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What are the effects of varenicline compared with nicotine replacement therapy on long term smoking cessation and clinically important outcomes? Protocol for a prospective cohort study

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3 **Title: What are the effects of varenicline compared with nicotine replacement therapy**
4 **on long term smoking cessation and clinically important outcomes?**
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Abstract

Introduction

Smoking is a major avoidable cause of ill-health and premature death. Treatments that help patients successfully quit smoking could have an important effect on health and life expectancy. Varenicline is a medication that can help smokers successfully quit smoking. However, there are concerns that it may cause adverse effects, such as increase in the occurrence of depression, self-harm and suicide, and cardiovascular disease.

Methods

In this project we will investigate the effects of varenicline compared to nicotine replacement therapies on: i) long-term smoking cessation and whether these effects differ by area level deprivation; and ii) the following clinically-important outcomes: rate of General Practice (GP) and hospital attendance; all-cause mortality and death due to diseases of the respiratory system and cardiovascular disease; and a primary care diagnosis of respiratory illness, myocardial infarction or depression and anxiety. The study is based on a cohort of patients prescribed these smoking cessation medications from the Clinical Practice Research Datalink (CPRD). We will use three methods to overcome confounding: multivariable adjusted Cox regression, propensity score matched Cox regression, and instrumental variable regression.

Ethics and dissemination

Ethics approval was not required for this study. This project has been approved by the CPRD's Independent Scientific Advisory Committee (ISAC). We will disseminate our findings via publications in international peer-reviewed journals and presentations at international conferences.

Strengths and limitations of this study

- We will use data from a large sample of patients prescribed smoking cessation treatment in UK general practices. This means we will have substantial power to detect even relatively small effects, or effects on rare outcomes.
- We will use three statistical approaches to overcome confounding. These approaches depend on distinct assumptions. Triangulating across different methods will help provide more robust evidence about the effects of these medications.
- Our study will use observational data and so results can suffer from unobserved confounding. We will report in detail the confounding structure, and detail the methods we used to overcome this limitation.
- The outcomes used in this study will be defined using diagnoses and interactions that occur as part of the patients' routine care. This means they may not be recorded consistently. We will mitigate this limitation by using validated code lists.

Introduction

Smoking is the major cause of preventable morbidity and mortality in the UK and internationally (1, 2). Smoking is also the principal cause of health inequalities and is responsible for most of the difference in healthy life-expectancy between the richest and poorest in our society (3) and those with and without mental health problems (4, 5). Smoking-related illnesses are estimated to cost the NHS approximately £5bn per year (6). Varenicline has been shown to be the most clinically effective smoking cessation medicine for short-term abstinence in randomized controlled trials (RCTs) (7). However, there is relatively little evidence for its long-term effectiveness and impact on clinical outcomes.

Concerns have been raised that varenicline may be associated with a higher risk of adverse events, including suicide and self-harm and cardiovascular events, than other smoking cessation interventions (8–11). Since 2009, the US Food and Drug Administration (FDA) has mandated that varenicline carry a black box warning (the agency's strongest safety warning) highlighting the increased risk of suicidal ideation and depression in patients prescribed varenicline. This was based on spontaneous reports to the FDA Adverse Events Reporting (FDA AERS) database (13). These warnings are meant to indicate causal effects of pharmaceuticals. However, there are an increasing number of experimental and observational studies that suggest there is little difference in risk of adverse neuropsychiatric effects of varenicline compared to nicotine replacement products (11, 14). In October 2014, the FDA decided that the black box warning on varenicline should remain; it is expected that this guidance will be updated after publication of the results of the EAGLES randomised trial in late 2015 (17, 18).

The committees decided that the black box warning on varenicline should remain, and expect to update their guidance after publication of the results of the EAGLES randomised trial in late 2015 (15, 16). Much of the evidence about the potential adverse effects of varenicline comes from observational studies, which are prone to confounding. We will add to the evidence base about the possible adverse and beneficial effects of prescribing different smoking cessation medications using three statistical approaches to overcome confounding: multivariable adjusted regression, propensity score regression and instrumental variable analysis.

