NCCHTA

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Protocol for Cut Down to Quit with Nicotine Replacement Therapies (NRT) in Smoking Cessation

Date: 29/05/2006

1 Title of the project:

Cut Down to Quit with Nicotine Replacement Therapies (NRT) for Smoking Cessation: systematic review and economic analysis.

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2 Name of TAR team and 'lead'

West Midlands Health Technology Assessment Collaboration (WMHTAC)

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3 Plain English Summary

Smoking is one of the greatest causes of illness and premature death in the United Kingdom. It causes a wide range of diseases, including cancers, breathing problems, heart attacks and other arterial disease that in extreme cases may require limb amputation. Giving up reduces the health hazards of smoking. Exposure to second hand smoke increases the risk of disease in non-smokers. Children are especially exposed to secondary smoke. Environmental tobacco smoke has been linked with lung cancer in non-smokers. The nicotine in tobacco causes addiction. After inhaling cigarette smoke nicotine reaches the brain where it brings about changes responsible for the craving of tobacco that makes it very difficult for people to stop smoking. About 70% of smokers say they would like to stop. Currently around a third of smokers attempt to quit in any given year. If smokers who wish to stop managed to do so the public health impact and individual benefits would be enormous. Therefore it is crucial that the people who want to stop continue to be encouraged to stop and are offered a means of doing so. A new strategy for this has been approved recently and has been called "cut down to quit". The idea is to cut down smoking gradually and then to give up altogether; it is thought that quitting from low level smoking will be easier than from a high level and that the procedure might suit people who believe that immediate quitting is unachievable or not what they want. To support people in this strategy they are given nicotine replacement therapy specifically nicotine-containing gum or inhalator. This report will look at the scientific research that assesses how well "cut down to quit" works, whether there are any associated harms and whether it provides good value for money.

4 Decision Problem

4.1 Purpose of the decision to be made

When smokers are repeatedly exposed to nicotine the number of nicotinic receptors in the brain increase and tolerance of these receptors to nicotine's effect occurs. Smokers develop tolerance to some of the behavioural and sympathomimetic effects of nicotine over time, a process called neuroadaptation.[1] When nicotine is stopped abruptly, withdrawal symptoms occur as a consequence of neuroadaptation. Most withdrawal symptoms associated with tobacco dependence are clinically and/or psychologically significant and include the following: aggressiveness, anxiety, confusion, impatience, inability to concentrate, irritability, nicotine craving, restlessness, constipation, dizziness, headache, sweating and difficulty sleeping.[2] Most withdrawal symptoms reach maximal intensity within 24 hours of cessation and diminish in intensity over two to four weeks.[2] Some symptoms such as desire to smoke can persist for months or even years after cessation. Many smokers consider there are benefits from smoking, such as control over weight gain and relief from stress, so that whilst the attempt to stop smoking persists there is a perceived loss of benefits.[2]

The pronounced withdrawal symptoms and tobacco craving that occur on trying to quit smoking may be offset by various therapies including several modes of nicotine replacement therapy (NRT). A previous Health Technology Assessment [2] found that NRT is a more effective intervention for smoking cessation than many other health care interventions, that it is associated with a low level of adverse events and that it is cost effective in terms of life years saved. However, some patients fail to quit despite the availability of NRT and others are not attracted to an intervention that aims to achieve quitting smoking immediately or in the very short term. For these reasons an additional strategy has been proposed that has been called cut down to quit (CDQ) [also known as 'cut down then stop' and 'nicotine assisted reduction to stop']. This aims at a structured gradual reduction in tobacco consumption while the patient is supported with NRT, eventually leading to an increased probability of complete cessation from smoking.

The report will assess the clinical effectiveness, cost effectiveness and adverse events' profile of cut down to quit with NRT when used to facilitate smoking cessation compared to placebo or no treatments or other smoking-cessation interventions.

