DETAILED PROJECT DESCRIPTION

1. Title:

How do smoking cessation medicines compare with respect to their neuropsychiatric safety: a systematic review, network meta-analysis and cost effectiveness analysis.

2. Summary of Research

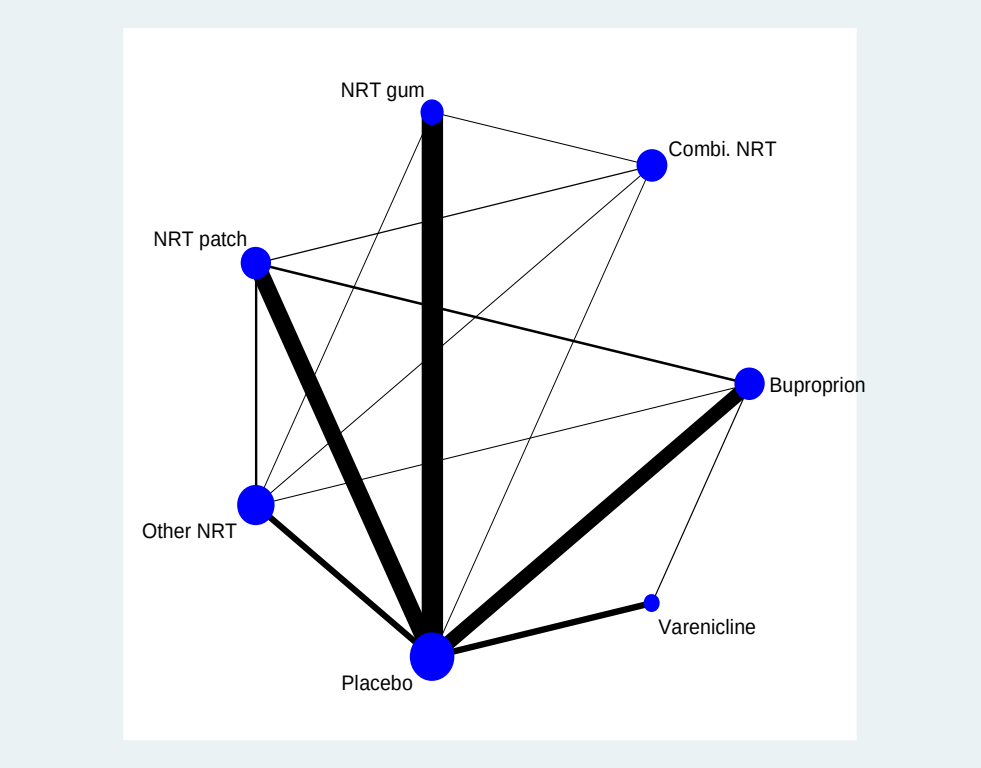
Cigarette smoking is one of the leading causes of early death in the UK and worldwide (1, 2). Each year, more than 100,000 people will die in the UK from smoking related diseases (3). NICE public health guidance (published in 2008) recommends the use of three medicines, varenicline, bupropion and nicotine replacement therapy (NRT), as aids to quitting smoking in the UK (4). Since the publication of the original NICE guidance, there have been ongoing concerns about the safety of the smoking cessation medicines, with particular respect to the neuropsychiatric safety of varenicline. Safety warnings regarding a potential increased risk of serious neuropsychiatric adverse events (depression, suicidal ideation and suicidal behaviour) in patients prescribed these medicines have been issued by regulatory agencies such as the Medicines and Healthcare products Regulatory Agency (MHRA) in the UK and the Food and Drug Administration (FDA) in the US (5, 6). These safety warnings were based on spontaneous reports to the UK Yellow Card Scheme and the FDA Adverse Events Reporting Database. Previous research into the neuropsychiatric safety of these medicines has provided inconsistent findings, adding to the debate (7). To date, there has been no comprehensive analysis of the neuropsychiatric safety of the smoking cessation medicines; previous systematic reviews have focussed on comparisons of varenicline with placebo (8-10). In addition, the cost effectiveness of these medicines in UK settings has not been investigated recently using the most up to date evidence. These analyses are important to inform the overall risk-benefit evaluation of the different smoking cessation medicines.

The main aim of this study is to conduct systematic reviews, network meta-analyses and health economic analyses to determine how the smoking cessation medicines compare with respect to their neuropsychiatric safety. Secondary aims include updating the evidence regarding the effectiveness and cardiovascular safety of these medicines for use in the cost effectiveness analyses. The health technologies that we will assess include varenicline, bupropion, nicotine replacement therapy as monotherapy and in combination treatment (i.e. varenicline combined with NRT, varenicline combined with bupropion and bupropion compared with NRT). For NRT, combinations of different formulations given concurrently, for example patch and gum, will also be assessed. Different dosages of treatments will also be examined. We will conduct detailed searches for published and unpublished literature and for previous economic evaluations. The primary composite safety outcome will be serious adverse events, defined as events that were life threatening or resulted in death, hospitalisation, significant disability or congenital defect. The primary set of neuropsychiatric outcomes will include major adverse neuropsychiatric events such as completed suicide, attempted suicide, suicidal ideation, depression and seizures. Secondary neuropsychiatric outcomes will include abnormal dreams, aggression, anxiety, fatigue, insomnia, irritability and sleep disorders. Outcomes related to effectiveness and cardiovascular safety will also be examined.

For each outcome, we will construct a network meta-analysis (NMA): this is an extension of standard meta-analysis which simultaneously combines evidence from *all* trials reporting that outcome, so long as treatments form a connected network (11). For example, Figure 1 shows a connected network of 7 smoking cessation treatments adapted from a Cochrane overview of reviews of smoking cessation at 6 months (12). NMA enables estimation of relative intervention effect estimates for every pairwise contrast, and the ranking of treatments according to the probability that each is the best, or worst for a given outcome (11). We will also update a previously reported economic model to assess cost-effectiveness of treatments for smoking cessation (13), and adapt it to incorporate adverse effects of treatments. If sufficient evidence is identified, then we will consider the following subgroups in the NMA and economic evaluation: heavy smokers, those with psychiatric illnesses, those with respiratory or cardiovascular disease and smokers who have made previous quit attempts. Results will be used to inform the optimal use of smoking cessation medicines based on current evidence.

The total project time is 26 months. Total time to conduct the systematic reviews including the retrieval of economic analyses, data extraction and preparation will be 14 months. Statistical analyses for the NMAs and the health economic analyses will be carried out in the final 12 months, together with writing of the project report and dissemination of the project's findings to the general public, healthcare practitioners and clinicians, academics (via peer reviewed publications and presentations at conferences), industry and policy makers including the MHRA and NICE. We will involve patients and the public throughout the project via members of the UK Centre for Alcohol and Tobacco Studies (UKCTAS) Smokers' Panel and the Elizabeth Blackwell Institute's Public Advisory Group.

Figure 1- Network diagram for effectiveness of smoking cessation treatments. Adapted from (12).



