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Economic evaluation of interventions which aim to prevent smoking relapse: systematic review and critical appraisal

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ABSTRACT

Aim: To carry out a systematic review of studies that have conducted economic evaluations on smoking relapse prevention interventions by critically appraising the quality of the methodology.

Methods: All relevant articles were identified by searching three electronic databases MEDLINE, EMBASE, Cochrane Library and reference lists of relevant articles. To be included, an economic evaluation of smoking relapse prevention needed to have been undertaken, modelling studies were permitted. Two reviewers screened all articles from the search for eligibility based on the predefined criteria for inclusion and a single reviewer extracted methodological details, study design and outcomes into summary tables. The methodological quality for the included papers was judged using the checklist recommended by the British Medical Journal (BMJ) for assessing economic evaluation studies.

Results: Eleven full text papers were retrieved and three studies met the inclusion criteria. Different interventions were assessed by each of the three, each of which was estimated to be cost-effective based on cost utility analysis. None of the three studies met all the criteria on the checklist.

Conclusions: At present few studies analysing the economic evaluation of smoking relapse prevention interventions have been conducted and further studies are required in this area. Future high-quality studies performed either by conducting clinical trials alongside economic evaluation or modelling economic evaluation from published trials are required. It is recommended that the associated methods are clearly stated including the viewpoint of the analysis.

Key words: economic evaluation, smoking, relapse prevention, quality-adjusted life years, systematic review.

1. Introduction

1.1. Background: The Health Problem

According to a World Health Organization's report on global tobacco epidemic (WHO, 2013), the use of tobacco through cigarette smoking has continued to be the leading cause of preventable death worldwide. The report estimates that tobacco use kills approximately six million people worldwide and causes more than half a million dollars worth of economic damage each year. Smoking is said to be a major cause of various other diseases that invariably lead to death. Wesley et al (1997) highlight smoking as the single most preventable cause of premature mortality in the United States. A Policy report on a smoke free future in England (Department of Health, 2010), lists the three most common smoking related diseases resulting in death as: lung cancer, chronic obstructive pulmonary disease (COPD) and cardiovascular diseases (i.e. heart and circulatory diseases). Fiore et al (2008) state that recent research has documented the significant health dangers associated with the involuntary exposure to tobacco smoke, however despite the risks associated with smoking and exposure to tobacco smoke, smoking has remained a prevalent issue.

There have been several smoking cessation studies aimed at assisting smokers give up smoking. According to Bolin et al (2007), the prevalence of epidemiological evidence highlighting the risks associated with smoking makes it possible to estimate the benefits of smoking cessation which can be seen in terms of avoided smoking-related morbidity and mortality. Wasley et al (1997), state that most smokers who contemplate quitting usually require several attempts before achieving sustained abstinence. In recent years, significant progress has been made in the development of cessation programs for tobacco smoking; however the best programs are known

to continually have high rates of relapse (Brandon et al, 2000). Ferguson et al (2005) make the point that up to 75% of smokers who receive treatment support from the United Kingdom NHS stop smoking services relapse within six months, this is in line with the estimate by Fiore et al (2008) that on the average, 70% of smokers who receive formal smoking cessation counselling relapse during the first year after quitting. The increasing rate of relapse has led to a rise in not only smoking cessation interventions but also interventions that help quitters maintain abstinence.

The main component of tobacco smoking that is responsible for the addictive nature of smoking is nicotine. Nicotine substance has been termed to be as addictive as cocaine and heroin, it triggers the release of dopamine and other neuro-transmitters in the brain, and this reinforces the smoker's dependence on tobacco (Cahill et al, 2011). McClure and Swan (2006) make the point that once tobacco smoke is inhaled, it travels down the small alveoli of the lungs at which stage absorption of nicotine into the blood is rapid and this absorption stimulates the blood. A reduction in the nicotine level contained in the blood results in withdrawal symptoms which could take the form of restlessness, loss of concentration, dizziness, increased appetite, irritability, nicotine craving, sweating, difficulty sleeping and headache. Withdrawal symptoms begin hours after the last cigarette; it reaches its peak within 24 hours and eases out gradually over about 2-4 weeks (Wang et al 2008; Kenny et al, 2012). Government policy considers a patient to have quit smoking if he or she has abstained from smoking for at least a week; however a relapse can be said to occur if an individual resumes smoking anytime after four weeks.

In practice, smoking relapse interventions are an extended form of smoking cessation interventions which often times require longer follow-up periods. Hayek et al (2009) indicates that there is no clear cut distinction between an intervention for smoking relapse prevention and an extended smoking cessation treatment owing to the fact that a relapse refers to the resumption of smoking at any time after the quit date. According to Brandon et al (2000), a review of the existing literature revealed three characteristics of interventions that relate to increased maintenance of abstinence in sub groups of smokers; the amount of treatment contact, coping skills training and the level of social support.

1.2. Description of Interventions

Smoking cessation and relapse interventions can be broadly classified into pharmacological interventions (also referred to as pharmacotherapy) and behavioural interventions. Pharmacological interventions involve the use of drugs or drug-related treatment and are aimed at reducing the effect tobacco smoking has on the body as well as addressing the withdrawal symptoms individuals are faced with at the onset of quitting smoking. Behavioural interventions on the other hand involve actions that have direct influence on individual behaviours. Main line pharmacological interventions are: Varenicline, Bupropion and Nicotine Replacement Therapy (NRT) (Cahill et al, 2011).

NRT is aimed at reducing an individual's motivation to smoke by gradually decreasing the nicotine level contained in the body as a result of smoking. An individual's craving for nicotine is reduced by supplying nicotine to the blood stream via alternative means other that smoking. It is the most common type of pharmacotherapy and is available in different formulations with the

form available to each country varying. Forms of NRT include nicotine gum, patches, inhalators, nasal spray, tablets and lozenges. Bupropion is described as the first non-nicotine based smoking cessation treatment. Cahill et al (2011) makes the point that it is preferred by smokers who have been unsuccessful at quitting using NRT or those who do not wish to use a nicotine-based treatment. It was licensed in the United States for use in 1997 and in the United Kingdom in 2000 and is available only via prescription. Varenicline is a selective nicotine partial agonist that was developed by Pfizer Inc. Its role as an agonist is to maintain moderate level of dopamine to counter the withdrawal symptoms in smokers and as an antagonist to reduce satisfaction smokers derive from smoking (Champion et al, 2008). Other available pharmacological interventions include Clonidine, Lobeline, Nortriptyline, Rimonabant, Nicotine vaccines as well as some forms of antidepressants.

Behavioural interventions are aimed at addressing the psychological effect of quitting smoking on the individual. It is often delivered in a variety of ways, some of which includes (but are not limited to) Cognitive Behavioural Therapy (CBT), group-based or individual counselling, mobile and internet support, self-help materials, hypnotherapy, acupuncture amongst others. CBT can be delivered through therapists in primary care or computer/internet based with the aid of pre-defined questionnaires tailored at understanding moods and altering thoughts as well. CBT as a form of smoking cessation and relapse therapy focuses on enhancing mood management skills by influencing the thoughts and activities that trigger the urge to smoke and decreasing relapse-related thoughts.

Self-help materials are usually in print and can be found in stop-smoking clinics and organizations and are often available online. They are provided to help abstinent smokers cope with withdrawal symptoms as well as reinforce their decisions to quit and usually contain the benefits that accrue to abstinent smokers such as diseases avoided, increase in productivity and quality of life and the benefits that accrue to the society as a whole. A notable self-help material is the Stay Quit booklets used by Brandon et al (2000) which was later renamed Forever Free booklets.

1.3. Importance of the review

Continued increase in the availability of smoking relapse prevention interventions will enhance the role economic evaluation plays in informing health care budget decisions and provision of guidelines for treatment. The validity of results obtained from economic evaluations should therefore be assessed and the quality of the methods applied should be critically examined by users of their results. The aim of this review is to provide an overview of studies that have conducted an economic evaluation of smoking relapse prevention interventions by critically appraising the quality of the methodology. This is in order to determine their adequacy for decision-making and also identify areas of improvement for future research. To the best of our knowledge, a review of economic evaluation studies of smoking relapse prevention intervention has not been conducted albeit there have been reviews of the effectiveness of smoking relapse prevention interventions for abstinent smokers, such as Agboola et al (2010).