4.2 Definition of the intervention

NRT can assist smokers in reducing smoking by replacing some of the nicotine formerly obtained from tobacco. Nicorette® Gum and Nicorette® Inhalator (Pfizer) are licensed for cut down to quit in the UK. The product range, cost, recommended dose or likely usage, are shown in Table 1 and Table 2. Both gum and inhalator should be gradually withdrawn. Approximate estimates of gum and inhalator costs for the cutting down to quit program (1year of treatment) are about £200-400 for gum and about £600-1200 for inhalator with the assumption that smokers use a maximum dose at the start of the treatment and reduce linearly to zero by the end of the treatment (assumed day 365); the range of costs quoted are derived from the range of different pack sizes that might be used.

Table 1 Nicorette Gum¥ for cut down to quit[3]

Product	Pack size	Cost RRP (ex VAT)	Dosage	Manufacturer
Nicorette Gum Freshmint	4mgx30stick	£3.99	Around 10 pieces, but not > 15 pieces per day (For smokers older than 18 only and >20 cigarette per day)	Pfizer (Pharmacia and Upjohn)
Nicorette Gum Freshmint, Mint and Original	4mgx105stick	£10.83		
Nicorette Gum Freshmint and Original	2mgx30stick	£3.25	Around 10 pieces, but not > 15 pieces per day (For smokers older than 18 only and >10 cigarette per day)	
Nicorette Gum Freshmint, Mint and Original	2mgx105stick	£8.89		

Table 2 Nicorette Inhalator¥ for cut down to quit[3]

Product	Pack size	Cost RRP (ex VAT)	Dosage	Manufacturer
Nicorette inhalator	10mgx6stick (starter pack)	£3.39	6-12 cartridges per day, (For smokers older than 18 only)	Pfizer (Pharmacia and Upjohn)
Nicorette inhalator	10mgx42stick	£11.37	6-12 cartridges per day, (For smokers older than 18 only)	

¥ *In order to ensure that the review considers all appropriate information on the effectiveness of cut down to quit with NRT, trials on the effectiveness of cut down to quit might include other gum and or inhalator products that are unlicensed as yet.*

4.3 Place of the intervention in the treatment pathway(s)

Nicorette Gum and Nicorette inhalator may help smokers who cannot stop abruptly to cut down the number of cigarettes they smoke prior to quitting and have been licensed for this purpose.[4] Treatment can be initiated after contact and discussion with healthcare professionals in primary care. Subsequent transfer to specialist might follow later. Nicorette Gum and Nicorette inhalator are available at "secure retail outlets" so smokers have the option to initiate and manage their own programme of treatment. An illustrative example of a structured cut down to quit program is shown below.[5]

Step 1: (0-6 weeks) – START CUTTING DOWN

- Smoker sets target for both the number of cigarettes per day to cut down and a date to achieve it by. (Recommend at least a 50% reduction for best results)
- Smoker advised to use Nicorette Gum or Inhalator as required to manage cravings
- Smoker advised to return if not cut down within six weeks

Step 2: (6 weeks up to 6 months) – CONTINUE CUTTING DOWN

- Smoker continues to cut down cigarettes using Nicorette Gum or Inhalator
- Goal should be to complete stop by 6 months
- Smoker advised to return if not managed to stop smoking within 9 months

Step 3: (within 9 months) – STOP SMOKING

- Smoker stops all cigarettes and continues to use Nicorette Gum or Inhalator to relieve cravings

Step 4: (within 12 months) – STOP NICORETTE

- Use of Nicorette Gum or Inhalator is gradually cut down, then stopped completely (within 3 months of stopping smoking)

The cut down to quit program might help smokers to gain confidence in their ability to do without cigarettes and be able to choose a stop date that is achievable for them.

Cut down to quit with NRT may be used as a stand alone intervention or with an adjunct such as motivational support.

4.4 Relevant comparators

Comparators include no treatments or placebo or other therapies that aid smoking cessation including non-pharmacological approaches such as motivational support, acupuncture and some pharmacological agents, of which bupropion is the only one licensed for this indication in the UK. Where cut down to quit is used together with an adjunct the appropriate comparator will be the adjunct element alone.