We will investigate the effects of varenicline on smoking abstinence because existing evidence from randomised controlled trials typically only followed participants for one year, and are not informative about long-term outcomes. We will investigate the effects of varenicline prescriptions on all-cause primary and secondary care utilization because smoking increases morbidity and imposes major costs on the health care services (17). We will examine differences in smoking cessation medication effectiveness by socio-economic position. A recent systematic review reported that stop-smoking services may be helping to reduce inequalities in smoking prevalence by preferentially targeting smokers of lower socio-economic position (SEP). Data from primary care records (THIN) show that between 2008 and 2010, smokers in more deprived groups were more likely to receive smoking cessation interventions (18). We will not investigate bupropion because it is rarely prescribed and systematic reviews have found that it is less effective than varenicline for smoking cessation (7).

First, we will investigate the effects of varenicline on rates of cardiovascular outcomes and respiratory illnesses, as previous research has suggested that patients prescribed varenicline may have different rates of these outcomes (9, 10). Second, we will investigate the effects of

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3 varenicline on depression and anxiety because there has been some reports that varenicline
4 may reduce the risk of these outcomes (14). Third, we will investigate the incidence illnesses
5 in the Clinical Practice Research Database (CPRD) using primary care diagnoses based on
6 Read codes, admission to secondary care using ICD-10 codes, and Office of National
7 Statistics (ONS) mortality records to maximise the number of events detected. We will use
8 validated code lists for each outcomes.
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10 11 **Methods and analysis**

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13 We will conduct a prospective cohort study of all patients prescribed varenicline or nicotine
14 replacement products in the CPRD. Exposure will be defined as the first prescription of either
15 varenicline or nicotine replacement therapy. We will investigate differences in the outcomes
16 described above. For the statistical analysis we will use Cox regression models adjusted for a
17 range of baseline confounders, propensity score matched Cox regression, and instrumental
18 variable analyses using physicians' prescribing preferences as instruments for the
19 prescriptions issued.
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22 **Inclusion and Exclusion Criteria**

23 We will include patients who were older than 18 and were prescribed medicines in British
24 National Formulary (BNF) category 4.10.2 (Nicotine Dependence) from 1st September 2006,
25 when varenicline was introduced to the UK, to the present. We will use patients prescribed
26 other smoking cessation products (nicotine patches, gum, lozenges, and inhalers) as controls
27 for patients prescribed varenicline. We will include patients whose records were classified as
28 'acceptable' by the CPRD from all up to standard GPs at least 18 months prior to date of
29 entry of each cohort (1st January 2005). Patient data are defined as "acceptable" by the CPRD
30 if they meet minimum quality control standards, for example their registration period with
31 their GP is valid.
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34 We will exclude patients who registered at a GP less than 365 days before the first recorded
35 prescription, to allow for high quality assessment of baseline data and possible confounders.
36 Patients prescribed bupropion in the year before their index prescription of varenicline or
37 nicotine replacement therapy will be excluded from the analysis. In the primary analysis we
38 will exclude patients initially prescribed both nicotine replacement therapies and varenicline
39 together, although in our previous analysis this only occurred for 0.25% of all prescriptions
40 (14).
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43 **Power calculations**

44 The following power calculations are based on effect sizes and confidence intervals observed
45 in our previously published results, which used data from 110,000 individuals prescribed
46 either varenicline or nicotine replacement therapy (14). Based on the rate of 18,000 new
47 prescriptions per year observed in the CPRD from 2006 to 2011 (14), we estimate that with a
48 further 4 years of follow-up the number of patients prescribed either varenicline or nicotine
49 replacement therapy will have increased by 72,000. Therefore the total expected sample size
50 for analysis will be around 180,000.
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53 In our previous analysis using CPRD data the age- and sex-adjusted hazard ratio for self-
54 harm/suicide for varenicline vs. nicotine replacement therapy at nine months was 0.73 (95%
55 CI: 0.54 to 0.99); after adjusting for possible confounders this became 0.90 (95% CI: 0.66 to
56 1.22) (14). A 70% increase in sample size would lead to a reduction of the standard error by a
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factor of 1.3, reducing the breadth of the above confidence interval in the adjusted analysis from 0.56 to 0.43.