The circles represent treatment "nodes" and the solid lines denote the presence of direct trial evidence comparing two treatments. Line thickness is proportional to the number of trials; the thicker the line, the more trials have compared treatments.

3. Background and rationale

Importance of the health problem to the NHS

Smoking is the major avoidable cause of preventable morbidity and premature mortality in the UK and internationally (1, 2). In 2012, more than 100,000 deaths and 1.6 million hospital admissions in adults were attributed to smoking in the UK (3). In addition, it is estimated that smoking related illnesses cost the NHS approximately £5 billion a year (14). Approximately 20% of all adults in Great Britain smoke; this prevalence has remained relatively unchanged in recent years (3). It is therefore unsurprising that the eradication of smoking continues to be a major Public Health and NHS priority.

Smoking cessation medicines and neuropsychiatric safety concerns

Three pharmacologic interventions: nicotine replacement therapy (NRT), bupropion and varenicline are currently licensed for use as smoking cessation medicines in the UK. NICE Public Health Guidance published in 2008 recommends the use of all three medicines by healthcare professionals and smoking cessation advisers as aids to help adults quit smoking, along with giving advice, encouragement and support, or referral to a smoking cessation service (4). However, this

recommendation is based on earlier NICE publications which are now out of date (15-17). Since the publication of the original NICE guidance, there have been ongoing concerns about the safety of the smoking cessation medicines, with particular respect to the neuropsychiatric safety of varenicline. In 2008, concerns about varenicline's neuropsychiatric safety led the Medicines and Healthcare products Regulatory Agency (MHRA) to issue warnings about varenicline in the UK (5). Similarly, since 2009, the Food and Drug Administration (FDA) has required that varenicline and bupropion carry black box warnings (the agency's strongest safety warning) on their product labelling in the US. This was done to alert patients and prescribers of the potential increased risk of serious neuropsychiatric adverse events (such as depressed mood, suicidal ideation and suicidal behaviour) associated with these medicines (6). These safety warnings were originally based on spontaneous reports made to the UK Yellow Card Scheme and the FDA adverse events reporting system. Last year, Pfizer, the manufacturer of varenicline, requested that the FDA remove the black box warning on varenicline's product labelling based on findings from newer research published since the original safety warnings. However, in October 2014, the FDA's Psychopharmacologic Drugs Advisory Committee and the Risk Management Advisory Committee voted to retain varenicline's black box warning (18).

Limitations of previous research

The ongoing debate regarding the neuropsychiatric safety of drugs for smoking cessation among drug regulators, researchers, prescribers and patients may be due to the inconsistent research findings in this area (7). Whereas studies without control groups (such as those using adverse event reporting data and case studies) (19-21) have reported increased risks of self-reported depression and suicidal/self-injurious behaviour in patients prescribed varenicline and bupropion, studies with control groups (such as observational cohort studies and experimental study designs, mainly RCTs and systematic reviews of RCTs) have reported the opposite, and found no evidence of an increased risk of these severe neuropsychiatric outcomes in patients prescribed these medicines (8-10, 22-25). However, there are important limitations associated with each of these study designs. First, studies which use spontaneous adverse event reports are limited by several factors. These include the severity of the adverse event (severe adverse events are more likely to be reported than less serious events), the length of time that the drug has been available (adverse events with newer drugs are more likely to be reported than events occurring with older drugs for the same indication) and media publicity about a drug (media reports often lead to increased reporting of adverse events to the Yellow Card Scheme, known as stimulated reporting) (26, 27). Second, observational cohort studies are prone to the effects of confounding by indication, which raises concerns about the validity of their findings (28). Confounding by indication may occur if an observed association between smoking cessation medicines and serious psychiatric events such as suicide is explained by the fact that smokers themselves are at increased risk of mental illness and suicide (29, 30). In two of the earlier cohort studies, varenicline and bupropion were found to be associated with a decreased risk of death from all causes (22, 23); this reported protective effect was most likely due to residual confounding in the studies.

How these limitations will be addressed

Experimental studies are less likely to suffer from uncontrolled confounding, however, to date, systematic reviews and meta-analyses of RCTs have mainly focussed on comparing the neuropsychiatric safety of varenicline monotherapy with placebo (8-10). Although this is an important research question, patients are unlikely to be prescribed placebo in real life settings to help them quit smoking. Therefore the neuropsychiatric safety of varenicline compared with other smoking cessation drugs is likely to be of greater relevance to patients, prescribers and regulators. To date, there have been no comprehensive reviews of the neuropsychiatric safety of the smoking cessation medicines in relation to each other. In addition, there have been no recent cost-effectiveness analyses to determine which smoking cessation medicine is the most cost effective in UK settings. In this project we will seek to address these outstanding research questions using systematic reviews, network meta-analyses and cost-effectiveness analyses.

4. Evidence explaining why this research is needed now

The health benefits of smoking cessation have been well documented. Varenicline has been shown to be the most clinically effective monotherapy for long term smoking abstinence (>6 months) and is recommended as first line treatment for smoking cessation along with bupropion and NRT in the UK (4, 12). However, the number of prescription items of varenicline dispensed in England decreased by 25% from a peak of approximately one million prescriptions in 2011 to almost 742,000 prescriptions in 2013 (31), possibly reflecting ongoing fears among prescribers and patients regarding varenicline's neuropsychiatric safety. It is important for patients, prescribers and regulators to know how smoking cessation medicines compare with each other with particular respect to their neuropsychiatric safety, to enable smokers wanting to quit and their healthcare professionals to make informed decisions about the risks and benefits of the different pharmacological treatments. A network meta-analysis (NMA) allows evidence synthesis to be performed when there are multiple competing interventions available, in order to make comparisons across all pairs of interventions in a coherent manner (11). In its simplest form, an NMA is the combination of direct and indirect estimates of relative intervention effect, where indirect evidence refers to evidence on intervention C relative to B obtained from A versus B and A versus C studies. If both direct and indirect estimates are available, they can be pooled to produce an internally coherent set of effect estimates of each intervention relative to any other, whether or not they have been compared in head to head trials (11).

For smoking cessation there are several competing alternatives: e.g. monotherapies of each of the smoking cessation medicines or combination therapies (i.e. varenicline combined with bupropion, varenicline combined with nicotine replacement therapy, bupropion combined with nicotine replacement therapy). For NRT, different formulations may also be given concurrently, for example patch and gum. NMA also allows multi-arm trials be incorporated without losing information (for example bupropion vs NRT vs varenicline). Furthermore, treatments may be given at different dosages, a NMA can handle this by defining each dose as a separate treatment and avoiding the need to 'lump' doses together.