4.5 Key factors to be addressed

The primary focus of this assessment will be clinical and cost outcomes from the perspective of the healthcare system (NHS) and Personal Social Services (PSS).

5 Methods

5.1 Synthesis of evidence of clinical effectiveness

The report will consist of a systematic review of systematic reviews and of randomised controlled trials (RCTs) evaluating the effectiveness of cut down to quit with NRT.

A broader range of studies will be considered for inclusion to establish the adverse events' profile of long term use of NRT (months), and may include: non-randomised controlled studies, cohort studies, case-controlled studies, surveillance studies and surveillance data. Pragmatic judgements on inclusion will be based on duration of treatment and length of follow-up relative to the included RCTs, number of patients and the number of studies requiring analysis.

We will employ conventional data synthesis methods, including meta-analysis as appropriate according to the heterogeneity of studies. Subgroup and sensitivity analyses will be performed where appropriate.

In addition we will explore the possibility of identifying individual patient data; this will require cooperation of trialists and/or manufacturers and may be limited by willingness to share data and the time constraints of the review. When and if the individual patient data is available, the analyses will be carried out at individual patient level. Each trial will be analysed separately. Results from each trial will be then combined. If data allows, time to event (quitting) analysis will also be carried out. The collection and analysis of IPD makes it possible to check detailed data, to assess quality of randomisation and follow up, to identify missing data.

5.1.1 Search strategy

Comprehensive searches will be undertaken to identify systematic reviews using an established search protocol (Appendix 8.1, page 2). For the effectiveness review the following sources will be searched for primary studies and other reviews:

- Bibliographic databases: Cochrane Library (Wiley), MEDLINE (Ovid) and MEDLINE In-Process (Ovid), EMBASE (Ovid), CINAHL (Ovid), PsycINFO (Ovid), Science Citation Index. Searches will date from 1992 onwards since cut down to quit interventions are very unlikely to predate 1992.
- Research registries of ongoing trials including National Research Register, Current Controlled Trials *meta*Register and Clinical Trials.gov
- Citations of relevant studies and reviews
- Further information will be sought from contacts with experts.

No language restrictions will be applied. Examples of search terms to be used include smok* or tobacco or nicotin*, nicotine next replacement next therap*, random*, control* near (trial* or stud*), gum or inhaler* or spray*

All titles and abstracts will be screened for relevance. Full paper manuscripts of any titles/abstracts which may be of potential relevance, will be obtained, and the relevance of each article will be assessed independently by two reviewers according to pre-defined criteria. Studies that fail to satisfy all criteria will be excluded and the reason for their exclusion noted. Any discrepancies will be resolved by consensus and where necessary a third reviewer will be consulted.

5.1.2 Inclusion criteria clinical effectiveness

Population:
Smokers who are currently unable or unwilling to quit abruptly.

Intervention:
NRT with Gum or Inhalator alone or as part of combination therapy (e.g. motivational support).

Comparator:
Placebo or no treatment, non-NRT drugs for smoking cessation, psychological interventions (e.g. motivational support) for quitting. Where the intervention embraced an adjunct therapy so also will the comparator.

Outcome measures:
Quit rates must be provided.

The main clinical outcome of interest will be the number of participants who are not smoking at for example 6, 12, or more months after the start of therapy. Other primary outcomes of interest will be smoking intensity, changes in attitudes to smoking (quitting and or cutting down), NRT consumption during treatment, health related quality of life, and adverse events.

Study design:
RCTs and Systematic reviews.

Operational application of inclusion criteria:
Studies in which the population are defined as unwilling or unable to quit “in the next month”, or “in the short term”, or “abruptly” or studies in which smokers have been excluded on the basis of their willingness to attempt to quit, will be judged “level 1 CDQ studies” and will be included.

