as a function of different relapse prevention interventions
2. Comparison of 4-week success rates as a function of mode of delivery (drop-in clinic, pharmacy one-to-one, practice nurse one-to-one, rolling group, fixed group etc.)
3. Comparison of retention and outcome as a function of method of acquiring medication (one-stop-shop via a Patient Group Direction, prescription from GP, direct supply etc.)
4. Demand for, use of, and effectiveness of, different NRT combinations, as a function of prescribing policy (e.g. with all NRT available on PGD or NHS prescription or with one available one purchased by the client separately).
5. Methods used to increase referrals from GP and secondary care sources and their association with reach and success rates.

The analyses for these studies will typically involve multiple random effects logistic regressions with the key independent variables entered together with measured confounders (including free prescription eligibility and age) and with the stop smoking services as a random variable and where appropriate practice as another nested variable. These analyses will be complex and require members of the team to have expertise in multi-level analyses.

## Technical feasibility
The success of this series of studies depends on the quality of data collection by the stop smoking services involved. AM has already undertaken work with these services to bring data collection up to the required standard and continuing this liaison and training will represent a significant part of his workload in the early part of the programme.

### b) 2.4. Study group 4: Evaluation of the Nicotine Cannon (AM, RW, JF, LS, EV, JS)
## Aims and justification
We have been undertaking preliminary research with a novel nicotine delivery device that may help some smokers to stop more effectively than existing products. This is an area in which there is already a great deal of research and development (e.g. 88, 89). However, to date no single form of nicotine delivery device has proved better than any other in helping smokers to achieve lasting abstinence in unselected smokers (58). It is currently believed that a device that could deliver nicotine more rapidly than current methods whilst still being acceptable in terms of local irritancy at the site of delivery would represent an advance. However, we believe that another factor could

also be important – the ability of smokers to adjust on a moment to moment basis the delivery of nicotine and comfort attached to this. The 'Nicotine Cannon' is a device that we believe allows this to a greater degree than existing nicotine delivery systems. It involves five nicotine inhaler cartridges arranged in parallel in a wide bore tube (the diameter of a spirometer mouthpiece) around a central hollow core. The user adjusts the concentration of nicotine vapour inhaled by covering the central core more or less with a finger.

Initial data with this device suggests that it has the capacity to deliver as much nicotine as a user may need and to do so rapidly (see Section A b) 6.). The next steps are to examine the pharmacokinetics in a larger group of smokers and to assess whether it has the capacity to relieve nicotine cravings more rapidly and completely than existing nicotine products.

## Methodology
Three studies are planned:

### b) 2.4.1. Pharmacokinetic study (Year 1)
The methodology will be the same as has been adopted for the pharmacokinetic study undertaken to date on two subjects (section b) 6.), but with an additional 10 subjects, all abstaining smokers (given that smokers will be the ultimate users of the product and there is evidence that smoking inhibits nicotine metabolism (90)).

This study will also assess ratings of acceptability of the products, subjective effects and acute side-effects using the protocol already tested. Subjects will self-administer each NRT product according to the manufacturers' instructions for the same length of time (10 minutes). In the case of the Cannon the subjects are instructed to take 10 puffs per minute. Blood will taken for measurement of nicotine: at baseline, halfway through administration (5 minutes), and at 1, 5, 10, 15, 30 and 60 minutes after administration of nicotine has ceased. In addition the subjects will complete a 10-point rating scale on the presence of any of the following symptoms: nausea, throat irritation, dizziness, feeling unwell, pleasant feelings and agitation. These self-report ratings are made at the same intervals that blood is taken and are marked between 1 (none) and 10 (extreme). The subjects will also be asked to rate momentary urges to smoke on a 10-point scale and overall level of acceptability of the product.