Rare outcomes, such as self-harm and suicide were used in previous analyses; in this project we will have greater power to explore more common outcome measures. For example, in the previous analysis the nine-month age- and sex-adjusted hazard ratio for all-cause mortality nine months after first prescription for varenicline vs. nicotine replacement therapy was 0.43 (95% CI: 0.35 to 0.53); after controlling for possible confounders this became 0.49 (95% CI: 0.40 to 0.61). A 70% increase in sample size would lead to a reduction of the standard error by a factor of 1.3, reducing the breadth of the above confidence interval in the adjusted analysis from 0.21 to 0.16.

For the effects of varenicline versus nicotine replacement therapy on all-cause mortality, instrumental variable analysis found a risk difference of 0.7 (95% CI: -3.3 to 4.7) per 1,000 patients treated after nine months. We estimate that a 70% increase in sample size would narrow the confidence intervals from 8.0 to 6.2.

Using data from our previous project, within two years of first prescription, we found 2,517 admissions for respiratory disease amongst 1,374 patients; 3,144 admissions for cardiovascular disease amongst 1,022 patients; and 3,277 admissions for depression or anxiety amongst 213 patients. This is more events than we found for suicide and self-harm in our previous study; therefore we believe that there will be enough events for this analysis.

To investigate differences in health care seeking behaviour of smokers by socioeconomic position we will combine the sample used for the health outcomes described above with a sample of all other patients indicated as a current smoker after the 1st of September 2006.

Data collection and linkage

We will use linked Hospital Episodes Statistics (HES) and ONS mortality data to define frequency of GP and hospital attendance, frequency of all-cause and cause-specific hospitalization and all-cause and cause-specific mortality. We will test these hypotheses using data from GP practices linked to external datasets only.

These are important hard outcomes for our study. We have already established that for certain outcomes, such as cause specific mortality the linked ONS data are more accurate (19). Whilst it is possible to investigate these outcomes using CPRD data from GPs, the data are less precise and consistently recorded. Thus analyses using linked data are likely to be more precise. Furthermore, the linked data provide direct evidence about secondary care attendance of patients via the HES data. Again, whilst there are some data about referrals to secondary care in the main tables of the CPRD, the data are not as comprehensive as HES data. Our outcomes of interest occur after September 2006; therefore, we believe that both the linked HES and ONS data will provide sufficient coverage for these outcomes.

Data analysis

Exposure measures

First time users of the smoking cessation therapies (varenicline or nicotine replacement therapy) will be defined as people who received at least one prescription of the product after the 1st of September 2006 but with no use of a related product during the 12 months before

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3 the index date (the first date on which a prescription was issued). Langley and colleagues
4 found the smoking cessation prescription data in the THIN database, which is closely related
5 to the CPRD, to be highly comparable to national dispensing data (20). The analysis will be
6 limited to the first treatment episode. This will mimic an intention-to-treat analysis in a RCT
7 (21). This ensures that the target parameter estimated in the observational study will be
8 comparable to the parameter estimated by a RCT. The prescriptions will be defined by the
9 therapy file in the CPRD, which contains a list of all prescriptions issued to patients by their
10 GP. Each therapy record records the date a prescription was issued, the quantity of drug
11 prescribed and the dosage.

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14 To mimic an intention-to-treat analysis in an RCT, in our primary analysis patients who are
15 initially prescribed nicotine replacement therapy, but later switch to varenicline, will be
16 allocated to nicotine replacement therapy and vice-versa. We will use an intention-to-treat
17 design for two reasons. First, whilst there are theoretical statistical models for estimating the
18 effects of treatment switching such as marginal structural models, these methods require the
19 strong assumption that there are no unmeasured confounders and typically require detailed
20 data on time-varying confounders, which are unlikely to be available in the CPRD. Second,
21 to our knowledge there are no instrumental variable methods to estimate the effects of
22 switching treatment.