Previous evidence synthesis studies in the area of smoking cessation medicines have the following limitations (*we describe in italics how the limitations will be addressed in this study*):

- Failure to comprehensively investigate the neuropsychiatric safety of smoking cessation medicines in a NMA by including data from all RCTs, irrespective of their duration. NMAs have been performed primarily to assess the effectiveness of smoking cessation medicines with limited safety analyses (12, 32), although more recently a comprehensive NMA investigating the cardiovascular safety of the smoking cessation medicines has been published (33). Previous NMAs of neuropsychiatric safety have only included RCTs identified by the primary effectiveness NMAs, which excluded RCTs of less than six months duration (13, 32). As adverse events may occur within hours or days of starting treatment (34), the previous safety NMAs would fail to capture adverse events reported in shorter duration RCTs and be of limited scope. *This limitation can be fully addressed by including RCTs of any duration in our NMA of neuropsychiatric safety.*

- Lack of sufficient data for nodes within the previous neuropsychiatric safety NMAs (13, 32). *We are confident that we will be able to address this limitation and identify sufficient data for the neuropsychiatric NMA proposed in this study for several reasons. First, as previously mentioned we will include trials of any duration. Second, our recently published systematic review and meta-analyses of death in patients prescribed varenicline compared with placebo included 68% more participants than a similar meta-analysis of serious adverse events in the Cochrane NMA study (10,647 participants from 36 trials, compared with 6,333 participants from 14 trials) (9, 12). Third, results from a large, Phase 4, industry sponsored, post-marketing trial to evaluate the neuropsychiatric safety and efficacy of varenicline versus placebo, NRT and bupropion in smokers with and without a prior history of psychiatric illnesses (known as EAGLES) are expected in late 2015 (35). More than 8,000 participants were included in the EAGLES trial, with approximately 2,000 participants in each of the four treatment arms (35). This study should have sufficient statistical power to adequately assess*

the occurrence of clinically significant neuropsychiatric adverse events with each treatment. Therefore, the inclusion of this trial in this study will substantially improve the precision of estimates of adverse events. We will also include data on adverse events from observational studies with control groups.

- The Cochrane Collaboration's NMA of effectiveness of smoking cessation medicines requires updating (12). The Cochrane NMA was restricted to RCTs that had been included in previous Cochrane reviews only and is therefore limited by the recency of the source reviews, which were published in 2007 (for bupropion) (36) and 2012 (for NRT and varenicline) (37, 38). There are no current plans by the study authors to update the Cochrane NMA (personal communication). *As information on effectiveness will be used in our cost effectiveness analyses, we will update the Cochrane NMA to include recently published trials.*

- None of the previously published NMAs have examined combined therapies of smoking cessation medicines (12, 13, 32) although the effectiveness and safety of combined treatments are increasingly examined in trials. Smoking cessation medicines are not currently licensed for use in combination in the UK. *Combined smoking cessation therapies will be included in this project as the analysis of both safety and efficacy data on co-prescribing could be of importance to regulators.*

- Previously published cost effectiveness analyses of smoking cessation medicines relevant to England and Wales are also out of date as these have mainly included effectiveness data obtained from the Cochrane study (13); in addition disutilities due to adverse events have not been incorporated previously. *These limitations will be addressed by including the most up to date information from our new NMA of neuropsychiatric safety and updating the NMAs of effectiveness and cardiovascular safety.*

The proposed systematic reviews, network meta-analyses and cost effectiveness modelling will examine important questions about the relative costs and benefits of different smoking cessation pharmacotherapies. It is expected that the study findings will be incorporated into the next full update of the 2008 NICE Public Health guidance on Smoking Cessation Services (4) (a partial update is scheduled to commence in November 2015).

5. Research plan

Our detailed research plan will be described in the following sections (Sections 6-21). We are a multidisciplinary team of epidemiologists, biostatisticians, public health clinicians, health economists and biological psychologists based within the University Of Bristol- School Of Social and Community Medicine, the Centre for Public Health, the Tobacco and Alcohol Research Group, the Centre for Research Synthesis and Decision Making (CReSyDa) and the University of Sheffield- School of Health and Related Research (ScHARR). We have a track record of collaborating and publishing research of the highest quality and impact. Please see Section 21 for a detailed description of the team members, their contributions and responsibilities and how this project will fit within the core aims of each of the centres.

6. Aims and Objectives

This study aims to compare the neuropsychiatric safety of the smoking cessation medicines in comparison with each other. The specific objectives are as follows:

- To perform a comprehensive systematic review and network meta-analysis of the neuropsychiatric safety of monotherapy with varenicline, bupropion and NRT and combination therapies in relation to each other, placebo or usual care.

- To update previous systematic reviews and NMAs (12, 13, 33) of the effectiveness and cardiovascular safety of monotherapy with varenicline, bupropion and NRT and combination therapies in relation to each other, placebo or usual care.

- To adapt a published economic model (13, 39, 40) to incorporate disutilities due to adverse events, in order to estimate the cost effectiveness of monotherapy and combination therapies of smoking cessation medicines within the context of the NHS and primary care settings in the UK.

- If sufficient evidence is available, we will explore the following subgroups in the NMA and economic model: heavy smokers, those with respiratory, cardiovascular or psychiatric illnesses and those with previous quit attempts.

- To provide recommendations on the relative costs and benefits of the different smoking cessation therapies to inform future updates to the NICE public health intervention guidance on 'Smoking Cessation Services' (4) .

7. Health technologies being addressed

These will include monotherapy with varenicline, bupropion and NRT and combination therapies of these medicines (defined earlier). For NRT combination formulations given concurrently will also be included, see Sections 10 and 15.

8. Design and theoretical/conceptual framework

This is an evidence synthesis study and will include network meta-analyses of the safety and effectiveness of pharmacologic interventions for smoking cessation in addition to economic decision modelling. We will conduct a novel network meta-analyses of the neuropsychiatric safety of the smoking cessation medicines and update existing network meta-analyses of their effectiveness (12) and cardiovascular safety (33). Network meta-analysis is an extension of standard meta-analysis which enables the simultaneous comparison of multiple interventions in a single model, whilst retaining the distinct identity of each intervention analysed (11) for inclusion in a comprehensive cost-effectiveness analysis.

9. Target population

All adult smokers who are seeking to quit smoking using prescribed smoking cessation therapies in NHS and primary care settings in the UK. This includes adult smokers accessing local authority stop smoking services.

10. Inclusion/Exclusion criteria

Inclusion criteria

For the network meta-analyses we will include the following:

- RCTs of <u>any</u> duration which report on at least one of our pre-stated safety outcomes for the <u>safety</u> analyses (see Section 15)

-Observational studies (with control groups) which report on at least one of our pre-stated safety outcomes for the <u>safety</u> analyses (see Section 15)

- RCTs of <u>6 months or more</u> duration which report on at least one of our pre-stated <u>effectiveness</u> outcomes for the effectiveness analyses (see Section 15)

- Monotherapy with varenicline, bupropion and NRT in any formulation at licensed and marketed dosages. Bupropion and varenicline are available as oral tablets. NRT is available as patches, gum, sublingual tablets, lozenges, inhalers and sprays (see Section 15)

-Combination therapies of the above medications including combinations of NRT formulations

-Phase 2, 3 and 4 trials

Exclusion criteria

We will exclude the following:

- Crossover trials, non-randomised trials, quasi-randomised trials and interrupted time series analyses

- Uncontrolled observational studies, for example case reports and case series (for the safety analyses)

- Non-smoking populations (sensitivity analyses will be performed including and excluding smokeless tobacco users)

- People less than 18 years old as varenicline and bupropion are only licensed for use in adults in the UK

- Pregnant and breastfeeding women as varenicline and bupropion are not licensed for use in these groups in the UK

- Alternative and complementary therapies for example hypnotherapy, acupuncture, aromatherapy and herbal therapies.