2. Methods

The Relapse prevention intervention defined by Hajek et al (2005) as “interventions that seek explicitly to reduce relapse rates after an acute treatment phase is successfully completed, or at some time after the quit date of a self-quit attempt” was adopted for this study.

2.1. Literature Search and Study Selection

The literature search involved identifying relevant reference sources, formulating a comprehensive search strategy for various sources, and documenting the results for each search. Economic evaluation is defined as “the comparative analysis of alternative courses of actions in terms of both costs and consequences” (Drummond et al., 2005). In identifying articles that were of relevance to the aim of this review, terms associated with economic evaluation (such as: costs, cost effectiveness, cost utility), smoking and its related outcomes (such as: smoking, relapse, recurrence, smoking cessation) were used for the search. The search terms undertaken were identical to those used in Gaultney et al (2011) and Song et al (2009) respectively, full lists of search terms are stated in Appendix 1. The reference lists of eligible articles were also screened for further relevant publications that may have been missed out, no study that met the inclusion criteria was found through this screening.

The search was not limited to a particular study design such as randomised controlled trials (RCT), as the type and nature of the subject matter might involve some modelling or secondary study design and a limitation would involve missing out potentially vital information contained in these papers. There were no restrictions as to the language of the published studies, provided the study has an already translated English version or could be easily translated.

A literature search was performed on the 24th of June 2013; this included electronic searching of MEDLINE (Ovid) 1946 – June 2013, EMBASE (Ovid) 1974 – 2013 and the Cochrane Library-{which includes NHS-EED and the Cochrane Database of Systematic Reviews} (Wiley) 2013. The same search strategy was used in MEDLINE and EMBASE while a similar but different strategy was used to search the Cochrane Library (this is detailed in Appendix 1 and total number of papers identified from each database is given in the flow diagram on Table 1). The results of the initial search were downloaded into Endnote® and articles that were duplicated from the multiple databases were removed prior to the start of the review.

2.2. Title and Abstract Review

All titles and abstract were screened for relevance by two independent reviewers. The title review was designed to capture all studies that reported on smoking or the use of tobacco. The abstract review was designed to identify articles that met the inclusion criteria in line with the aim of the study. An abstract was excluded if it did not satisfy all inclusion criteria (highlighted in the preceding paragraph) and the reason for their exclusion was recorded with some of the reasons stated as: smoking cessation study with no relapse measured, not an economic evaluation, no cost analysis conducted. Any discrepancies between the two reviewers at this stage were resolved by a third reviewer. One of which was whether to include a systematic review paper on smoking relapse prevention, however based on the fact that the paper did not involve an intervention and a control treatment, the paper was excluded from the review. Full copies of articles deemed to be of potential relevance were then obtained and underwent another independent review by a single reviewer to determine their eligibility for full data extraction and review.

2.3. Inclusion and Exclusion Criteria

The included studies must have carried out a full economic evaluation. Study design was not limited and could either be randomised controlled trials, retrospective cohort studies or simulation modelling studies in which participants had either quit smoking prior to the study or at baseline assessment for the purpose of preventing relapse. There were no restrictions as to the form or type of intervention (pharmacotherapy or otherwise) used provided it was reported clearly by the researcher of the study as intended to prevent relapse to smoking. There was no preference to the form(s) of comparators used and it could vary from a placebo, usual care, the best treatment alternative or doing nothing.

Full economic evaluation can either be a cost-effectiveness analysis (CEA), a cost-benefit analysis (CBA), or a cost-utility analysis (CUA). When comparing two interventions aimed at addressing the same health problem, cost-effectiveness analysis relates costs to a common effect and its results are stated in terms of cost per unit of effect or effect per unit of cost, effect in this instance can be measured as life-years gained, which is usually valued on an incremental basis. Cost-utility analysis relates the incremental cost of an intervention to the incremental health benefit attributable to that intervention, health benefits are measured in term of utility. Utility is used to measure the benefits that accrue from a health care intervention and reveals individuals or society's preference for a particular set of health outcomes. Utility analysis enables comparison of costs and effects of different interventions by using generic outcome measures which are usually expressed as quality-adjusted life-years (QALYs). A common method of generating utility is through the use of health-status based questionnaires such as the EQ-5D or SF-6D where by respondents are required to rate certain aspects of their well being on a scale.

Results of CUAs are expressed in terms of cost per QALY gained or cost per healthy year. Cost-benefit analysis values the costs and the benefits of alternative interventions in monetary terms. CBA makes it possible to estimate the amount of resources used up or saved by each intervention. The results of CBA are stated either in the form of a ratio of costs to benefit or as a simple sum which represents the net benefit of one intervention over the other (Drummond et al, 2005).

2.4. Data Extraction

Data extracted from each full paper is outlined in Table 1. All included papers were carefully examined and the data extracted and analyzed by one reviewer. Details of the key components of the economic evaluation methods extracted from the included papers are presented in a tabular form in Appendix 2. Data from studies with more than one publication that are based on the same data were extracted and reported as a single study; and in the case where there were discrepancies in the reported results or outcomes, information from the fullest study report was used.

Table 1 Data extracted from included papers

Study characteristics
- Author(s) and year of publication
- Country of study
- Type of economic evaluation
- Time period of study
- Intervention
- Treatment

Participants
- Sample size (mean age)
- Sex
- Co-morbidities
- Inclusion criteria

Cost data and sources
- Cost items and perspectives

- Cost data sources
- Mean cost of intervention
- Discount rate
- Currency year

Outcomes data and sources

- Outcome(s) used in economic evaluation
- Measurement point(s) for effects
- Effectiveness of interventions
- Efficiency data sources

Cost effectiveness

- Incremental cost
- Incremental effect
- Cost-effectiveness ratio
- Sensitivity analysis and results
- Subgroup analysis and results
- Author's conclusions
- Funding source

2.5. Quality Assessment

Shemilt et al (2008) makes the point that, critical appraisal of health economic studies can be informed by the use of checklists that have been developed to guide the assessment of methodological quality. The methodological quality of the included studies for this review were assessed using the British Medical Journal (BMJ) checklist for assessing economic evaluations (Drummond and Jefferson, 1996). This checklist containing 35 items (outlined on Table 2) evaluates aspects of economic evaluation studies under three main sub-headings: study design; data collection and analysis and interpretation of results. Each item on the checklist was assigned a 'Yes' or 'No' and in some cases based on the study design and in cases where the item was not incorporated at all in the study, a 'not applicable' was assigned. In cases where enough information was not provided to determine a clear answer to the question, the paper was scored a 'no' for the item in question.

Table 2 – List of BMJ Checklist applied in quality assessment

Item	**Study Design**
1.	The research question is stated.
2.	The economic importance of the research question is stated.
3.	The viewpoint(s) of the analysis are clearly stated and justified.
4.	The rationale for choosing alternative programmes or interventions compared is stated.
5.	The alternatives being compared are clearly stated.
6.	The form of economic evaluation used is stated.
7.	The choice of form of economic evaluation is justified in relation to the questions addressed.
	Data collection
8.	The source(s) of effectiveness estimates used are stated.
9.	Details of the design and results of effectiveness study are given (if based on a single study).
10.	Details of the methods of synthesis or meta-analysis of estimates are given (if based on a synthesis of a number of effectiveness studies.
11.	The primary outcome measure(s) for the economic evaluation are clearly stated.
12.	Methods to value benefits are stated.
13.	Details of the subjects from whom valuations were obtained were given.
14.	Productivity changes (if included) are reported separately.
15.	The relevance of productivity changes to the study question is discussed.
16.	Quantities of resource use are reported separately from their unit costs.
17.	Methods for the estimation of quantities and unit costs are described.
18.	Currency and price data are recorded.
19.	Details of currency of price adjustments for inflation or currency conversion are given.
20.	Details of any model used are given.
21.	The choice of model used and the key parameters on which it is based are justified.
	Analysis and interpretation of results
22.	Time horizon of costs and benefits are stated.
23.	The discount rate(s) is stated.
24.	The choice of discount rate(s) is justified.
25.	An explanation is given if costs and benefits are not discounted.
26.	Details of statistical tests and confidence intervals are given for stochastic data.
27.	The approach to sensitivity analysis is given.
28.	The choice of variables for sensitivity analysis is given.
29.	The ranges over which the variables are varied are justified.
30.	Relevant alternatives are compared.
31.	Incremental analysis is reported.
32.	Major outcomes are presented in a disaggregated as well as aggregated form.
33.	The answer to the study question is given.
34.	Conclusions follow from the data reported.
35.	Conclusions are accompanied by the appropriate caveats.