### b) 2.4.2 Ad-lib smoking and acute withdrawal study (Year 2)
This will be a comparative study of the nicotine cannon and three existing products (the nicotine inhalator, the nicotine nasal spray and the 4mg nicotine lozenge), plus a placebo cannon. The primary outcome measures will be ratings of urges to smoke and acceptability of the products. The subjects will be 150 smokers of at least 15 cigarettes per day (30 in each group). The subjects will attend the laboratory in the afternoon or evening while still smoking normally. Measures will be taken of smoking history, addiction to cigarettes, expired-air CO. They will complete the mood and physical symptoms scale (MPSS) (91) to provide a baseline for assessment of withdrawal symptoms. They will be randomly allocated to one of the five groups and given instructions on use. They will be instructed to use their nicotine delivery system to minimise their urges to smoke but to smoke 'if they feel they need to'. For commercial products they will be asked to use the product as instructed in the labelling. For the nicotine and placebo cannons, they will be instructed to use at least 10 per day but in any case to use them as often and intensively as required. They will also be asked to complete a diary of cigarette use and use of their nicotine products. They will return after 24 hours and complete the MPSS as well as providing rating of the acceptability of their product. Their expired-air CO will be measured. They will then be instructed to abstain completely for 24 hours and return 24 hours later for a similar set of measurements. During this 24 hour period they will complete a diary of their nicotine product use.

The primary outcome measure for the ad-lib smoking phase will be the number of cigarettes smoked. The secondary measures will be reduction in expired-air CO from baseline, usage of the products, ratings of acceptability of the nicotine product, and MPSS ratings at the end of the 24-hour period with the baseline ratings as covariates (92).

The primary outcome measure for the abstinence phase will be MPSS ratings at the end of the period using baseline ratings as covariates. The secondary outcomes measures will be ratings of acceptability of the products and usage of the products.

### b) 2.4.3 RCT of effect of the nicotine cannon on abstinence (Years 3 to 5)
Depending on the findings from the two previous studies, it is proposed to conduct a randomised comparative trial of the cannon on 6-month continuous abstinence rates using as a comparator the most effective NRT product available at the time. This will be a conventional two-arm trial in smokers of 10 or more cigarettes per day not contra-indicated for NRT. The proposed sample size will be 700 which will give the study sufficient power to detect a clinically meaningful difference between the products. Outcome assessment will use the Russell Standard (93).

The rationale for development of this novel nicotine delivery system is that it is distinctly superior in terms of assisting abstinence than existing products while being at least as acceptable to smokers. That is the reason for using an active comparator rather than a placebo. The main threat to validity of such a study is the fact that it cannot be undertaken using a double-blind protocol. In this respect it is similar to a behavioural intervention. However, this threat can be minimised by ensuring that the outcome assessment is undertaken blind to experimental condition as advised in the Russell Standard and it is also possible to compare outcome with ratings of subjects' expectations measured at the start of the trial.

This trial will only be of value if the preceding studies show evidence of superiority of the cannon over existing products. If that does not happen, then it would be possible to use the resources to mount a trial involving cytisine (see section b) 2.5.) as part of the ongoing evaluation of that drug.

### Technical feasibility
There are no significant barriers to undertaking this study. The protocols have all been tested and the proposed randomised trial involves a standard methodology in widespread use.

### b) 2.5. Study group 5: Evaluation of Tabex (cytisine) as an aid to cessation (RW, JS)
### Aims and justification
Funding has been granted by the National Prevention Research Initiative for a full-scale randomised controlled trial of cytisine to aid smoking cessation. Cytisine is a compound derived from Larburnum which has properties that make it potentially effective in helping smokers to stop. It is a 'partial agonist' quite selective for the acetylcholine receptor subtype that is believed to be central to nicotine dependence: composed of alpha-4, beta-2 subunits. Thus cytisine has a high affinity for that receptor but a low efficacy at the receptor. This means that it may have enough efficacy to reduce cravings caused by nicotine withdrawal but not to produce dependence. At the same time by binding to the receptors it may produce sufficient blockade to reduce the rewarding effects of nicotine from a cigarette if a smokers should lapse. This compound was the starting point for a new medication to aid smoking cessation, varenicline, developed by Pfizer. The Phase III trial results for varenicline show powerful efficacy in aiding smoking cessation – greater than for bupropion (unpublished data). Cytisine is produced commercially by a pharmaceutical company based in Sofia, Bulgaria and marketed as 'Tabex'. The main potential benefit of Tabex is that a course of treatment is extremely inexpensive. If it is safe and effective it would make effective treatment available to millions of smokers worldwide who would not be able to afford other medications.