- Psychotherapies will also be excluded unless they are included as co-treatment with a pharmacologic intervention.

-E-cigarettes. Although e-cigarettes are nicotine containing products, they are not licensed for use as smoking cessation aids. In addition there is a lack of reliable and good quality literature on their role in smoking cessation (41, 42). Therefore e-cigarettes will not be considered in this project.

11. Setting/context

The study will contain RCTs in any setting that meet the inclusion criteria described previously in Section 10. Observational studies with control groups will be included in safety analyses. Eligible settings will include but are not limited to primary care practices, hospitals including inpatient and outpatient clinics, universities, workplace clinics, nursing or residential homes.

12. Search strategy (see also Section 15)

We will work with an information specialist to identify trials for inclusion in the network meta- analyses. We will search the following databases: MEDLINE, EMBASE, PsycINFO, Web of Science, Clinicaltrials.gov and Cochrane Databases including the Cochrane Database of Systematic Reviews (CDSR), the Database of Abstracts and Reviews of Effectiveness (DARE), the Cochrane Central Register of Controlled Trials (CENTRAL), the NHS Economic Evaluation Database (NHS EED) and the Health Technology Assessment Database (HTA).

We will also manually search the reference lists of relevant research articles and previous reviews and communicate with authors to identify unpublished information; in a previous study we had a 75% response rate from corresponding authors for studies published after 2006 (9).

Safety

We anticipate that there is likely to be large numbers of new comparisons to add to the network from more recent trials which would not have been incorporated into the earlier Cochrane reviews. Based on the number of trials identified in the previous cardiovascular NMA (33) and the systematic review of neuropsychiatric adverse events (9) we expect to identify sufficient RCTs for to enable us to perform safety network meta-analyses.

For the neuropsychiatric safety network meta-analyses we will build on the basic search strategy included in the cardiovascular network meta-analysis by Mills et al. (2014) (33) which identified trials published prior to March 20th 2013 (see Appendix A) . To specifically locate studies of adverse events we will follow recommendations provided in Section 14.5.2 of the Cochrane Handbook of Systematic Reviews (43) and will conduct both key word and subject heading searches. For example, in Medline we will include the subheading “adverse events” and “complications” combined with both the brand

names and generic names for each drug. For the side effects we will include specific keyword searches such as “insomnia”, “side adj effect$”, “neuropsych$” in combination with the drug names. Searches will be conducted with the help of an information specialist.

We will also update the cardiovascular network meta-analysis with more recently published trials identified from our new search strategy (33).

Details of study outcomes are described in Section 15.

Clinical effectiveness

As the search strategy in the Cochrane network meta-analysis of the effectiveness of pharmacological interventions for smoking cessation (12) was based on identifying previous Cochrane systematic reviews, it will not be used. However, three of the 12 Cochrane reviews identified in the Cahill et al (2013) (12) network meta-analysis are relevant to the current study, Hughes et al. (2007) (36) ,Cahill et al. (2012) (37) and Stead et al. (2012) (38). The Hughes et al. (2007) review (36) was updated in 2014 (44). The search strategies from these three Cochrane reviews (or updated versions where available) will be modified to exclude medicines that are not included in this study. We will re-run each of the modified search strategies to identify more recent trials for inclusion in the current study.

Cost effectiveness

The economic model will be based on a replication by colleagues at the University of Sheffield (13) of the widely used Benefits of Smoking Cessation in Outcomes (BENESCO) model (39, 40). A key disadvantage of this model is that it does not include adverse effects of treatments. We will further adapt the Sheffield model (13) to incorporate disutilities associated with neuropsychiatric and cardiovascular treatment-related adverse events. The searches used for the network-meta-analyses will be re-run with a cost-effectiveness filter to identify studies reporting information on utilities, disutilities, resource use, and costs, which will be used to inform the economic evaluation.

13. Identification of full text reports

Inclusion and exclusion criteria are described previously in Section 10. Two investigators will independently screen abstracts identified from the search strategies to determine whether full text reports should be obtained. The same two investigators will independently identify eligible full text reports for inclusion based on specific criteria. Data extraction is described in the next section. We will include a PRISMA diagram (45) to set out the results of the search and to indicate the number of included and excluded trials. The reasons for excluding any studies identified by the search will be documented in tables.

14. Data extraction

Data extraction will be carried out by one investigator and checked by a second investigator. Information will be collected on the study design (duration of treatment, description of allocation concealment and blinding), study participants (inclusion and exclusion criteria, country, region, population studied, and baseline characteristics such as ethnicity, sex, smoking history), intervention and comparison groups (including the smoking cessation intervention, whether or not there was co-treatment, dosage and formulation), our predefined primary and secondary outcomes of interest including measures of effectiveness and safety outcomes, losses to follow up and study sponsor (see Section 15). This information will be entered on to data extraction spreadsheets. We will also record information on the risk of bias for each trial; the Cochrane tool for assessing the risk of bias will be used (see Section 15) (46). All of the extracted information will be summarised in tables.

15. Data analysis

Type of Studies

We will include clinical trials comparing the smoking cessation pharmacotherapies (as monotherapy or in combination treatments) with placebo, each other or usual treatment. The trials should include some form of random allocation to either group and report one or more of our pre-specified outcomes.

Multi-arm trials will be included. For adverse events, observational studies which include control groups will also be included.

Types of participants

Participants will include smokers aged 18 years and over of all ethnicities in the general population. Planned subgroup analyses will be performed in specific populations of smokers as follows: those with psychiatric illness (for example depression, schizophrenia, bipolar disorder, substance misuse), cardiovascular disease (for example peripheral vascular disease, acute coronary syndromes and post myocardial infarction), Chronic Obstructive Pulmonary Disease, diabetics, heavy smokers (defined as people who smoke >20 cigarettes per day) and those with previous quit attempts.

Interventions

Table 1 summarises the three main pharmacologic monotherapies for smoking cessation by formulation and dosage using the British National Formulary (BNF) July 2015 version (http://www.evidence.nhs.uk/formulary/bnf/current). Combination therapies and combinations of NRT formulations will also be included in the analyses. Additionally, co-treatment with behavioural interventions such as counselling will be included by duration (<30 minutes and >30 minutes).