2.6. Data synthesis and analysis

It was expected that studies would differ significantly in terms of the study design, the type of intervention as well as the study participants; therefore a meta-analysis would not be suitable. A narrative synthesis was therefore planned in order to analyse and report study findings. As opposed to a meta-analysis, a narrative synthesis does not include quantitative synthesis. The main summary measure for effectiveness was the incremental cost effectiveness ratio (ICER) and the abstinent ratio at follow up between intervention and control groups where data was supplied.

3. Results

3.1 Number of studies identified

The search strategy yielded a large number of studies from each of the electronic bibliographic databases searched. Figure.1 depicts the study selection process that was conducted for this review. After duplicates were removed from the search results, 699 papers were identified, of which 473 were excluded during the initial screening of the titles. These papers were clearly not related to smoking. 215 more papers were excluded after screening abstracts. The main reasons for exclusion were that most of the studies, though smoking-related were not economic evaluations and the papers that were economic evaluation studies analyzed smoking cessation interventions with participants recruited for the studies being current smokers as opposed to former smokers.

The full list of smoking-related papers excluded at the abstract stage with reasons for exclusion is presented in Appendix 3. Of the 11 articles retrieved for full inspection, 3 were smoking relapse prevention study protocols and were not suitable to be the included in the review as they contained a prospective plan of on-going studies that are yet to evaluate costs and benefits of the

interventions being examined. 2 papers measured smoking cessation only and 1 was an exact duplicate of one of the included studies. The last 2 papers contained the costing aspect of the included papers and shared the same study sample characteristics (Chirikos et al, 2004; Ruger et al, 2009). To avoid repeated presentation of same results, these two papers were excluded however references were made to them in the data extraction table. The data extracted from the 3 papers included in this review are presented in Appendix 2.

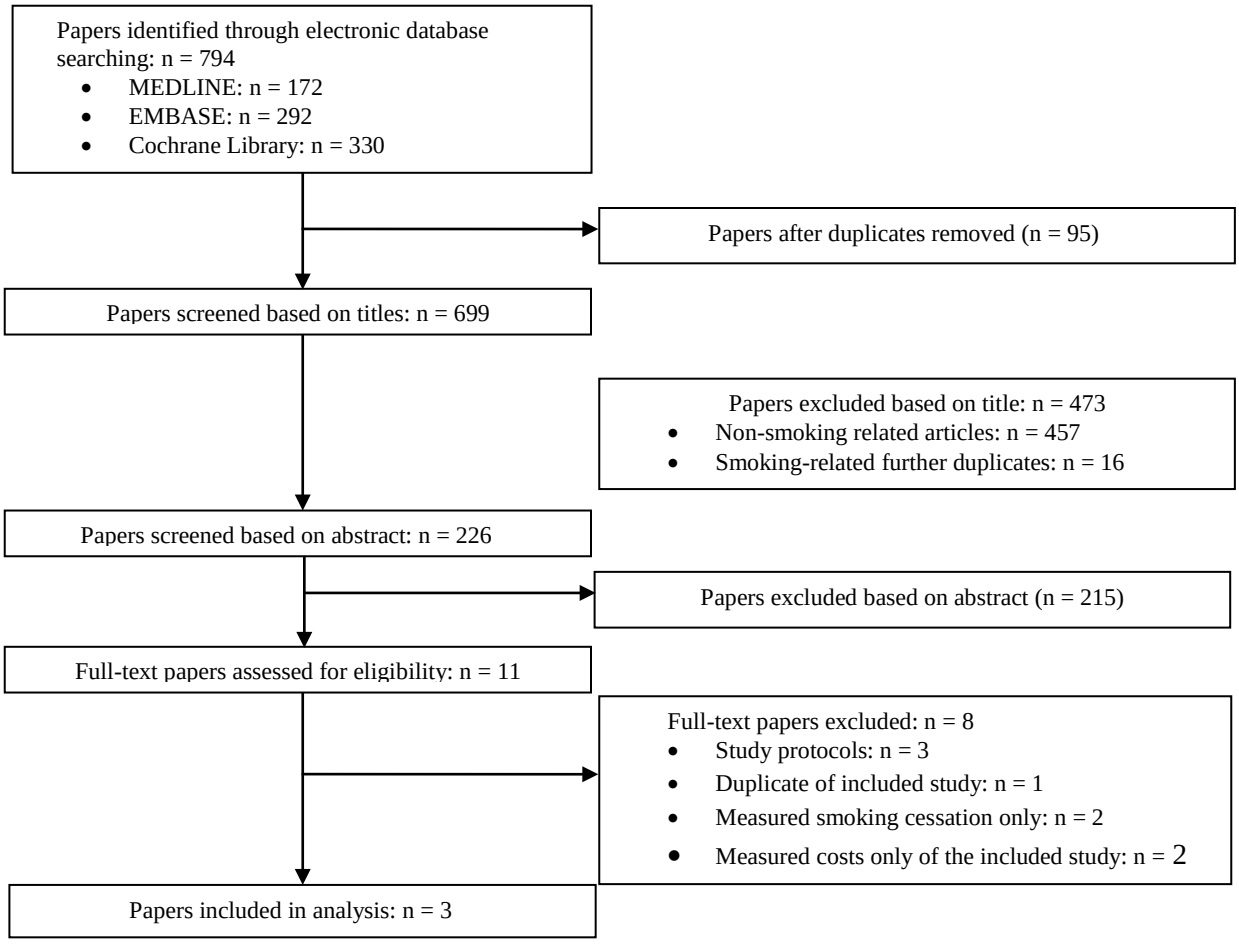


Figure 1 – Study selection flow diagram.

3.2. Description of the included studies

Of the three included papers, two of the papers {Brandon et al (2004) and Ruger et al (2008)} were funded by the National Cancer Institute and both studies were carried out in the United States while the third paper by Coleman et al (2010) was a Health Technology Assessment paper and the study was published in the United Kingdom (it should be noted that this was a modelling study based on results from systematic reviews of published trials from different countries, which in effect makes study findings more reliable and somewhat generaliasable). All papers were published between the years 2004 – 2010. Details of the comparators and sources of effectiveness are included in the data extraction table. Details of the quality of the methodology for each study using the BMJ checklist are provided in Table 3. All three papers were cost-effectiveness analysis studies. Brandon et al (2004) and Ruger et al (2008) were both randomised controlled trials whilst the paper by Coleman et al was a modelling study with data generated from already published trials. Based on earlier discussions, the characteristics and design of the included studies were analysed based on the form of intervention used, that is, pharmacological or behavioural intervention.

3.2.1. Behavioural interventions

Brandon et al (2004) evaluated the efficacy and cost-effectiveness of a minimal intervention to prevent smoking relapse using a smoking relapse prevention intervention named ‘Forever Free’ which contained eight booklets. The study aimed at analysing the effects of different levels of content and contact. The intervention was divided into four categories: (a) low contact-low content (minimal contact condition) involved mailing of a single booklet, (b) low contact-high content (massed mailing condition) involved mailing all eight booklets at once, (c) high contact-

low content (repeated letters condition) involved mailing of a single booklet followed by seven short supportive letters at 1, 2, 3, 5, 7, 9, and 12 months, (d) high contact-high content (repeated mailings) involved mailing all eight booklets at same intervals as (c).