Tabex has been licensed in Central and Eastern Europe for more than 40 years as a smoking cessation medication but has attracted no interest in the West. The NPRI trial will be the first clinical trial carried out to modern standards. The NPRI funding covers the running costs of the trial but not RW's time so this will need to be covered by the CR-UK programme grant. This will involve monitoring and supervision, dealing with problems as they arise, data analysis and report writing.

In addition, a programme of further studies is planned to bring the medication to a point where it can be licensed. It is planned to have a meeting of a working group with Professor Witold Zatonski in Warsaw and researchers in the US working in collaboration with the manufacturers at the World Conference on Tobacco of Health in July 2006. Funds are being sought from CRUK in this

programme grant to support the involvement of the HBRC in this venture. This will involve staff time to engage in coordination and training activities, developing protocols, monitoring, data analysis and disseminating the findings

An obvious question is why this programme should be funded out of charitable funds. The reason is that the manufacturers are not in a position either with regard to expertise or finances to undertake the necessary work and the importance of this medication lies in its extremely low cost. It no longer has patent protection and so in principle any company could manufacture it. This provides a safeguard against profiteering should the programme of research prove successful.

## Methodology

The NPRI Tabex trial methodology is a conventional placebo-controlled double-blind RCT with 6- and 12-month follow-up using the Russell Standard outcome assessment. The course of medication is as specified in the labelling for the drug in Poland where the trial will be carried out.

The methodology of subsequent trials and studies will depend on discussions with the working group. It is likely that at least one further placebo-controlled RCT will be required for licensing the medication as currently formulated using the existing dosing regimen. Other studies comparing different dosing regimens and comparing cytisine against existing smoking cessation medications are also likely to be required. Further phase I and phase II studies are desirable but these can be conducted by other partners in the working group.

## Technical feasibility

Extensive work has gone into ensuring that the NPRI-funded Tabex trial runs successfully. The feasibility of the remaining studies in the programme depends on external funding, but given the potential worldwide impact of this programme of research, there is considerable interest from a number of quarters and confidence is high that funding will be secured.

### b) 2.6. Study group 6: The Process of Change studies (EV, JF, LS, AM, RW)

### Aims and justification

This series of studies will build on work already under way and planned for the final year of the current programme to construct a more accurate picture of the process by which smokers become long-term ex-smokers. Part of the problem has been the absence of a comprehensive theory of addiction that addresses the potentially diverse ways in which it manifests itself. As noted earlier RW has recently developed a theory that attempts to address this gap.

Existing theories focus on particular aspects of addiction: some focus on the development of habits through reward and punishment and associations between cues and the addictive behaviour; others focus on desires and urges that stem from an acquired drive resulting from chronic exposure to a drug; other focus on beliefs, norms and values attaching to addictive behaviours; still others focus on 'identity'. The new theory recognises the potential importance of all of these factors, perhaps to different degrees in different individuals. Moreover, it recognises that our actions at any one time can only be influenced by forces acting at that time and that motives such as evaluative beliefs and plans (for example to become a life-long non-smoker) must be strong enough at all times when the opportunity to lapse occurs to overcome desires and impulses generated by the immediate internal environment (e.g. drive) and external environment (e.g. reminders and triggers). In addition, it recognises that human motivation is 'chaotic' in the sense used in 'chaos theory'. The theory makes a number of predictions with regard to attempts to stop smoking (see earlier discussion). The theory also suggests a number of themes that could usefully be explored when considering the causes of relapse. These include: 1) Markers of a failure to make a complete 'chaotic' switch in the motivational system indicated by such things as whether the decision to quit involved an element of procrastination before being acted upon; 2) Continued drive as evidenced by persistent desires and urges to smoke even in the absence of smoking cues. New evidence from a study of extended use of the new nicotine partial agonist, varenicline, strongly suggests that for some smokers the drive to smoke arising from what are fundamentally pharmacological mechanisms persists in some smokers for at least 6 months (unpublished data from the varenicline maintenance study); 3) Persistence of cue-driven habit mechanisms as evidenced by urges and desires to smoke associated with particular triggers. Smokers often report