Some studies may fail to unambiguously define the population with regard to quitting. Where details of the population indicate only the inclusion of smokers unwilling or unable to quit (i.e. no time scale specified), but willing to change smoking behaviour, such studies will be judged “reduction studies” or “level 2 CDQ studies”) and will be included provided that quit rates are reported.

Studies in which the included smokers are neither stated as unwilling or unable to quit and information regarding their desire of cutting down is not provided will be excluded.

If the application of these criteria yields few included studies there will be a discussion with NICE at the earliest possible opportunity.

5.1.3 Caveat to and comment on inclusion criteria

The rationale for the inclusion criteria and their operational application is contingent upon the following:

- NRT study populations appear to be poorly, inconsistently or ambiguously defined with regard to willingness/ability for quitting, cutting down and continuing smoking.
- Lack of clarity regarding studies[A] and their populations considered by the MHRA in approving NRT license for CDQ.

5.1.4 Exclusion criteria

See operational application of inclusion criteria.

5.1.5 Adverse effects

For the evaluation of adverse events a broader range of study designs, in addition to RCTs, may be considered; the benefit of extending study design beyond RCTs will be assessed pragmatically (see above). Such studies will be selected under the following specific categories: studies whose primary objective was to investigate the incidence of adverse events; investigations related to some specific aspect of the safety of the agent, e.g. effect on cardiovascular function. Events of interest will be those occurring during NRT consumption while smoking (in cut down to quit programme), and those associated with long term use of NRT.

5.1.6 Potential sub-groups to be examined

See section 5.1.9

[A] MRHA refer to support for the license application provided by seven good quality RCTs as follows: "*..seven well-designed (double blind, randomised and placebo-controlled) studies were submitted to demonstrate efficacy and safety--five with nicotine gum and two with inhalator)..*" ;however no citations were provided and enquiries to MRHA established that the identity of studies remains confidential information.

5.1.7 Data extraction strategy

Data will be extracted by one reviewer using a standard data extraction form (see example, Appendix 8.2, page 2), and independently checked for accuracy by a second reviewer. Disagreements will be resolved by discussion and with involvement of a third reviewer if necessary. Where information is missing, this information will be sought from the authors. Data from studies with multiple publications will be extracted and reported as a single study; in the case of reported discrepancies the most recent publication will be utilized.

5.1.8 Quality assessment strategy

The quality of the individual studies will be assessed by one reviewer, and independently checked for agreement by a second reviewer. Any disagreements will be resolved by consensus and if necessary a third reviewer will be consulted. The quality of included studies will be assessed according guidelines proposed in NHS CRD Report No.4.[6]

5.1.9 Methods of analysis/synthesis

Details of the extracted data and quality assessment for each individual systematic review and RCT of effectiveness will be presented in structured tables and as a narrative description.

Where possible, data from different durations of follow-up will be examined separately. Greater emphasis will be placed upon data derived from longer follow-up periods. Where possible continued abstinence rather than point prevalence will be used to report levels of smoking cessation.

The possible effects of study quality on the effectiveness data will be discussed. Where possible, subgroup analyses will be conducted to assess differences in effectiveness between different participant groups.

Based on the nature of the outcome (binary, continuous or time-related) an estimate of effect size will be calculated for each individual study. Where possible, and appropriate, effect sizes will be pooled across studies using meta-analytic methods.

Should IPD be available, time to event analysis will be employed to examine time related rates of cutting down and of quitting, using models that incorporate patient level variables.

If data is available, the following subgroups will be examined related to cut down to quit with NRT: age, sex, ethnicity, occupation, employment status, extent of social support,

cardiovascular disease, pregnancy, length of smoking, intensity of smoking and social class.

5.2 Synthesis of evidence of cost-effectiveness

5.2.1 Search strategy

A comprehensive search for literature on the cost-effectiveness of cut down to quit with NRT for smoking cessation will be conducted. Studies on costs, quality of life, cost effectiveness and modelling will be identified from the following sources:

- Bibliographic databases: MEDLINE (Ovid), EMBASE (Ovid), Cochrane Library (Wiley internet version) (NHS EED and DARE), Office of Health Economics HEED database.
- Internet sites of national/international economic units

Searches will not be limited by language restrictions.