The study design was a single-centre randomized controlled trial (RCT); this design method is considered gold standard for assessing the efficacy of interventions as it provides a higher level of internal validity. The study recruited 895 potential participants of which 704 returned completed baseline forms. 431 participants who reported at least one week of abstinence at the time of baseline questionnaire completion were randomized into one of the four intervention conditions listed above: 111 to (a), 115 to (b), 100 to (c) and 105 to (d). A greater percentage of the study population were women (66%) with a mean age of 51 years. The minimal contact group was used as the base case for which the cost effectiveness result was conducted. Follow-up questionnaires were sent to participants at 12, 18 and 24 months. A high response rate was recorded with 74.9%, 82.6% and 84.9% returning follow-up questionnaires at each follow-up period respectively. Analysis was carried out on an intention to treat basis in order to enable comparability of the research result to those of smoking cessation studies. A logistic regression model was used to evaluate the effect of contact versus content and the results showed no statistical significant difference between contact and content interaction for any of the three conditions.

Abstinence from smoking at 24-months was used as the outcome of interest for the cost-effectiveness analysis. In conducting the cost-effectiveness analysis, the costs of each arm of the trial was tallied, extra utility values (QALYs) attributable to successful smoking cessation for various age-gender groupings were projected and several cost/outcome ratios that reflect the

economic worth of the relapse prevention interventions were computed. The utility values (QALYs) attributable to smoking cessation for various age-gender groupings based on life-time parameter were obtained from published literature. The perspective on cost was not stated in this study, it was however stated as "payer's perspective" in cost paper by Chirikos et al, (2004). Cost figures used were said to reflect the value of all inputs used to produce each condition. The costs included were, direct expenses of the booklets, time and motion estimates of clerical input which was measured by hourly wage rates of correspondence clerks in the United States, and also estimates of other overhead expenses less any research-related costs of the trial.

The study conducted two ICERS to appraise the economic value of the intervention. Using the minimal contact group (MCC) as the base case, the first ICER¹ was derived by dividing the incremental cost of a given condition by the incremental difference in the 24-month follow-up abstinence rate. The second ICER² was derived by dividing the incremental cost of a given condition by the incremental QALY of that condition (that is, the estimated 4% discounted QALY attributable to quitting multiplied by the difference in the 24-month abstinence rates between the condition and the MCC). The Incremental cost for massed mailing, repeated letters and repeated mailing conditions were given as $21.25, $26.00 and $43.94 respectively. 24-month follow-up abstinence rate for massed mailing and repeated mailing conditions were 11.4% and 12.2% and QALYs discounted at 4% for both conditions were 0.2561 and 0.2741 respectively. The 24-month abstinence rate for the repeated letter was 2.4%, however with reference to the minimum contact condition; the repeated letters condition did not produce superior outcomes. The ICER¹ for massed mailing and repeated mailing conditions compared to minimum contact condition were $186 ($\frac{21.25}{11.4} * 100$) and $360 ($\frac{43.94}{12.2} * 100$) per 24-month abstinence with ICER² for both conditions given as $83 ($^{21.25}/_{0.2561}$) and $160 ($^{43.94}/_{0.2741}$) per QALY

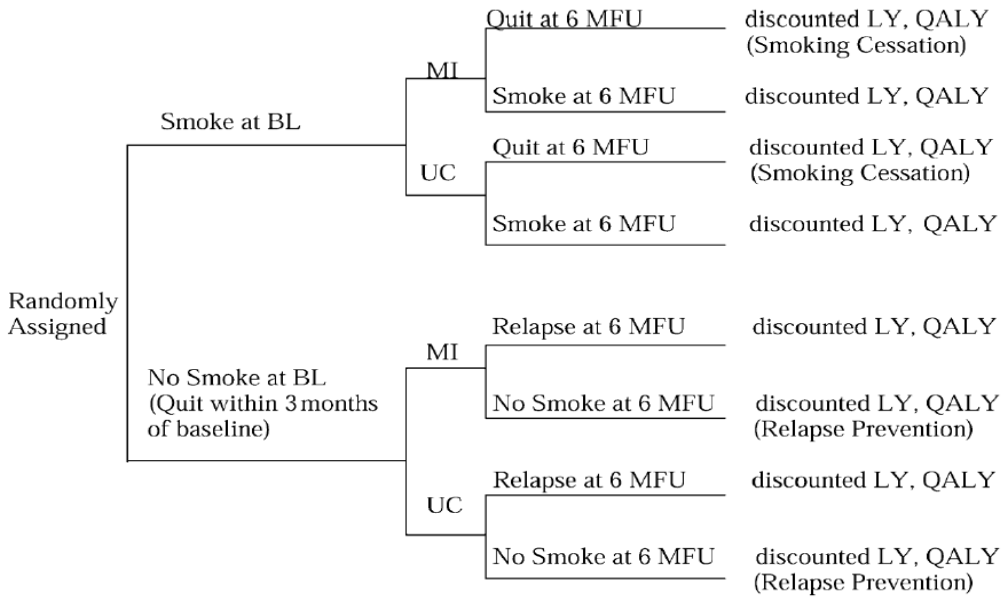
respectively. Successful and permanent quit was estimated to add 2.25 QALYs to life expectancy of the average study participants.

The cost-effectiveness of motivational interviewing compared to usual care for smoking cessation and relapse prevention among low-income pregnant women was conducted by Ruger et al (2008). The study aimed at estimating the clinical benefit and costs in terms of life-years and quality-adjusted life years saved when low-income pregnant women quit smoking and continue to abstain. The design of the study was a multi centre randomized controlled trial with women recruited from multiple obstetrical sites in Boston, USA. Motivational interviewing in this trial involved: educating participants about the impact of smoking on mothers and their unborn child, helping participants increase their self-efficacy for smoking cessation and abstinence as well as evaluate their smoking behaviours. The intervention also provided information on reducing exposure to environmental tobacco smoke and provided feedback to participants about their household nicotine level. The control intervention – usual care, involved provision of standard prenatal care from participants' health care provider at clinic site and an outline of the harmful effects of smoking during and after pregnancy that lasted up to five minutes. This intervention also included provision of self-help materials.

Eligibility criteria for the study included having been a smoker within three months of baseline (for smoking relapse) or being a current smoker (for smoking cessation), being pregnant for less than 28 weeks and receiving prenatal care at one of the participating sites, able to speak Spanish or English and not receiving inpatient drug treatment. The study enrolled 302 participants (which constituted 72.6% of eligible recruited participants) into either the treatment arm (motivational

interviewing) or the control arm (usual care) of the trial. A total of 156 participants received motivational interview sessions with an average of three home visits with each session lasting about an hour while 146 received usual care as indicated above. Baseline characteristics of the participants were comparable across both arms in terms of age, marital status, education, smoking status, with slight variation in race. Follow up was carried out one month after the intervention and six months postpartum.

In order to achieve the set aim of the study, a model was developed from within the trial, separating smokers from non-smokers at baseline. For each arm of the trial, the model was sub-divided into two to analyse whether smokers quit at six months follow-up or continued smoking and whether non-smokers remained abstinent at six months or relapsed. The model is illustrated in Figure 2 below.



Source: Ruger et al (2008), pg. 192

Figure 2: Model of the strategy for smoking cessation and relapse prevention among pregnant women.

This review will however only report results for the non-smokers at the baseline fraction of the model as this is the result of interest. 21 participants out of 156 in the motivational interviewing arm of the trial and 28 participants out of 146 in the usual care arm were recruited for the purpose of relapse prevention. Analysis was carried out from an extended societal perspective. Cost items were valued alongside the clinical trial, costs collected were those necessary to reproduce the intervention in a non-research setting and they included: staff time related to intervention delivery, cost of analysing environmental nicotine used in motivational interviewing (the reason for including this cost is unclear as it is not likely to arise in routine clinical practice and its inclusion can limit the generalisability of the study result), costs of training staff and the costs of producing the self-help materials used. Patient time was included as a direct cost and published net economic cost data were included to capture the societal costs. These costs include: cost savings for neonatal intensive care, chronic medical conditions and acute conditions during the first year of life and also cost savings for maternal health. Costs were calculated in 1997 United States dollars. Disaggregated level of resource use as well as unit costs were presented in a different paper (Ruger et al, 2009).