urges to smoke that come unexpectedly or when there is a crisis or situation normally associated with smoking; 4) Evidence of chronic or acute distress that depletes mental resources necessary for the exercise of self control, and the expectation of escape from which may make a resumption of smoking attractive; 5) Evidence of continued feelings of attraction to smoking; 6) Evidence of full-scale adoption of a non-smoker identity (see also 94, 95); 7) The extent to which the person's social and physical environment is populated by triggers, including other people smoking. This has been an area that has been most studied to date and the importance of situational factors is well-established (see e.g. 36).

The theory also suggests themes relevant to the relapse process. These include: 1) How far the first lapse arose from a conscious decision to resume smoking, a thoughtless act or a conscious decision to make a temporary exception to the rule of abstinence. Surprisingly we could find no studies that examined this issue. Preliminary analysis of this concept piloted in the co-investigator's current work on another study indicates that conscious decisions to resume smoking are rare but this needs to be studied systematically; 2) How far the effect of the cigarette lived up to expectations. This is an area that has also received little attention. There has been extensive research on the 'abstinence violation effect' in which a lapse creates dissonance and feelings of failure that may lead to full relapse (e.g. 37). But we know very little about whether the cigarette smoked in a stressful situation actually relieved the stress, for example; 3) Changes in identity following lapses. The patterning of smoking behaviour following the lapse in terms of recovery of abstinence or pattern of transition to regular smoking has been studied but PRIME Theory proposes a focus, not only on rekindling of habit mechanisms and effects on self-efficacy but also on the categorical label that smokers give themselves (non-smoker, smoker still attempting to stop, resumed smoker etc.).

The four projects currently under way that will feed into the studies for the new programme are: the 'Understanding Relapse study' (section c) 2.), the study on perceived voluntary restraint on smoking urges (section b) 6.), the hypnotherapy pilot study (section b) 6.), and a study being undertaken by LS for his PhD in which he has interviewed smokers and ex-smokers on all aspects of their motivation to smoke and not to smoke.

The proposed series of studies on process of change would build on the findings from the current work. It will also need to take full account of work going on elsewhere on relapse (34-38, 96-99). Apart from the ongoing work of Shiffman's group, the studies will be informed by the innovative research of Wietkowitz and colleagues who have applied chaos theory concepts to relapse in addiction (100-102).

**Methodology**
**b) 2.6.1. Interviews with smokers and ex-smokers (Year 1)**
The interview study will begin during the latter stages of the CRUK-funded 'understanding relapse' study and follow up the results from that study as well as the others that are ongoing. It is proposed that it will involve in-depth interviews with 100 smokers, recent ex-smokers and long-term ex-smokers recruited from the STS panel. The interviews will be conducted face-to-face either in the participants' homes or at the HBRC. The interviews will be based around a comprehensive motivational assessment as proposed by PRIME Theory. This attempts to determine for each individual the range of motivational forces contributing to their ongoing behaviour and what they can recall of successful and unsuccessful attempts at behaviour change.

Table b) 2.6.1.1. shows a preliminary grid which has been developed based on PRIME Theory that is intended to form the basis for a comprehensive motivational assessment involving all levels of the motivational system. The interviews will be used to populate the cells of the grid as far as possible or to adjust the grid if it turns out that it does not accommodate smokers' responses. It should be noted that in principle the grid could be populated using behavioural or physiological markers and not just interview responses. Indeed, it is an open question how far the grid can be populated using different methods.

This study will collect data using an open response format but not be a 'qualitative study' in the formal sense. Responses to the open format questions will be catalogued using methods used in survey research to ensure that they capture the full range of responses rather than attempting to arrive at themes and the extent to which they fit within the motivational grid will be assessed.