Outcomes

Safety analysis

The primary composite safety outcome will be serious adverse events defined as events that were life threatening or resulted in death, hospitalisation, significant disability or congenital/birth defect. Safety outcomes will be grouped under the following headings:

-Neuropsychiatric outcomes. The primary neuropsychiatric outcomes will be major adverse neuropsychiatric events (MANE) which will include completed suicide, attempted suicide, suicidal ideation, depression and seizures. Secondary neuropsychiatric outcomes will include abnormal dreams, aggression, anxiety, fatigue, insomnia, irritability, sleep disorders and somnolence.

-Cardiovascular outcomes. The primary cardiovascular outcomes will be major adverse cardiovascular events (MACE) which will include cardiovascular death, nonfatal myocardial infarction (i.e. unstable angina) and non-fatal stroke based on the FDA definition (47). Secondary cardiovascular outcomes will include transient ischemic attack, congestive heart failure, palpitations and arrhythmias.

-Other outcomes. These will include adverse events such as nausea, headache, dry mouth, skin rash and pruritus.

Effectiveness analysis

The primary effectiveness outcome will be sustained smoking cessation i.e. abstinence for a minimum of six months as determined by biochemically validated continuous or prolonged abstinence at the longest reported time point in intention to treat analyses. We will extract information on abstinence at each time point for which it is reported to allow a survival model to be estimated (following the approach used by (48, 49). Reductions in smoking will not be included. Secondary outcomes will include reduction in craving and reduction in withdrawal symptoms.

Search methods for identification of studies

Search methods for the identification of studies have been described previously in Section 12.

Table 1: Summary of pharmacologic interventions by dose and formulation

Treatment and formulation	Lower dose	Standard dose	Higher dose
Bupropion			
Oral extended release tablets	<150 mg bd	150 mg bd	>150mg bd
Varenicline			
Tablets	<1 mg bd	1 mg bd	>1 mg bd
Nicotine replacement therapy			
Patch (16 hrs)	<15 mg (5mg/ 16 hours or 10 mg/16 hours)	15 mg (15 mg/16 hours)	>15 mg (25mg/16 hours)
Patch (24 hrs)	< 14 mg (7 mg/24 hours)	14 mg (14 mg/24 hours)	>14 mg (21 mg/24 hours)
Gum		2 mg per piece (maximum 15 pieces daily)	4 mg per piece (maximum 15 pieces daily)
Nasal spray		0.5 mg per metered spray (up to 2 sprays every hour, maximum 64 daily)	
Mouth spray		1 mg per spray (up to 4 sprays every hour, maximum 64 daily)	
Lozenge	1mg or 1.5 mg per lozenge (1 lozenge every 1-2 hours, maximum 15 daily)	2mg (1 lozenge every 1-2 hours, maximum 15 daily)	4 mg (1 lozenge every 1-2 hours, maximum 15 daily)
Sublingual tablet		2mg per tablet (up to 1 tablet per hour, maximum 40 daily)	2mg per tablet (up to 2 tablets per hour, maximum 40 daily)
Inhalator		10mg per cartridge (maximum 12 cartridges daily)	15mg per cartridge (maximum 6 cartridges daily)

Key- mg- milligram; bd- twice daily

For nicotine replacement therapy the higher dose is generally used in smokers who smoke >20 cigarettes per day.

Assessing study eligibility, data extraction and assessing risk of bias

The processes for assessing trial eligibility and data extraction have been previously described in sections 13 and 14. We will work in close collaboration with the Centre for Research Synthesis and Decision Making (CReSyDa); two of the co-investigators, DC and NW are members of this group. CReSyDa has substantial expertise in conducting systematic reviews of randomised controlled trials and other study designs, multi parameter evidence synthesis, economic evaluation and decision

making within the School of Social and Community Medicine. The Centre has strong links with the Cochrane Collaboration.

For RCTs the Cochrane tool for assessing the risk of bias will be used to determine whether there is high, low or unclear risk of bias in the following domains: random sequence generation, allocation concealment, blinding or participants and personnel, blinding of outcome assessment, incomplete outcome data, selective outcome reporting and other sources of bias (46). Two investigators will independently assess the risk of bias in each of the trials. Discrepancies will be resolved by referring to the original publication and discussion with a third individual. As yet, there is no consensus around the specific items which are necessary for evaluating the risk of bias in different types of observational study designs. However, as previously stated, observational studies with no control groups will be excluded.

Statistical methods

We will conduct standard meta-analyses for each pairwise comparison of treatments and each outcome. We will present results of both fixed- and random-effects meta-analyses in 'forest' plots: where these estimates differ we will consider possible reasons for the heterogeneity, such as risk of bias indicators and other pre-specified potential effect modifiers. If sufficient evidence is identified, we plan to consider the following subgroups in all analyses: heavy smokers, those with psychiatric illnesses, those with respiratory or cardiovascular disease and smokers who have made previous quit attempts. Between-study heterogeneity will be quantified using the between-study variance (τ^2).

For each separate outcome, we will also construct a NMA which will be compared to the pair-wise results. As previously described, a network meta-analysis is an extension of standard meta-analysis which enables the simultaneous comparison of multiple interventions in a single model, whilst retaining the distinct identity of each intervention analysed (11). It also enables the ranking of treatments according to the probability that each is the best, or worst, for a given outcome. The NMA will be conducted in a Bayesian framework using OpenBUGS software and will use the code developed by Dias et al. (2013) (50). Where possible we will consider the combination therapies as separate interventions, but will explore models for the effects of the component therapies using a main effects model and a 2-way interaction model (allowing pairs of therapies to have either a bigger or smaller effect than would be expected from the sum of their effects alone). Both fixed and random effects models will be fitted. For the random effects analysis we will assume homogeneous between-study variability across studies. We will assess the goodness of fit of each model to the data by calculating the posterior mean residual deviance. This is defined as the difference between the deviance for the fitted model and the saturated model, where the deviance measures the fit of the model using the likelihood function. The Deviance Information Criterion (DIC), which is equal to the sum of the posterior mean of the residual deviance and the effective number of parameters PD, will be used as a basis for model comparison (51). The DIC penalises the posterior mean residual deviance (a measure of model fit) by the effective number of parameters in the model (as measure of complexity) and can therefore be viewed as a trade-off between the fit and complexity of the model.

Validity of a NMA depends on the assumption that there is no effect modification of the pairwise intervention effects or, that the prevalence of effect modifiers is similar in the different studies. This key assumption has been referred to variously as transitivity (52), similarity (53) and consistency (54). A clinical and epidemiological judgement of the plausibility of this assumption requires assessment of the inclusion/exclusion criteria of every trial in the network, to assess whether the patients, trial protocols, doses, administration etc. are similar in ways that might modify treatment effect. We will compile a table of important trial and patient characteristics and visually inspect the 'similarity' of factors we consider likely to modify treatment effect.