The primary outcome measure was relapse prevention as measured by whether each participant had smoked within the previous 30 days prior to assessment; a relapse prevented implied that the participant was abstinent at follow-up. Saliva samples were collected for saliva cotinine analysis as a way of verifying smoking status biochemically. Quit and relapse prevention rates were converted into life years saved and quality-adjusted life years saved by using estimates from published data as a measure for effectiveness. These estimates indicated that female quitters and abstainers aged between 25 and 29 years saved 1.43 life years and 1.94 quality-adjusted life

years at a discount rate of 3%. The mean intervention cost per participant (which comprised of intervention delivery cost, staff travel time and training) was given as $309.2 for motivational interviewing and $4.85 for usual care. Societal costs were however not reported.

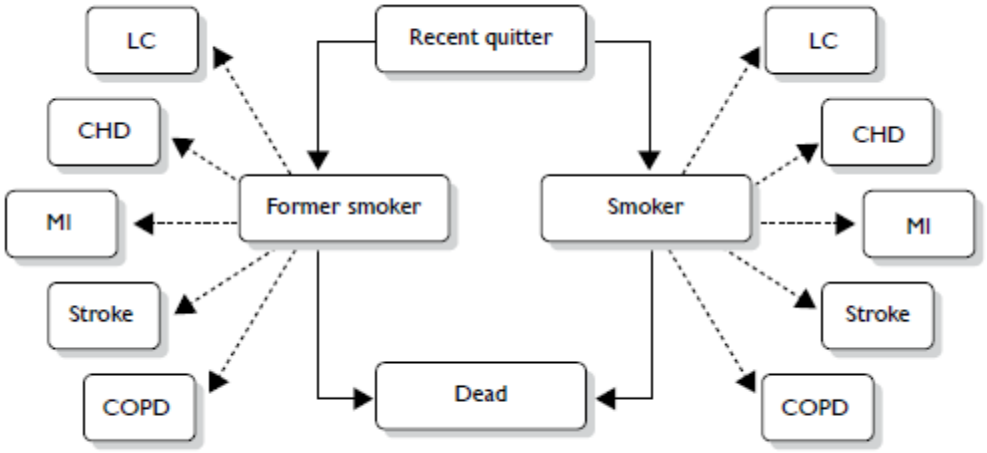
At 6 months postpartum, motivational interviewing participants had twice (9 out of 21) the relapse prevention rate as the usual care participant (5 out of 28) with a p-value of 0.055. Based on utility values derived from published data, female quitters and abstainers aged 25 to 29 years were estimated to save 1.43 life years (LYs) and 1.94 QALYs discounted at 3%. Compared to usual care (UC), the incremental cost for motivational interviewing per participant was estimated to be $304, with incremental life years and incremental QALYs given as 0.36 and 0.49 respectively. Motivational interviewing was reported to prevent relapse more effectively than UC and the incremental cost per QALY among ex-smokers that received motivational interviews compared to UC ex-smokers was an estimated $628/QALY.

One-way and two-way sensitivity analysis was conducted by varying the number of relapses prevented from 3 to 12 per 21 ex-smokers (baseline ratio 9/21), discounted QALYs gained from 0.025 to 2.000 (baseline assumption of 1.94) and cost per participant from $250 to $2000 (baseline of $309). Results from the one-way sensitivity analysis revealed that increasing the percentage of relapse prevented by 15% resulted in an approximated 36% decrease in the incremental cost per QALY ratio which was deemed not proportional to effectiveness. When discounted LY or QALY saved were assumed to be as low as 0.025, motivational interviewing's incremental cost-effectiveness for relapse prevention was said to have reached $48,700 per LY or QALY saved. If the cost was $2000 per participant, the cost-effectiveness ratio was reported to remain favourable at $5600 per LY saved and $4100 per QALY saved compared to UC. When

two-way sensitivity analysis was conducted and the cost per participant was assumed to be $2000, the incremental cost-effectiveness of motivational interviewing compared to UC was $23,400/LY saved and $17,300/QALY. It was therefore concluded that using either of the sensitivity analysis methods, motivational interviewing was deemed cost effective compared to UC for preventing relapse.

3.2.2. Pharmacological interventions

In the Health Technology Assessment conducted by Coleman et al (2010), a cohort simulation model was developed to determine the cost-effectiveness of interventions for preventing smokers who had recently become abstinent from relapsing. This cost-effectiveness analysis was based on findings from a preceding systematic review of the effectiveness of relapse prevention intervention reported in the same paper. The review suggested that extending treatment with Bupropion, NRT and Varenicline may be effective at preventing smokers who had achieved abstinence from relapsing. The study therefore aimed to test this hypothesis by assessing the costs and outcomes associated with these three pharmacological interventions compared to no intervention using a hypothetical cohort of 1000 smokers who had recently initiated quit attempts (recent quitters). A cohort simulation model was developed to examine changes in abstinent smokers' behaviour and associated co-morbidities in 6-monthly cycles over the lifetime of the cohort smokers. Recent quitters in each cycle could either relapse (i.e. become a 'smoker'), remain abstinent (i.e. a 'former smoker') or die. In each cycle, smokers and former smokers had a chance of experiencing either one of five potential co-morbidities, namely: lung cancer (LC), coronary heart disease (CHD), chronic obstructive pulmonary disease (COPD), myocardial infarction (MI) or stroke. The model is presented in Figure 3 below.



Source: Coleman et al (2010), pg 48

Figure 3 – Model illustrating the movement between health states.

It was assumed that the probability of a cohort individual being a smoker or former smoker developing one or more of the comorbidities in each cycle varies with their age. The researchers conducted a literature search to enable them to identify appropriate data sources for which estimates for parameters used in the model could be derived. Data required were, mortality and prevalence of each comorbidity based on age, gender and smoking status and also the costs and utility (quality of life) associated with the comorbidities. The utility scores for each cohort smoker that had LC, Stoke, CHD, MI and, COPD were estimated to be 0.58, 0.48, 0.80, and 0.73 respectively. A current smoker with no comorbidity had a utility score of 0.75 while a former smoker with no comorbidity had a utility score of 0.78. Average annual cost (reported in 2008 pounds) for LC, Stroke, CHD, MI, COPD were estimated to be £5501, £2061, £1063, £2175, and £926 respectively. In order to enable comparability between the costs and utilities of the interventions with 'no intervention', the number of people with each comorbidity in each cycle was multiplied by the associated cost and utility of that comorbidity and then summed together

to calculate an overall estimate for cost and utility. The process and methods for this calculation were explicitly described with examples thereby increasing transparency in reported figures.

The cost-effectiveness of each relapse prevention intervention (NRT, Varenicline and Bupropion) were determined by inputting the intervention costs into the cohort and modelling their impact on cohort utilities, using estimates from the aforementioned systematic review for which the study aim was based on. For the base-case model, it was assumed that the background rate of quitting smoking among all smokers was 2% and relapse prevention intervention used by the cohort population would have the same efficacy as in clinical trials. Costs of the relapse prevention intervention were collected from the British National Formulary (BNF) records. Costs and outcomes were discounted at 3.5% per year. Incremental cost effectiveness was carried out by comparing each of the interventions to 'no intervention' in terms of total costs and QALYs.

The base-case result from the analysis is illustrated below;

Intervention	Cost (£)	QALY
Bupropion	6755	12.76
No intervention (bupropion trial)	6822	12.69
NRT	7050	12.63
No intervention (NRT trial)	7039	12.58
Varenicline	6794	12.79
No intervention (varenicline trial)	6704	12.75
No intervention (pooled data)	6981	12.61

Maximum cost per QALY for all treatment was £2106. All three interventions were considered cost effective against a willingness-to-pay threshold of £20,000 per QALY with an ICER for NRT and varenicline given as £265 and £2106 respectively. Bupropion was reported to be relatively more cost effective with a cost saving of £68 (£6822 - £6755) and an incremental QALY of 0.07 (12.76 – 12.69).

One-way sensitivity analysis was conducted by varying background quit rate (1.2% and 2.8%) and holding other variables constant. Compared to no intervention, the incremental cost/QALY for Bupropion, NRT and Varenicline were estimated to be -£85/0.07, £1/0.05 and £79/0.04 respectively at a background quit rate of 1.2%. Using a background quit rate of 2.8%, incremental cost/QALY for Bupropion, NRT and Varenicline were given as -£54/0.06, £21/0.04, and £99/0.04 respectively. All the interventions were seen to be cost effective with variation in background quit rate and Buropion remained more effective and less costly compared to NRT and Varenicline.