*Table b) 2.6.1.1: Framework for a comprehensive motivational assessment based on PRIME Theory*

| Factors that motivate smoking or militate against attempts to stop or success of attempts | General dispositions | Environmental factors | Smoking-related dispositions |
|---|---|---|---|
| Plans | e.g. Tendency to procrastinate, failure to implement plans | e.g. lack of mental space to develop plans | e.g. finding thoughts of stopping aversive |
| Responses | e.g. Imitative disposition | e.g. presence of smoking 'models' | e.g. disposition to copy smoking behaviour |
| Impulses and inhibitory forces (often cue driven) | e.g. reduced ability to control impulses | e.g. learned triggers | e.g. strong habit patterns directly generating impulses, increased attentional resources to smoking-cues |
| Motives (wants and needs) | e.g. lack of alternative sources of pleasure, limited ability to imagine future events, higher priorities using up mental resources, disposition to 'lose interest' in goals | e.g. reminders of pleasures of smoking | e.g. strong memories of smoking enjoyment, powerful nicotine 'drive', persistence of withdrawal symptoms, attraction to social aspects of smoking |
| Evaluations (beliefs/cognitions) | e.g. lack of health concern, positively valuing ill-health, disposition to avoid thinking about unpleasant future events | e.g. pro-smoking communications in media | e.g. believing that smoking serves valued functions, beliefs about negative outcomes following smoking cessation such as weight gain |
| Identity | e.g. Smoker identity, low self-esteem, incoherent or fragmented identity, 'rebelliousness' | e.g. attractive images of smoking | e.g. feeling unable to stop smoking, liking the identity of the smoker |

It is hypothesised that the process of stopping smoking stems from elements of identity that create wants and needs that conflict with smoking. Because of the particular motivational dynamics around smoking, this must translate into dissatisfaction with 'being a smoker'. Whether and when this translates into a quit attempt depends on the balance of motivational forces operating at particular time. The transition that occurs is one of identity into a variant of 'attempting to stop smoking', 'non-smoker', 'trying not to smoke' etc. The issue then becomes whether the inhibitory forces generated by the wants and needs resulting from this new identity are sufficient to overcome the myriad wants, needs and impulses to smoke that will arise over the coming days, weeks and months.

## b) 2.6.2. Survey and follow-up study (Years 2 and 3)
A fixed response questionnaire will be developed to test specific hypotheses relating to the process of change and try to narrow down explanations for findings observed to that point. The

questionnaire will be given to a sample of 500 smokers from the STS and use a fixed format version of the comprehensive motivational assessment grid to determine for each smoker their temporal profile of motivational tension regarding smoking. It will specifically compare the predictive power of this approach with the best available predictors drawn from the existing models in attempting to predict short- and medium-term attempts to stop smoking, use of aids in those attempts and the success of those attempts. Thus there will be follow-up questionnaires monthly from the baseline for 6 months. This study will have 80% statistical power to detect an improvement in predictive power by logistic regression amounting to approximately 10% of the variance. It is not possible to be more precise because the precise distributions and interrelationships between predictor variables are not known.

### b) 2.6.2.3. Testing intervention elements (Years 2 to 5)
It is proposed to undertake a series of studies to examine the effects of interventions arising out of the other studies on variables that are believed to contribute to motivation to smoke, to stop smoking and to remain stopped. The precise nature of these studies cannot specified at this stage but it is important to plan for them now as empirical tests of the theory as well as feeding into work on the Clean Bill of Health study (see section b) 2.8.). Each study will probably involve no more than 100 participants and the outcome measures will be key motivational markers. The goal will be to find effects that are substantial and therefore able to be detected with these samples.

### Technical feasibility
There are no obvious grounds why these studies should not be able to be completed as intended. The STS will provide a large pool of participants from which to draw. The major threats to the validity of the data come from recall bias and error. It has been found that smokers are quite poor at remembering details of lapses, including their mood at the time and the triggers (97). The focus in the present series of studies will be on global aspects that may be more easily recalled, such as the extent to which they formulated a conscious intention to resume smoking. However, the work planned prior to the start of the new programme will need to examine issues of validity of self-reports of this kind.