Evidence inconsistency can be considered an additional layer of heterogeneity that occurs in networks of evidence when there is a discrepancy between a direct and indirect estimate of treatment effect, for example when the consistency assumption (described above) is violated. Inconsistency is a property of 'closed loops' of evidence. We will visually inspect the network diagram to identify the extent of potential inconsistency (the number of loops) and use model fit and selection statistics to informally assess whether it is evident. If inconsistency is suspected we will explore it formally using a "node-splitting" approach (54). Node-splitting allows the analyst to split the network-wide information contributing to summary effect estimate B vs. C into the evidence from studies directly compare B with C and the remaining 'indirect' evidence for B vs. C when the direct comparisons are removed. The extent of the disagreement between the direct and indirect estimates defines the magnitude of inconsistency.

The effectiveness estimates from the NMA will be entered into a probabilistic economic model [9] Based on existing, published models and trial-based cost-effectiveness analyses [10-12] we will build a health economic decision model to address the question which is the most cost-effective medicine for smoking cessation.

Health economic modelling

We will further adapt the Sheffield model (13) to incorporate treatment-related adverse events. We will review the literature to identify disutilities and costs associated with neuropsychiatric and cardiovascular treatment-related adverse events. Acknowledging that we may not find many studies in a smoking cessation population, we will also search for studies reporting disutilities and costs for the same events in other populations. We will take advice from our clinical advisers as to which populations that we find evidence for will be most similar to the smoking cessation population of interest. The Sheffield model is a cohort simulation model that considers a single quit attempt, and assumes that quitters either remain quitters, or relapse and do not subsequently quit. If we find sufficient data, we will extend this to allow for a subsequent successful quit attempt. There are 9 health states describing the most common sequelae of smoking: COPD, CHD events, Stroke, Asthma exacerbations, lung cancer, and death. If sufficient evidence is available, the network meta-analysis will deliver efficacy estimates for the following subgroups: heavy smokers, those with psychiatric illnesses, those with respiratory or cardiovascular disease and smokers who have made previous quit attempts. If sufficient evidence can be identified on the inputs to the Sheffield model for these subgroups, then we will perform subgroup analyses in the economic evaluation.

We will compare all interventions and combinations of interventions that we have sufficient information on from the Network Meta-Analysis. Our primary focus is on pharmacological treatments, however some of the evidence may consider these in combination with behavioural interventions, and these co-interventions may differ across trials. We will take advice from our clinical advisors and patient representatives as to the co-interventions of most relevance to the UK setting for inclusion in the health economic model, although this will also be limited by the evidence that we have available. A UK NHS perspective is taken, with future costs and benefits discounted at a rate of 3.5% per year. We will present results from a probabilistic model that accounts for uncertainties in the model inputs. The results from the economic model will be summarised as expected costs, Quality Adjusted Life Years (QALYs), and Expected Net Benefit at willingness to pay per QALY thresholds of £20,000 and £30,000. A fully incremental analysis will also be reported. Uncertainty will be presented with cost-effectiveness acceptability curves and frontiers. The sensitivity of the optimal decision to parameter uncertainty will be explored using expected value of partial perfect information (EVPPI) which represents an upper limit on the returns from further research eliminating uncertainty on specific subsets of parameters.

16. Dissemination and projected outputs

We anticipate five groups for whom the results of this research will be of interest (i) the general public (ii) clinicians and healthcare practitioners, (iii) academics (iv) policy makers and (v) industry.

Dissemination to the general public

Dr Thomas and Professor Munafò will work closely with the UK Centre for Tobacco and Alcohol Studies (UKTCAS) Smokers' Panel. We have provided the panel with a lay summary of the research plan and have received feedback about our aims and objectives for the project. If the project is funded then we will liaise with this group on two further occasions as follows. Midway through the project we will present initial findings and discuss strategies for dissemination. Towards the end of the project we will present the project's findings and discuss plans for further dissemination and future research.

We will also obtain feedback on our proposals from the Elizabeth Blackwell Institute's (EBI) public advisory group (http://www.bristol.ac.uk/blackwell/about/organisation/public-advisory/). The EBI panel consists of members of the public who advise researchers. Similar to the smokers' panel, the EBI panel will be consulted over the course of the project.

Social media, for example blogs and twitter will also be utilised to disseminate key findings. Possible outlets include Sifting the Evidence (http://www.theguardian.com/science/sifting-the-evidence), a health and science blog hosted by The Guardian and written by Dr Suzi Gage. Other suitable outlets for dissemination include the Tobacco and Alcohol Research Group blog (http://targ.blogs.ilrt.org/) and independent blogs such as the Mental Elf blog (http://www.nationalelfservice.net/mental-health/) which has strong links to our research group; our previous research on the neuropsychiatric safety of varenicline and smoking cessation medicines (9, 22) has previously been published on this blog (55, 56).

Dissemination to healthcare practitioners and clinicians

Dr Thomas is a NIHR Clinical Lecturer in Public Health and splits her time equally between the Public Health and Wellbeing Division at South Gloucestershire Council and the School of Social and Community Medicine, University of Bristol. Dr Thomas will work with specialist health improvement practitioners for Smokefree South Gloucestershire who are based at the Public Health and Wellbeing Division. Smokefree South Gloucestershire commissions and provides smoking cessation services in GP practices, pharmacies and other community settings in South Gloucestershire, delivers training to health professionals (nurses, GPs and smoking cessation advisors) and works in partnership with local mental health providers and the voluntary, community and social enterprise (VCSE) sector. Dr Thomas has worked with the specialist health improvement practitioners to develop and deliver bite sized training modules on the safety and efficacy of varenicline and other smoking cessation medicines to health care professionals and smoking cessation advisors. Research findings can also be disseminated using the Smokefree professionals website. We will also engage with other organisations in the South West region such as Smokefree Bristol.

Dr Thomas will also use her connections with the South West Public Health network to disseminate findings to other Public Health professionals in the region at the South West Development School and the South West Public Health Scientific Conference. These events target a varied audience of Public Health professionals including those based at Local Authorities, Clinical Commissioning Groups, Public Health England and local Universities. Dr Thomas has previously presented plenary sessions on the neuropsychiatric safety of smoking cessation medicines at the South West Public Health Scientific Conference in 2013 and 2015.

Findings from this project will also be disseminated to the Preventing Addictions Health Integration Team (HIT) of Bristol Health Partners. Bristol Health Partners is a collaboration among local authorities in the region, NHS organisations and the Universities. The Preventing Addictions HIT aims to reduce the harm caused by excessive alcohol use and substance misuse, including the harms caused by smoking.

Dissemination to academics

The research protocol will be registered on the PROSPERO database (http://www.crd.york.ac.uk/PROSPERO/). We will produce a report describing our methods and setting out the clinical effectiveness, safety and cost effectiveness of the smoking cessation

medicines to be published as an HTA monograph. Findings from the project will be disseminated through other conventional academic routes such as peer reviewed publications and presentations and regional, national and international conferences. Possible conferences include the Society for Social Medicine conference and the Society for Research on Nicotine and Tobacco conference. All research articles will be published as open access articles and we aim to publish our findings in high impact journals such as the British Medical Journal and the Lancet to maximise dissemination. Findings will also be disseminated through the University of Bristol School websites.