Two reviewers will independently screen all titles and abstracts for relevance. Any discrepancies will be resolved by consensus and where necessary a third reviewer will be consulted.

5.2.2 Inclusion and exclusion criteria

Any relevant studies that evaluate cost-effectiveness or cost-utility of cut down to quit with NRT will be eligible for inclusion, e.g. RCTs, prospective/retrospective cohort studies, and simulation modelling studies.

The outcome measures should be incremental cost per quitter, or per life year saved, or ideally, per quality adjusted life year gained (QALYs) compared with no or alternative interventions. Studies reporting cost-benefit of interventions for smoking cessation will also be included.

5.2.3 Quality Assessment Strategy

Quality assessment for assessments of cost effectiveness will be done using standard criteria.[7, 8]

Studies will be summarised on the basis of key items of information including: form of economic analysis, comparator/s, perspective, time horizon, modelling, effectiveness data, health state valuations, resource use data, unit cost data, price year, discounting.

5.2.4 Methods of analysis/synthesis

In order to explore the cost-effectiveness of cut down to quit with NRT, we may expand existing decision analytic models or develop our own decision-analytic model depending on the results of our literature reviews. The choice of model will be dependent on both the appropriate structure of the model and the quality of previously published models. If the data allows we will conduct a probabilistic sensitivity analysis, otherwise we will conduct one-way and two-way sensitivity analyses.

The cost-effectiveness analysis will be expressed in terms of incremental cost per quality adjusted life year. The perspective for the reference case model will be NHS/PSS. Subject to the availability of suitable data, the costs and benefits of different service strategies and optimum care package (e.g. setting, dosage, supervision, monitoring, etc) will be explored in sensitivity analysis. The appropriate discount rate (3.5% for both costs and benefits) will be applied.

6 Other considerations

The review team are not expecting to receive any industry dossier on this topic, and apart from seeking IPD, no industry dossier will be specifically sought by the review team for this report.

The team undertaking this review will work closely with the ARIF team undertaking brief reports on the recent license extension in the use of NRT for specific populations (pregnant women, adolescents and people with CVD),[9,10,11] and NRT combination therapies. Any studies identified during searches for these brief reports relevant to CDQ will be considered for inclusion in this review.

7 Competing interests of authors

None.

8 Appendices

8.1 Appendix 1 Search strategy for systematic reviews

1. Cochrane Library
- Cochrane Reviews
- Database of Abstracts of Reviews of Effects (DARE)
- Cochrane Central Register of Controlled Trials (CENTRAL)
- Health Technology Assessment (HTA) database

2. ARIF Database
An in-house database of reviews compiled by scanning current journals and appropriate WWW sites. Many reviews produced by the organisations listed below are included.

3. NHS CRD
- DARE
- Health Technology Assessment Database
- Completed and ongoing CRD reviews

4. Health Technology Assessments and Evidence Based guidelines
- NICE appraisals and work plans for TARs, Interventional Procedures and Guidelines programmes, Public Health excellence
- Office of Technology Assessment
- NHS Coordinating Centre for Health Technology Assessments
- Canadian Co-ordinating Office for Health Technology Assessment
- New Zealand Health Technology Assessment
- Wessex STEER Reports
- Agency for Healthcare Research and Quality (AHRQ)
- National Horizon Scanning Centre
- SIGN (Scottish Intercollegiate Guidelines Network)

5. Clinical Evidence

6. Bandolier

7. National Horizon Scanning Centre

8. TRIP Database

9. Bibliographic Databases
- Medline – systematic reviews
- Embase – systematic reviews
- Other specialist databases

10. Contacts
Cochrane Collaboration (via Cochrane Library), Regional experts, especially Pharmacy Prescribing Unit, Keele University (& MTRAC) and West Midlands Drug Information Service for any enquiry involving drug products.