### b) 2.7. Study group 7: Activating emotional processes to motivate smoking cessation (LS, JF, JS, EV, RW.) (This is dependent on external funding)
### Aims and justification
One promising approach for smoking cessation interventions that fits well with the tenets of PRIME Theory as well as common-sense, is the use of personalised information of smoking-induced health damage provided by biomarker feedback (103). Simply telling people they are at risk of developing a disease in the current climate when they know this and have habituated to the message or developed defence mechanisms, is rarely sufficient to change behaviour (104). Personalised information can counteract perceptions of invulnerability to the health consequences of tobacco-use, which are common among smokers (105), thus raising threat perceptions and fear, which motivate behaviour change to reduce this threat (106). Visual personalised biomarker feedback showing harm is postulated to have a significant impact on threat perceptions as imagery allows for the spanning of the conscious-unconscious continuum more readily than language (107) and is therefore less likely to be filtered through the conscious critical apparatus.

The emotional processing model (108) proposes that emotions are represented by information structures in memory, an 'emotion network'. These fear structures are thought to be prepropositional in nature (109) carrying interpretative information about the feared stimulus situation, and about verbal, physiological and overt behavioural responses to it. This fear memory structure is not entirely accessible to consciousness; however, it can be activated through the presentation of fear-inducing material, which provides the necessary arousal (108) leading to emotional processing of information.

This study proposes to test a novel smoking cessation intervention utilising biomarker feedback to instigate emotional processing. Specifically, we suggest providing smokers in primary care with ultrasonic photographic evidence of damage to their carotid arteries incurred from smoking. This approach has been shown to be effective in a study based in the Seychelles (110). However,

whether these findings are generalisable to the UK, whether this approach can be easily implemented in the primary care settings and which processes underlie this behaviour change remains to be determined.

## Methodology

Because this study focuses on the cardiovascular system, we are seeking funding from the BHF for the running costs but we are asking CRUK to provide limited funding for supervision, planning, protocol development and report-writing relating to the study. This study aims to include two groups. In the treatment group, smokers attending a designated GP practice will be provided with an ultrasound Doppler scan of their carotid artery estimating carotid intima-media thickness, distensibility and signs of plaque. This scan will be carried out by a qualified ultrasonographer to ensure quality standards who will also deliver the intervention. During the scan, the results, which are shown on a screen, will be explained to participants and compared with that of a non-smoker. In addition, participants will be provided with information regarding the link between arterial damage and smoking, an accompanying leaflet and a picture print-out of their own arterial scan. Participants in the treatment group will also receive a standard cardiovascular risk assessment and will be encouraged to quit smoking. In the control group, participants will also receive a standard cardiovascular risk assessment but will not receive any biomarker feedback or leaflet. Smokers in the control group will also be advised to quit. Participants would be followed up 6 months after the intervention to ascertain biochemically validated smoking status, quit attempts and smoking cessation behaviours.

## Technical feasibility

The technical feasibility of this study depends on securing external funding and co-operation with the general practices involved. RW has close links with local general practices so this is not expected to be a problem. The co-applicants on the BHF grant include a respected cardiologist with extensive experience of the method and a highly experienced ultrasonographer who works with this cardiologist. If we are unable to secure external funding for this study, it is proposed to undertake a more limited investigation with minimal running costs to explore in more detail the lasting motivational effect of these kinds of images using the kind of motivational grid described in section b) 2.6.

### b) 3. Overview

A summary of the key research questions is given in Box b) 3.

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**Box b) 3. Key research questions:**

1. What is the true rate of progress in reducing tobacco smoking prevalence in the UK? (Study 1)
2. What is the true rate at which smokers are attempting to stop smoking in the UK and how is this changing over the period of the programme? (Study 1)
3. What is the true rate of utilisation of aids to smoking cessation in the UK and how is this changing over the period of the programme? (Study 1)
4. What is the impact of the UK's recent policy change with regard to NRT provision on smoking cessation patterns? Is there an increase in cutting down to stop as opposed to complete cessation and does this translate into higher smoking cessation rates? (Study 1, Study 2.1, Study 2.8)
5. What is the true rate of success of attempts to stop smoking overall and with the use of different aids to cessation and in response to different triggers such as advice from a health professional? (Study 1 and Study 2.1).
6. How do rates of making quit attempts and use of aids to quit attempts vary with socioeconomic group (Study 1) and income and educational level? (Study 1 and Study 2.1)
7. How do success rates of quit attempts and effectiveness of different aids to quit attempts vary with socioeconomic group? (Study 1, Studies 2.1-2.5, Study 3, Study 5)
8. What is the stability of parameters of smoking behaviour: cigarette consumption, FTND and its elements, saliva cotinine? (Study 1, Study 2.5)