3.3. Methodological quality

The BMJ (Drummond and Jefferson, 1996) 35-item checklist was applied to the included studies and the results are summarized below. Further details of the checklists for each paper are detailed in Table 3.

3.3.1 Study design

All three papers (100%) clearly stated a research question and the importance of the research question. These were mainly addressed in the papers while stating the aims and objectives. Ruger et al (2008) conducted their analysis from a societal perspective. The perspective assumed for analysis in the Coleman et al (2010) study was not explicitly stated but a health provider's perspective can be inferred based on the justification for the study and reference made to the UK National Health Service (NHS), the Brandon et al (2004) study did not state the viewpoint of their analysis neither was any form of justification made available. Failure to state the viewpoint of the analysis made it difficult to determine if the appropriate costs were valued. All papers

justified rationale for choosing the interventions used in their studies and clear descriptions of alternatives used were provided as indicated above. Cost-effectiveness analysis was carried out in all the studies with justification for the choice of analysis given except in the Brandon et al study.

3.3.2. Data collection

All the included studies generated effectiveness estimates from within the study with details of the design and methods of synthesis as well as the results of effectiveness appropriately given. Brandon et al (2004) and Coleman et al (2010) used QALY to value benefits while Ruger et al (2008) used QALYs as well as LYs to value benefits. It should however be noted that none of the included studies generated utility values from within the study, values used were obtained from previously published trials. While this was appropriate for the Coleman et al study considering that it was a modelling study, Ruger et al and Brandon et al studies were randomized controlled trials and generating utility values from within the trial would have increased the validity of the values. It is important to note that two utility data sources (Fiscella and Franks, 1996; Rogers and Powell-Griner, 1991) were applied to both the Ruger et al and Brandon et al studies and given the gap in the years in which the studies were published, the applicability of the values to the study participants is questionable as factors that influenced the values may have changed over time.

Primary outcome measures used for economic evaluation in the included studies were clearly stated. The main outcome measure used in the Coleman et al study was the proportion abstinent from smoking during each six monthly cohort cycle; it was assumed that at zero months, the

proportion abstinent from smoking was 100 percent. The Brandon et al study used a 7-day point prevalence abstinent rate at the 24-month follow-up as the outcome of interest for the economic evaluation aspect of their study while Ruger et al used abstinence at follow-up as the outcome of interest for relapse prevention. All included studies did not report separately report the quantities of resource use from their unit costs. The methods for estimating quantities and unit cost were provided only in Coleman et al. The currency and price data for the included studies were clearly stated, Ruger et al and Brandon et al expressed costs in United States dollars while Coleman et al used UK sterling. The range of cost collected varied across each study given the study perspective, methods for estimating quantities and unit costs were not reported in Brandon et al and Ruger et al.

Productivity changes were not included in any of the studies therefore a discussion of the relevance of productivity changes was not necessary. Price adjustments for inflation was only reported in Brandon et al with a 2000 price year being used. Ruger et al made use of a within-trial model while Coleman et al made use of a cohort simulation model. Both studies provided adequate justification for the key parameters on which the model was based and clearly outlined how participants are expected to move in the model given the baseline assumptions. No form of modeling was carried out in the Brandon et al study.

3.3.3. Analysis and interpretation of results

All three studies discounted benefits ranging from 3% to 4% per year. Coleman et al (2004) was the only study to discount costs and benefits and the same rate (3.5%). The justification for choice of discount rate(s) used was stated as the ‘conventional/recommended rate’ in all three studies. According to Drummond et al (1996), most government recommended rates vary

between 3% and 6%, therefore the rates used in the included studies can be deemed appropriate. Costs in Brandon et al were incurred only in the first year and this was explained as the reason why costs were not discounted, Ruger et al (2008) however did not provide justification for not discounting costs. Two studies (Coleman et al. 2010; Ruger et al. 2008) made allowance for uncertainty by conducting sensitivity analysis with a clearly stated approach and assumptions. This makes it easy to evaluate the robustness and meaningfulness of the conclusion. All three studies performed incremental analysis of both cost and benefit and conclusions were based on the interpretation of the ICER. Ruger et al and Coleman et al presented major outcomes in both aggregated and disaggregated forms while major outcomes in Brandon et al were presented only in an aggregated form. Presenting the disaggregated form of major outcomes increases the transparency of the study results.

First author	Item No.	1	2	3	4	5	6	7	8	9	10	11	12
Brandon et al		Yes	Yes	No	Yes	Yes	Yes	No	Yes	Yes	Not applicable	Yes	Yes
Coleman et al		Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Not applicable	Yes	Yes	Yes
Ruger et al		Yes	Yes	Yes	Yes	Yes	Yes	Not clear	Yes	Yes	Not applicable	Yes	Yes
Total 'Yes'		100%	100%	67%	100%	100%	100%	33%	100%	67%	33%	100%	100%

contd.	13	14	15	16	17	18	19	20	21	22	23
Brandon et al	No	Not applicable	Not applicable	No	No	Yes	Yes	Not applicable	Not applicable	No	Benefit only
Coleman et al	No	Not applicable	Not applicable	No	Yes	Yes	No	Yes	Yes	No	Yes
Ruger et al	No	Not applicable	Not applicable	No	No	Yes	No	Yes	Yes	Cost only	Benefit only
Total 'Yes	0%	-	-	0%	33%	100%	33%	67%	67%	0%	33%

contd.	24	25	26	27	28	29	30	31	32	33	34	35
Brandon et al	Yes	Yes	No	Not applicable	Not applicable	Not applicable	Not applicable	Yes	No	Yes	Yes	Yes
Coleman et al	Yes	Not applicable	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Ruger et al	Yes	No	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Total 'Yes'	100%	33%	33%	67%	67%	67%	67%	100%	67%	100%	100%	100%

Table 3 – Critique of included studies according to the BMJ checklist

3.4. Discussion

The principal finding of this review is that the various interventions used in the included studies were judged to be cost-effective in comparison to the control interventions used. The included studies appropriately reflect the forms of smoking relapse prevention interventions available, two of the studies used behavioural interventions while the third study compared three pharmacological interventions. Coleman et al (2010) based their conclusions on a NICE benchmark of £20,000 per QALY and Brandon et al based theirs on the conventional cut-off point of $50,000 per QALY used in economic evaluations of similar studies. Ruger et al (2008) however did not indicate a benchmark for which the conclusion of effectiveness can be compared. Brandon et al (2004) and Ruger et al (2008) identified the limited generalisability of their findings to other settings as a weakness to their study based on the characteristics of their study participants as well as recruitment and randomization methods. The failure to consider uncertainty in the study by Brandon et al (2004) limits the robustness of the study findings and conclusions.

These three studies, though differing in many aspects: study design, forms and type of intervention used, participants and recruitment methods and assumptions, all established that interventions used were cost effective in their individual respects. Certain aspects of each included study provides useful research findings on the effectiveness of smoking relapse interventions and these findings can be used to form the basis for further research. This review of economic evaluation studies on smoking relapse prevention interventions reveals the scarce studies that have been conducted in this subject area. In recent years, there has been increasing demand for evidence on both the clinical and cost effectiveness of interventions. This is mainly to enlighten healthcare providing bodies and individuals on the relative cost and clinical

effectiveness of treatment options and aid budget decision making. This dearth of studies on this subject also provides justification for further studies.

The methodological quality of economic evaluations in smoking relapse prevention can be improved upon. The included studies were not performed purely in accordance to the BMJ checklist used for this review and in some cases where checklist items were reported, the viewpoint was not clear often making it difficult to assign a 'yes' or 'no' answer. Whilst the BMJ checklist is not the only checklist for assessing economic evaluations, certain criteria such as providing allowance for uncertainty by conducting sensitivity analysis, reporting quantities of resource use separately from their unit cost and discounting cut across all checklists, were however not reported or conducted in the included studies.