8.2 Appendix 2 DRAFT Data Extraction Form

Trial details	*Trial ID*	
	Intervention / Control	
	Target maintenance dose / duration	
	Patient condition-type	
	Type of trial design	
	Co-therapy elements	
	Setting	
	Study start and end dates	
	Centres (n) / Country	
Trial design	*Run-in phase*	
	Titration phase (including details of schedule & frequency of doses)	
	Maintenance phase dose/ duration	
	Withdrawal phase dose/ duration	
	Comments on design	
Quality assessment for RCTs	*Was assignment of treatment described as random?*	
	Was method of randomisation described?	
	Was the method really random?	
	Was allocation of treatment concealed?	
	Who was blinded to treatment?	
	Was method of blinding adequately described?	
	Were eligibility criteria described?	
	Were groups comparable at study entry?	
	Were groups treated identically apart from the intervention?	

	Was ITT used?			
	Were withdrawals stated?			
	Were reasons for withdrawals stated?			
	Was a power calculation done?			
	Comments			
Quality assessment for observational studies	*Was the population base described?*			
	Were recruitment / eligibility criteria reported?			
	Was there consideration of possible confounding factors?			
	Were losses to follow up reported?			
	Were losses to follow up > 20%?			
	Were other interventions received differentially during follow up?			
	Was missing data (group or time point data) accounted for?			
	Comments			
Eligibility criteria	*Inclusion criteria (pre / post randomization / enrollment)*			
	Exclusion criteria			
Baseline characteristics			***[control]***	***[study drug]***
	Number randomized			
	Number analysed			
	Age (wks, mos, yrs) (mean, SD; median, range)			
	Male:female n : n			
	Duration of dependence (wks, mos, yrs) (mean, SD; median, range)			
	Age at start smokings (wks, mos, yrs) (mean,			

	SD; median, range)			
	Newly treated with study intervention, n (%)			
	Previously treated with study intervention, n (%)			
	N^o: (1,2,3 etc) concomitant therapies, n (%)			
	Concomitant non-drug treatments, n (%)			
	Previous treatments, n (%) (please specify)			
	Ethnicity (%)			
	Professional /employment			
	Employed (%)			
	Educational level			
	Marital / other status			
	Comments			
Monitoring and outcomes	*Smoking consumption (self reporting etc)?*			
	Were arrangements for blinding mentioned?			
	Who recorded outcome?			
	How often outcome measured?			
	Frequency / type of health-care contacts			
	Primary outcome(s) reported including timepoints if repeated			
	Smoking cessation			
	Ad hoc' outcomes reported (if emphasised and not in methods)			
	Comments			
Results unadjusted where available			***[control]***	***[study intervention]***
	Median follow-up			
	Maintenance dose achieved			
			Results (diff, or	***CI for difference;***

			by arm)	***p-value***
	outcome(s)	*details to be clarified*		
	Outcomes	*details to be clarified*		
	Outcomes	*details to be clarified*		
	Comments (including whether unadjusted results reported)			
Adverse Events	*Criteria for reporting*		***[control]***	***[study drug]***
	Events n/N			
	Comments			
Conclusions	*Author's conclusions*			
	Our conclusions			

9 Details of TAR team

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3. Karen Biddle, Administrator, biddlek@bham.ac.uk, 0121 4146774
4. Ms Elaena Wells, Senior manager, E.K.Wells@bham.ac.uk, 0121 4147450

10 Timetable/milestones

Event	**Deadline / Date**
An agreed protocol	12/04/06* protocol submission to NICE:19/05/06 suggested revised agreed protocol deadline: 26/05/06
Progress report to NCCHTA/NICE	12/09/06
Draft report	16/10/06
Finalised report	09/11/06

*negotiation between WMHTAC, NCCHTA and NICE of the exact topic to be addressed for the 1 TAR unit of capacity available for this report meant that this milestone was not met. Whether there are any knock on effects of this delay are unknown at present.

11 References

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