Dissemination to policy makers

This project will enhance the evidence base and inform advice to prescribers and patients. This project will enhance the evidence base and inform advice to prescribers and patients. Key findings will be collated and provided to the Medicines and Healthcare products Regulatory Agency to input into evidence based recommendations which may be used to inform future NICE guidance on smoking cessation interventions.

Dr Welton and Dr Caldwell are members of the Centre for Research Synthesis and Decision Making (CReSyDa) which has strong links with the Cochrane Collaboration and the National Institute of Health and Care Excellence (NICE) Decision Support Unit (DSU). Professor Stevenson is a member of NICE Appraisal Committee C. We have excellent links with policy makers and non-governmental organisations as part of the UK Centre for Tobacco and Alcohol Studies. We will produce briefing notes to disseminate to key agencies and stakeholders, such as Action on Smoking and Health UK and the Tobacco Policy Group at the Department of Health.

Dissemination to industry

Findings will also be disseminated to industry, including the different manufacturers of the products.

17. Plan of investigation and timetable

We propose a 26 month project beginning in September 2016. Main project phases are set out in Table 2 below. The project steering group will have quarterly meetings throughout the project.

Table 2 Project timetable

Timescale (months)												
1-2	3-4	5-6	7-8	9-10	11-12	13-14	15-16	17-18	19-20	21-22	23-24	25-26
Trial search and retrieval												
Trial assessment and data preparation												
			Search and report retrieval for economic analysis									
							Network meta-analysis and cost- effectiveness analysis					
									Analysis and Dissemination Phase			
Quarterly meetings of steering group throughout the Project												

18. Project management

Day to day management of the project will be the responsibility of the systematic reviewer from months 1 to 8 and the experienced research associate appointed to perform the network meta-analysis and economic evaluation from months 9 to 26. General supervision will be provided by KT

throughout the project and DC from months 15-26. KT will also provide support during the trial identification and data extraction process. Quarterly meetings of the project steering group are planned to review progress (MS will provide input via teleconference or email). Due to the complexity of some of the analyses, support has been requested from other project applicants, namely DC, NW and MS. Staff will draw on the experience and expertise of the team throughout the period of the proposed work project.

19. Approval by ethics committees

Ethics approval is not required for this evidence synthesis project as it involves analysis of secondary data from RCTs.

20. Patient and Public Involvement

A lay summary of our proposal was reviewed by participants of the UK Centre for Tobacco and Alcohol Studies (UKCTAS) Smokers' Panel. The Panel consists of 25 current smokers and recent quitters, based in Bath. Meetings are held twice per year; each meeting has a theme and includes presentations from Centre members, students and external colleagues. All proceedings are taped and transcribed. Ideas and feedback are used to generate new research questions, write new grant proposals and ensure that the language used in publications and study materials is accessible to the public. In between meetings panel members are involved with UKCTAS researchers in developing ideas for research, commenting on proposals and participating in studies. Members of the Panel also contribute to the design of teaching and in the past have given talks at events and conferences.

An outline of a related proposal (NIHR HTA 14/49/49) and a summary of the current proposal was presented to the Elizabeth Blackwell Institute's Public Advisory Group. This is a panel of lay members of the public who advise researchers at the EBI. Novel avenues for dissemination of study findings were suggested, including dissemination via local authorities in the region, Bristol City Council and South Gloucestershire Local Authority and initiatives such as the Wellbeing Charter (http://www.wellbeingcharter.org.uk/); local media, such as via Dr Philip Hammond on BBC radio Bristol and dissemination directly to smoking cessation advisors associated with pharmacies and GP practices (see Section 16).

Feedback has already been obtained on this protocol via phone conversations and emails between the PI and members of the Panel. During the course of the project we will meet with the UKCTAS smokers' panel two further times. We have requested support for consumer input into the project (including review and feedback on presentations and lay summaries of manuscripts by Panel members) and for staff to attend meetings with the Smokers Panel. We will also consult with the EBI Patient Advisory Panel midway through and towards the end of the project to obtain feedback on our results, gauge further ideas for dissemination and discuss future research plans.

21. Expertise and justification of support required

Research Team Expertise

The multidisciplinary team has a wide range of experience in relevant HTA disciplines, including systematic review and evidence synthesis, network meta-analysis and biostatistics, cost effectiveness analysis and public health.

Dr Kyla Thomas (KT) is a NIHR funded academic clinical lecturer in Public health within the Centre for Public Health based at the School of Social and Community Medicine. She will provide clinical public health and pharmacoepidemiology expertise with particular expertise in examining the safety of the smoking cessation medicines, as evidenced by two recent papers published in the BMJ (9, 22). She will provide 10% of her time to the project and will be responsible for overall project management. She will also contribute to writing the project report and publications. Her remaining time will be spent on complementary research on related NIHR HTA and MRC grants, suicide and self-harm prevention

and on working with colleagues in the Public Health and Wellbeing Division at South Gloucestershire Council, the Clinical Commissioning Group and the voluntary community and social enterprise sector to improve mental health and wellbeing among local residents. She has worked with specialist health improvement practitioners at Smokefree South Gloucestershire to develop and deliver bite sized training sessions for smoking cessation advisors and GPs.

Dr Deborah Caldwell (DC) is a lecturer in Public Health Research at the School of Social and Community Medicine and has just completed a MRC post-doctoral fellowship based on developing methodology for network meta-analysis. She has extensive expertise in the application of network meta-analyses techniques to a wide range of applications and is a co-convenor of the Cochrane Comparing Multiple Interventions Methods Group. She will lead the supervision of the network meta-analyses and will contribute to preparation of the project report and publications.

Dr Nicky Welton (NW) is a Reader in Evidence Synthesis at the School of Social and Community Medicine and has completed a MRC methodology fellowship on methods for value of information (VOI) analyses. She is co-lead of the Evidence Synthesis and VOI theme of the ConDuCT Hub for trials methodology research. She has a wide experience of methods for evidence synthesis (including network meta-analysis) to inform cost effectiveness models and cost-effectiveness modelling that inform reimbursement decisions for health technologies by organisations such as NICE. She is also deputy director for the NICE Clinical Guidelines Technical Support Unit which is based in the School and is a member of the NICE Technology Appraisal Committee. NW will lead the supervision of the cost effectiveness analyses and will be involved in writing the project report and publications.

Professor David Gunnell (DG) is a Professor of Epidemiology based in the School of Social and Community Medicine. He is a Public Health Physician with expertise in pharmacoepidemiology and psychiatric epidemiology, in particular the epidemiology of suicide and suicidal behaviour. He is a former member of the MHRA's Pharmacovigilance Expert Advisory Group and a current member of the Department of Health Suicide Prevention Advisory Group. He has conducted and collaborated on a number of studies investigating psychiatric adverse drug reactions to antidepressants and smoking cessation products. He will provide epidemiological and public health input to the project.