Certain limitations can be identified in this review, first is the restriction to smoking relapse prevention intervention only. The implication of which is that some economic evaluations of smoking cessation with extended follow up period of which relapse would have been analysed were not included. There is also the possibility of missing out some studies as a result of the keywords used which is not uncommon in systematic reviews. The distinct study characteristics also made it impossible to draw a conclusion on the most cost effective intervention or make specific budget policy recommendations.

4. Conclusion

Work undertaken to access the cost-effectiveness of interventions aimed at preventing smoking relapse is still in its infancy as can be seen by the years (2004 – 2010) in which the included studies were published. The result from the systematic search reveals that relatively more research has been conducted on the economic evaluation of smoking cessation interventions but

not on smoking relapse intervention. The following recommendations can therefore be made for researchers conducting economic evaluations of smoking relapse prevention interventions. Firstly, it is highly recommended that economic evaluations are conducted alongside clinical trials and inputs consumed in the interventions are measured and valued prospectively. This improves the reliability and validity of intervention costs. In cases where economic evaluation is being modelled from published clinical trials, authors should clearly state all assumptions and ensure important caveats are discussed. Secondly, the perspective for which the analysis is being conducted should be clearly defined. This would make it possible for users of the results to determine if appropriate costs relating to their individual setting have been considered. Failure to define a clear perspective could result in the overall cost-effectiveness ratio being misinterpreted. Thirdly, standard methodological process should be incorporated into the study by using appropriate checklists to ensure that all relevant items are evaluated and reported appropriately. Generally, study findings should be reported with a high level of transparency in order to increase the generalisability of the results from one setting to another.

5. Overview of Identified Protocols from the Search

From the systematic search for literature in this review, three study protocols on relapse prevention intervention were identified. These studies were not included in the review as they are current on-going studies and results of the effectiveness of the interventions or otherwise have not been established. It is however note worthy to highlight the characteristics of these studies as well as examine the proposed methods in the studies. The three studies are outlined in Table 4 below.

Table 4 – On-going economic evaluation studies on relapse prevention

1.	Berndt et al (2012) Title - Effectiveness of two intensive treatment methods for smoking cessation and relapse prevention in patients with coronary heart disease: study protocol and baseline description. Trial registration – Dutch Trial Register NTR2144
2.	Cummins et al (2012) Title - Nicotine patches and quitline counselling to help hospitalized smokers stay quit: study protocol for a randomized controlled trial. Trial Registration – Smoking cessation in hospitalized smokers NCT01289275
3.	Song et al (2012) Self-help materials for the prevention of smoking relapse: study protocol for a randomized controlled trial. Trial Registration – Current Controlled Trials ISRCTN36980856

The effectiveness of two intensive treatment methods (telephone counselling (TC) and face-to-face (FC)) for smoking cessation and relapse prevention in patients with coronary heart disease is being conducted by Berndt et al (2012). Baseline descriptions of randomized patients were also included in the protocol. The design of the study is a multi-centre randomized controlled trial and is being conducted across eight cardiac wards of leading clinical and academic hospitals throughout the Netherlands. The trial is reported to have received appropriate ethics approval.

The criteria for inclusion in the study for patients were, being an adult (≥18 years), admitted to any of the participating cardiac wards for less than 96 hours and admitted because of coronary heart disease (which could be acute coronary syndrome, stable angina, or other forms of chronic and acute heart disease), smoking on average ≥5 cigarettes per day in the month prior to admission and having quit smoking less than four weeks before admission. The main exclusion criterion was language limitation. A power and sample size calculation was reported to have been conducted for the main outcome – seven-day point prevalence abstinence at 12 months follow-up. This calculation showed that 193 patients per condition were needed to detect significant differences in the outcome measure and the possible interaction effects of the interventions with motivation to quit and socio-economic status. After recruiting, 245 cardiac

patients were randomized into the usual care condition, 223 into the experimental condition of TC and 157 into the experimental condition of FC (It should be noted at this point that the number in the FC condition is lower than the estimated required number from the sample size calculation). Patients were predominantly male with a mean age of 57 years.

All patients received standard in-hospital treatment for smoking cessation which was termed as 'usual care' and comprised of an assessment of smoking behaviour and brief personalized quit advice. Two experimental conditions were then developed consisting of TC and FC both together with nicotine replacement therapy. Smoking behaviours of patients in these groups were assessed, smoking patients were advised to quit and patients were referred to health professionals providing telephone counselling or face-to-face counselling outside the ward. In addition, nurses provided nicotine patches and information on their necessity to eligible patients. Telephone counselling (TC) was provided by professional counsellors while face-to-face counselling (FC) was provided by cardiac nurses trained in providing smoking cessation counselling. The two counselling methods differed in mode of delivery and the intensity of counselling. TC was reported to last for three months and consists of seven telephone sessions lasting between 10 and 15 minutes. FC also lasts for three months and consists of six face-to-face sessions of 45 minute and a follow-up call eight weeks after the last session. Follow-up data were collected at six months and 12 months after discharge.

The primary outcome measure for effectiveness in this trial is seven-day point prevalence abstinence from smoking at six and twelve months follow up. Secondary outcome measures include continued abstinence, quit attempts and health outcomes. Health outcomes to be measured at follow up are new coronary events and hospital readmissions for coronary events. For the economic evaluation arm of the trial, a cost-effectiveness analysis will be conducted to

compare these outcomes with the costs of the interventions. At six and twelve months follow up periods, costs and resource use data reported to be collected will include: visits to the general practitioner; cardiology outpatient visit; health related costs (not defined); informal care costs and health related quality of life. Resource use recorded will include, counsellors time, use of materials, use of nicotine replacement patches and specialists time. These are said to be recorded prospectively by the counsellors. To this end, the researchers have stated that a health-economic Markov Model will be built to estimate long term costs and health effects.

Cummins et al study is a randomized controlled trial to test the effects of two interventions – nicotine patches and quitline (telephone) counselling to help hospitalized smokers stay quit using a 2 x 2 factorial design. Interventions are described as (1) nicotine patches (delivered for eight weeks as a step down program) dispensed to participants upon discharge from the hospital and (2) proactive telephone counselling provided by the state quitline after discharge. Study participants are randomized to receive either one of usual care, nicotine patches, quitline counselling, or both patches and counselling.

Telephone counselling is described as a state funded service provided by the California Smokers' Helpline (CSH) which has been in operation since 1992. The difference between this standard telephone counselling provided to any smoker and the intervention in this trial is that a counsellor initiates the first call whereas in the standard service a smoker calls the state quitline. For the trial, counsellors are required to make at least 10 attempts to reach the participant for the first counselling call. The initial call is estimated to last 30 to 40 minutes and involves discussing the participants' quit experience during and after hospital stay and set up a quitting plan accordingly. Follow up sessions are expected to last about 10 to 15 minutes. Participants randomized into the patch condition will receive an eight-week supply of nicotine patches. The

patches are dosed according to the number of cigarettes participants smoked daily using a step-down regimen. Those who smoked six to ten cigarettes daily will receive six weeks of 14mg and two weeks of 7mg patches while those who smoked eleven or more cigarettes daily will receive four weeks of 21mg and two weeks of 7mg patches. Usual care is described as the hospital's standard care and typically includes a brief bedside intervention that lasts about ten minutes and involves a nurse or a respiratory therapist encouraging quitting, providing educational materials and supplying the number for the state quitline.

The study is based on an initial pilot study conducted by the research team using usual care versus nicotine patches at discharge plus proactive quitline counselling. This pilot study recruited, randomized and evaluated 126 participants for a period of two months and the results showed that the intervention group (nicotine patches plus proactive quitline counselling) was three times more likely to be abstinent at follow-up than the usual care ($P < 0.01$). This pilot study was also carried out in order to power the study and determine how many participants will be required to determine a statistically significant effect. The specific aims of the study include (1) to demonstrate the effect of the two interventions: nicotine patches at discharge and proactive telephone counselling after discharge on the abstinence rate of hospitalized smokers, using a 2 x 2 factorial method, (2) to compare the cost-effectiveness of the three intervention conditions: patches alone, counselling alone, and the combined interventions against the usual care condition, (3) to examine if the patient's medical diagnosis (such as, cardiopulmonary) is a moderating factor for intervention effects such that patients with a certain diagnosis benefit more than patients with other diagnoses and (4) to establish a practical model of a hospital-quitline partnership that can be adopted by other state quitlines and hospitals.