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9.  How does a smoker's history of quit attempts in the past year affect his or her quitting behaviour and success of quit attempts? (Study 2.1)
10. How does experience of illness influence quitting behaviour? (Study 2.1, Study 2.7)
11. What are the short- and medium term gains in physical and mental health associated with smoking cessation? (Study 2.1, Study 2.3)
12. What is the consistency of the experience of withdrawal symptoms over different quitting episodes? (Study 2.1, Study 2.5)
13. Does the UK's national strategy of cessation services and reimbursement of smoking medications result in different attitudes and behaviour among UK smokers compared to smokers in other countries such as the US and Canada? What are the most important cross-national differentials predicting cessation? (Study 2.1, Study 2.8)
14. How effective is nicotine nasal spray when used in a general practice setting with minimal support? (Study 2.2)
15. To what extent do predictors of short- and long-term relapse differ? (Study 2.3)
16. What is the best measure of addiction to cigarettes in terms of predicting failure of quit attempts (Study 2.3)?
17. Is there a difference in efficacy of nicotine patch versus nasal spray versus the combination? (Study 2.4)?
18. Does peak plasma nicotine concentration following a cigarette predict ability to sustain abstinence and response to nasal spray versus patch better than saliva cotinine? (Study 2.4)
19. Is it possible, using detailed assessment of smoking and smoker characteristics to predict which smokers will do better on nasal spray versus patch? (Study 2.4)
20. Do smokers who return for treatment in a smokers' clinic after different intervals differ in prognosis after controlling for other predictors? (Study 2.5)
21. Does treatment modality (e.g. one-to-one, group treatment etc.) influence smoking cessation outcome controlling for other factors (Study 2.5, Study 3)
22. Are there smoker or smoking characteristics that differentiate responsiveness to treatment with NRT versus bupropion? (Study 2.5, Study 2.6)
23. Are there genetic markers that differentiate responsiveness to treatment with NRT versus bupropion? (Study 2.5, Study 2.6)
24. What are the parameters of saliva cotinine distribution in populations of smoking and non-smoking adults and in children and how do these vary as a function of sociodemographic factors and smoking variables? (Study 2.7)
25. How has formally allowing the 'cut down then stop' indication for some NRT products influenced smoking cessation patterns in different countries? (Study 2.8)
26. How far do differences in relapse prevention strategies used by different stop smoking services affect long-term success rates controlling for other factors? (Study 3)
27. How far do 4-week success rates of different services vary as a function of differences in mode of service delivery (e.g. drop-in clinic, rolling group, fixed groups, one-to-one pharmacy support etc.) in the NHS stop smoking services? (Study 3)
28. How far are recruitment and retention in NHS stop smoking services influenced by methods of acquiring medication such as PGDs? (Study 3)
29. What is the demand for, use of and effectiveness of different methods of providing NRT combination therapy (e.g. all available on PGD, client purchasing the second medication separately)? (Study 3)
30. How effective are different methods of increasing referrals into the NHS services by GPs and secondary care? (Study 3)
31. Does the Nicotine Cannon provide smokers with an acceptable method of delivering nicotine in sufficient doses and sufficiently rapidly to provide relief of withdrawal symptoms and craving to a greater degree than existing nicotine products? (Study 4)
32. Is the Nicotine Cannon more effective than the best currently available product in aiding smoking cessation? (Study 4)
33. Does Tabex (cytisine) increase the chances of long-term success of quit attempts to a greater extent than placebo and is the medication safe? (Study 5)
34. What is the most effective dosing regimen for cytisine? (Study 5)