Professor Marcus Munafò (MM) is a Professor of Biological Psychology based at the School of Experimental Psychology and will provide experience of tobacco research as Head of the Tobacco and Alcohol Research Group in Bristol. He has published many high profile studies on the causes and consequences of smoking. He has worked closely with the MHRA, NICE and the Department of Health on tobacco control issues. MM will contribute to the project report and preparation of manuscripts for publication and will disseminate our findings to interested policy makers via contacts at groups such as Action on Smoking and Health, UK and the Tobacco Policy Group at the Department of Health.

Professor Matt Stevenson (MS), is a Professor of Health Technology Assessment at the University of Sheffield. He has published over twenty full Health Technology Assessments (six as lead author) and over 70 peer-reviewed manuscripts in total. MS is a member of a NICE Technology Appraisal Committee and also is technical director of ScHARR-TAG, one of the academic institutions undertaking health technology assessments for NICE. MS has published on the cost-effectiveness of the clinical and cost effectiveness of cytisine compared with varenicline for smoking cessation. MS will act as an advisor on the modelling undertaken to estimate cost-effectiveness.

We expect to appoint an experienced systematic reviewer as well as an experienced research associate with skills in network meta-analysis techniques and economic evaluation.

We expect to be supported by an Information Specialist with expertise in developing search strategies for identifying the relevant trials for the reviews and the economic analyses.

We also have the support of a MHRA representative. A letter of support has been uploaded.

Justification of support costs

We have requested support costs for the following staff: an Information Specialist contracted at 85 hours, a Systematic Reviewer at 100% FTE from months 1-8 and a Research Associate who is experienced in network meta-analysis techniques and economic evaluation at 100% FTE from months 9-26. The systematic reviewer will coordinate the project and have day to day management responsibility from months 1-8; the experienced research associate will have this role from months 9-26.

The systematic reviewer will assess trial eligibility, assess risk of bias, extract relevant outcome data and prepare the dataset for the NMA. The experienced research associate will prepare and populate the network diagram, undertake reviewing of the literature to parameterise the economic model, develop the structure of the cost effectiveness model and its coding and perform the cost effectiveness analyses. The experienced research associate will also contribute to the writing of the report and journal papers.

KT will be costed at 10% for the duration of the project and will provide overall management of the team and overall supervision of the project. KT will also be involved in data checking with the systematic reviewer and will supervise the systematic review methodology required for the network meta-analyses. DC will be costed at 5% from months 1 to 14 and at 10% from months 15-26. With KT, DC will supervise the systematic review methodology required for the network meta-analyses; DC will also supervise the statistical analyses for the network meta-analyses. NW and MS will supervise the economic modelling. MS will be costed at 1.5% from months 1 to 26. All other co-investigators will be costed at 1 hour per week for the duration of the project. All co-investigators will contribute to preparation of the project report and publications and be involved in the quarterly meetings of the project steering group.

We have included costs for two workstations, Stata licenses, inter library loans and translation of foreign language publications. We have requested support for consumer input into the project and for staff to attend meetings with the Smokers Panel. We have requested resources for presenting the research at one international and two national conferences. We have costed two open access publications.

University Settings

The research described in this application will be conducted within the School of Social and Community Medicine, University of Bristol and the Health Economics and Decision Science Section of the School of Health and Related Research, University of Sheffield.

Internal collaborations will include:

- The Centre for Public Health- the centre focuses on the conduct of research into the health of the population with the aim of protecting health and wellbeing, preventing ill-health and reducing health inequalities. Dr Thomas and Professor Gunnell are members of the Centre for Public Health which forms part of this school.
- The Centre for Academic Primary Care- the centre conducts high quality research relating to primary care and general practice. Dr Nicky Welton is a member of the Centre for Academic Primary care which forms part of this school.
- The Tobacco and Alcohol Research Group- this group focuses on examining the effects of nicotine and alcohol together with the biological and psychological factors underlying addiction. Professor Marcus Munafo leads this group.
- Centre for Research Synthesis and Decision Making- the centre brings together groups within the School with substantial expertise in conducting systematic reviews of RCTs, economic evaluation and decision making. It has strong links with the Cochrane Collaboration and the

NICE Decision Support Unit. Dr Nicky Welton and Dr Deborah Caldwell are members of this group.

- The NIHR School for Public Health Research- this is a collaboration between eight leading academic centres with excellence in applied public health research in England with a primary aim of building the evidence base for effective public health practice. Professors Munafo and Gunnell and co-investigators for the University of Bristol.
- The NIHR School for Primary Care Research- this is a partnership between eight leading academic centres for primary care research in England with a primary aim of increasing the evidence base for primary care practice through high quality research and strategic leadership. Dr Nicky Welton is one of the co-investigators for the University of Bristol.
- NIHR Collaboration for Leadership in Applied Health Research and Care (CLAHRC) West- CLAHRC West's mission is to actively engage all partners in the conduct of applied health research and the implementation of relevant research evidence to improve health and healthcare across the Greater Bristol area. Professor Gunnell is lead of the Public Health theme for NIHR CLAHRC West.

External collaborations will include:

- The West of England (WoE) Academic Health Science Network (AHSN). The WoE AHSN is a collaboration between the NHS and academic institutions in the South West which aims to improve patient and population health by translating research into practice. The network works to put evidence generated by CLAHRC West into practice.

- The Health Economics and Decision Science (HEDS) Section of the School of Health and Related Research (ScHARR), University of Sheffield- the purpose of HEDS is to promote excellence in health care resource allocation decisions. Professor Matt Stevenson leads the ScHARR Technology Assessment Group.

Intellectual property

Although the outputs from the project are not likely to have commercial value, there is considerable potential for patient benefit. We will ensure that the findings of the network meta-analyses and economic evaluation are widely disseminated to the general public, clinicians and healthcare professionals, academics and policy makers (as described in Section 16). Our plans for patient and public involvement have already been described (see Section 20). The involvement of patients and the public in our proposal also offers potential for patient benefit as lay summaries of the relative effects and safety of smoking cessation medicines will inform patient choice.

22. Flow diagram

Evidence synthesis studies are not required to upload flow charts.

23. Version number 1, date 14/06/2016

Appendix A Search Strategy included in Mills et al. (2014) (33)

Ovid Syntax

1. random:.tw,sh,pt. OR placebo:.tw,sh.
2. (clinical trial OR controlled clinical trial).pt.
3. ((single or doubl: or tripl: or treb:) AND (blind: or mask:)).tw,ab
4. OR/1 – 3
5. Tobacco Use Cessation Products [mesh]
6. nicotine OR NRT OR nicotine replacement
7. bupropion OR zyban
8. varenicline OR champix OR chantix
9. OR/5 – 8
10. smoking [mesh]
11. AND 9 AND 10

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