The above study is being conducted in the United States of America through two health-care systems (University of California, San Diego (UCSD) and Sripps) with a total of five hospitals in San Diego County. The study is funded by the National Cancer Institute and ethical approval was received from appropriate institutions. The estimated study population (as determined by the power calculation) will be 1640. In order for participants to be eligible for inclusion in the study, they have to be hospitalized adults smokers (18 years and over) who had smoked in the previous 30 days and are interested in staying quit or planning to quit upon discharge. Study participants must speak English or Spanish, provide sufficient contact information for the intervention and evaluation, receive physician's approval for study participation and provide signed informed consent. The exclusion criteria includes an anticipated hospital stay of less than 24 hours which the researchers have deemed too short to enable them to conduct a necessary assessment, receive consent and administer intervention. Pregnant smokers will also be excluded based on the existing debate on the suitability of using nicotine patches during pregnancy.

Data are collected from participants at baseline and subsequently evaluation calls are made at two and six months after baseline. To achieve the primary aim of the study which is stated as determining the effect of proactive telephone counselling and nicotine patch use on successful quitting among hospitalized smokers, self-reported thirty-day abstinence at six-month is used as the primary outcome. The secondary aim of the trial reflects the economic evaluation aspect of the study and is stated as determining the cost effectiveness of the intervention and assessing the possible moderating effects of diagnosis. Participants' diagnosis (cardiovascular-pulmonary versus other diagnosis) will also be analyzed to examine the moderating effects of the intervention. The study assumes that the goal of the hospital and quitline is to maximize benefits that accrue to participants. Costs per quitter will therefore be evaluated. Costs items to be valued

include personnel costs (staff time using salary and benefits based on the personnel completing the various tasks) and general costs, although not defined, it is assumed to be evenly distributed across callers since smokers are randomized. QALYs will be evaluated to assess cost-effectiveness from the patients' perspective. Quality of life weights to be used for the analysis will be based on health literature and life expectancy.

The study by Song et al (2012) is a randomized controlled trial aimed at evaluating the effectiveness and cost-effectiveness of using self-help materials to prevent smoking relapse. A previous meta-analysis conducted by the researchers proved coping skills training interventions significantly reduced smoking relapse in community quitters who had been able to quit for at least one week at baseline. The results also showed that interventions using self-help materials seem as effective as those based on individual or group counselling. The researchers were uncertain whether the result from their meta-analysis and the individual trials by Brandon et al. (2004) were generalisable to four-week quitters who used the National Health Service (NHS) stop smoking service and therefore set out to test this hypothesis.

Participants in this trial will be randomized into either the relapse prevention group to receive self-help material (Forever Free booklets) or the control group to receive a current smoking cessation booklet (Learning to Stay Stopped). A full pack of Forever Free booklets contains eight self-help materials (same as used in Brandon et al, 2004). The booklets were revised and updated where the researchers deemed necessary to make the materials suitable to British users and the United Kingdom NHS given that the booklets were originally prepared for users in the United States. The booklet administered to the control group named 'Learning to Stay Stopped' is eight-paged and contains brief and comprehensive issues related to smoking relapse and provides brief

recommendations on how to cope with cravings and tempting triggers. After randomization, a letter and appropriate booklets based on trial group will be sent to participants for use at home.

The target population for this trial is four-week quitters treated in the NHS Stop Smoking Service Clinics. The trial is being conducted in Norfolk, England and participants will be recruited from two NHS Stop Smoking clinics in the region (SmokeFree Norfolk & Norfolk Community Health and Care). To be included in this study, four-week quitters will be biochemically verified in the NHS Stop Smoking Service clinic and sign a consent form to participate in the trial. Smoking relapse prevention by coping skills training based on research is considered ineffective for women who have stopped smoking during pregnancy. Pregnant quitters will therefore be excluded from the trial; also quitters who cannot read educational materials in English will be excluded. The trial will also excluded other quitters from families at the same address provided a family member has been included.

A power calculation was carried out for the study and an estimated 1,400 participants will be required in total with at least 700 in each arm to determine a statistically significant effect. Data will be collected and recorded at baseline and at follow-up periods. Primary outcome (reported as following the Russell Standard) will be prolonged abstinence from four months to twelve month with no more than five lapses confirmed by Carbon Monoxide reading CO<10ppm at the 12-month assessment. Secondary outcome is defined as seven-day self-report point prevalence abstinence at three months and a seven-day biochemically confirmed point prevalence at 12 months. Participants who decline verification will be assumed to have relapsed and be counted as smokers.

For the economic evaluation aspect of the trial, a cost effectiveness analysis from the health service perspective will be conducted. Data that will be collected to conduct this analysis will

include, resource use associated with self-help materials and any additional stop smoking services and cessation products at follow-up interviews. Other resources such as visits to the General Practitioner and hospital admissions which are expected to affect the intervention will be monitored. Utility values that will be used to evaluate benefits will be the QALY gained associated with each intervention during the study period and the EQ-5D will be used to estimate these values. This in effect means that the QALY values will be generated from within the trial by administering the EQ-5D questionnaire during the study period at baseline and appropriate follow-up.

5.1. Comments on study protocols

In line with the observations, recommendations and conclusions from the systematic review, a significant improvement can be seen in current studies on the economic evaluation of relapse prevention intervention. The Song et al (2012) study will be generating utility values (QALY) from within their study using the EQ-5D which can be seen as a plus to their study as it will increase the validity of the research findings and it's transferability given that the characteristics of the participants for which the values are obtained will be known. The study also states the perspective (health service perspective) for which the analysis will be conducted thereby making it easy to evaluate if appropriate costs have been considered. The perspective in Berndt et al (2012) and Cummins et al (2012) were not stated in the protocol. It was observed that information on the economic evaluation aspect of the trials is limited as opposed to the detailed process of establishing clinical effectiveness. It is however believed that the plan of analysis will be detailed in the final report after completion of the trials. Berndt et al stated that the level of resource use will be recorded prospectively by counsellors involved in the trial process; this equally can be seen as good practice as it ensures accuracy in recording.

While it remains to be seen what the eventual results from these trials will be, their study protocols have been detailed enough to increase the transparency of the study process and the results will no doubt push the boundaries of economic evaluation of relapse prevention intervention and consequently lead to further research in this field.

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List of Abbreviations

BMJ – British Medical Journal
BNF – British National Formulary
CBA – cost-benefit analysis
CBT – cognitive behavioural therapy
CEA – cost-effectiveness analysis
CHD – coronary heart disease
COPD – chronic obstructive pulmonary disease
CUA – cost-utility analysis
FC – face-to-face counselling
GP – general practitioner
ICER – incremental cost-effectiveness ratio
LY – life years
MI – myocardial infarction
NHS – National Health Service
NICE – National Institute for Health and Clinical Excellence
NRT – nicotine replacement therapy
TC – telephone counselling
QALY – quality adjusted life years
RCT – randomised controlled trials
UC – usual care
WHO – World Health Organization

APPENDIX 1 – Search Terms
MEDLINE and EMBASE Search

1. Smoking
2. smoking cessation
3. relapse
4. recurrence
5. economics
6. econom*
7. costs
8. costly
9. costing
10. pharmacoeconomics
11. pharmacoecon*
12. budget*
13. expenditure*
14. energy
15. 12 not 13
16. Value for money
17. cost-eff*
18. cost-ben*
19. cost-util*
20. 1 or 2
21. 3 or 4
22. 20 and 21
23. 5 or 6 or 7 or 8 or 9 or 10 or 11 or 14 or 15 or 16 or 17 or 18 or 19
24. 22 and 23

Cochrane Library

1. "smoking" and ("relapse" or "maintenance")
2. economics
3. econom*
4. costs
5. costly

6. costing
7. pharmacoeconomics
8. pharmacoecon* or Budget*:ti,ab,kw (Word variations have been searched)
9. 'value for money':ti,ab,kw (Word variations have been searched)
10. cost-eff* or cost-ben* or cost-util*:ti,ab,kw (Word variations have been searched)
11. expenditure
12. energy
13. #11 not #12
14. #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #13
15. #1 and #14