35. How does cytisine compare in effectiveness with other smoking cessation medications? (Study 5)
36. Does PRIME Theory provide a more complete and accurate account of the process of stopping smoking than existing models, including the patterning and experience of quit attempts and the process and experience of relapse? (Study 6, Study 1, Study 2.1)
37. Does PRIME Theory generate predictions regarding attempts to stop smoking and success of those attempts that are more accurate than what can be achieved using existing models? (Study 6, Study 2.1)
38. Does PRIME Theory generate intervention elements for promoting and aiding quit attempts that are better than what is currently available? (Study 6)
39. Does showing smokers personalised images and information relating to cardiovascular damage from smoking increase motivational tension about being a smoker more than generic and non-imagery related personalised health advice? (Study 7)
40. Does biomarker feedback that provides visual information about atherosclerotic plaque in the primary care setting; (a) increase the probability of using existing smoking cessation services; (b) increase motivation to stop smoking; (c) increase the probability of attempting to quit; (d) increase smoking cessation rates? (Study 7)

b) 4. Communication and dissemination activity

A very important element of the programme is to continue to provide guidance to policy makers and clinicians on the effectiveness of particular interventions strategies. This has formed an important element of the work in the previous programme and should continue to do so. Aside from the expected papers in scientific journals and conference presentations, senior members of the team will undertake specific activities as follows:

**Robert West:**
1. Continued membership of the Cochrane Smoking Cessation Group's editorial team
2. Development and updating of national and international smoking cessation guidelines
3. Advice to policy makers in the UK and overseas concerning the most up-to-date evidence on effective interventions
4. Continued membership of NICE Programme Development Groups for guidance relating to tobacco control
5. Continued membership of the editorial board WHO Treattobacco.net global treatment guidelines
6. Contribution to the Global Treatment Partnership project to develop smoking cessation treatment worldwide
7. Contribution of review articles on key smoking cessation interventions
8. Continued provision of support and advice to Stop Smoking Services in the UK and presenting at key regional and national conferences
9. Continuing as Editor-in-Chief of the journal, Addiction
10. Continuing as member of the editorial board of the newly established journal, Smoking Cessation
11. Sitting on steering committees and advisory boards for studies and programmes relating to smoking cessation
12. Continuing as a trustee and director of QUIT and providing them with advice and training based on the latest research findings

**Andy McEwen:**
1. Continue as Programme Director of the UK National Smoking Cessation Conference (UKNSCC)
2. Continue as Director of the Smoking Cessation Services Research Network (SCSRN)
3. Advice to policy makers in the UK concerning the most up-to-date evidence on effective interventions
4. Continued provision of support and advice to Stop Smoking Services in the UK and presenting at key regional and national conferences
5. Sitting on steering committees and advisory boards for studies and programmes relating to smoking cessation

6. Continue as Assistant Editor, Addiction

**John Stapleton:**
1. Contributing to NICE guidance
2. Contributing to Cochrane systematic reviews
3. Contributing to ASH working papers
4. Expert statistical advisor for Addiction
5. Advisor to Department of Health

### b) 5. Building capacity

**Smoking Cessation Service Research Network (SCSRN):** The SCSRN will evaluate and promote clinical good practice. The network will also nurture and support NHS Stop Smoking Services in collecting reliable data for research purposes.

**Tobacco Research UK (TRUK):** The team will also continue work that has been started on TRUK. This is a network of tobacco researchers in the UK and an associated website that aims to provide an easy way of sharing ideas and resources. This project was started within the period of the last programme but lack of staff resources prevented it from developing further.

**Post-doctoral researchers:** This programme aims to create the next generation of world-class researchers into the field and the generation after that. AM represents the next generation and JF, LS and EV represent the following generation. We are fortunate in having attracted these researchers to the field and the next task is to retain them and develop their expertise.

**PhD students and pre-doctoral researchers**: The team will also continue to attract and train PhD students with a view to creating the next generation of tobacco researchers. The pre-doctoral research LSt will be encouraged to register for a PhD and ultimately provide a much needed contribution from the discipline of anthropology to the field of tobacco research in the UK.

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