23 24 25 **Outcome measures**

26 27 28 **Outcome 1: Smoking abstinence**

29 In the CPRD smoking status is indicated by whether the patient is a current, former or never
30 smoker. As GPs are paid to record smoking status smoking behaviour is robustly recorded in
31 the CPRD (22). Marston and colleagues found that 84% of patients had smoking status
32 recorded within a year of registering at a GP, and that smoking prevalence rates by age were
33 similar in CPRD and the Health Survey of England (22). Booth and colleagues found that the
34 difference in prevalence of smoking estimate between the CPRD and the Health Survey for
35 England was less than 1%, and the mean difference was 0.1% (95% CI: -1.5% to 1.7%) (23).
36 Using unpublished data from CPRD sampled as part of the research reported in Thomas et al.
37 (2013) we found that 74% of patients prescribed smoking cessation medication had a
38 subsequent record indicating smoking status (14). Of these 66% were indicated as current
39 smokers and 33% as ex-smokers. We will initially define a patient as relapsed if they have
40 any record indicating that the patient is a current smoker after their first prescription of a
41 smoking cessation therapy. We will not be able to determine the smoking status of patients
42 who do not return to the GP. Therefore, we will perform sensitivity analyses to examine
43 whether the assumptions made about the smoking status of individuals who are not observed
44 affect the results. For example, we will conduct a sensitivity analysis to see if the results are
45 altered by assuming that patients with missing data have relapsed, or by assuming that
46 patients with missing outcomes have achieved abstinence.

47 48 49 **Outcome 2: Frequency of GP and hospital attendance**

50 We will define service use as the number of visits to GP and hospitals in the 3, 6, 9, 12, 24
51 and 48 months after first prescription. We will define GP appointments using the clinical data
52 file of the CPRD. This includes all the diagnoses and symptoms that GPs record about all of
53 their patients. As with the other outcomes, the vast majority of diagnoses and symptoms
54 include the date on which the data were added to the database. We will use these dates to
55 calculate the number of times each patient attends primary care. We will define the hospital
56 visits outcome using the linked HES data. We will investigate all-cause hospitalisation and
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three specific causes of hospitalisation: 1) diseases of respiratory system (ICD-10=J00-J99), 2) cardiovascular disease (ICD-10=I00-I52) and 3) anxiety and depression (ICD-10=F31.3, F31.4, F31.5, F32, F40-F48). This is available for approximately half of the sample. Again these data contain the date on which the event occurred, which we will use to define attendance to secondary care within 3, 6, 9, 12, 24 and 48 months after first prescription.

Outcome 3: All-cause and cause-specific mortality

We will define all-cause and cause-specific mortality using the linked ONS mortality dataset. These include the date of death and cause of death using ICD-9 codes. We will investigate three specific causes of mortality: 1) diseases of respiratory system (ICD-10=J00-J99), 2) cardiovascular disease (ICD-10=I00-I52), and 3) anxiety and depression (ICD-10=F31.3, F31.4, F31.5, F32, F40-F48).

Outcome 4: Incident respiratory illness, myocardial infarction, depression or anxiety

We will define the adverse event outcomes using the diagnosis records from the Clinical and Referral files in the CPRD. These files record all the diagnoses that the GPs input into their computer system. Each record in the table is given a diagnosis code based on the Read code categorisation. We will use validated Read code lists, for the three adverse event outcomes, respiratory illnesses, myocardial infarction or depression and anxiety, please see the cited papers for Read code lists (24–26). For eligible patients we will extract all records from the Clinical and Referral Tables that indicate the patient either received a specific diagnosis or were referred for a specific diagnosis. As with the therapy records for prescriptions described above, each Clinical and Referral Record indicates the date the information was inputted into the system. We will use this date to define the date that the diagnosis was made. We will define a set of outcomes within 3, 6, 9, 12, 24 and 48 months after first prescription.

Confounding factors

We will include gender, age in years at time of first prescription, previous psychiatric illness/consultation, previous use of psychotropic medications such as hypnotics, antipsychotics and antidepressants, previous self-harm, measures of alcohol consumption where appropriate mean/median number of GP visits per year, body mass index, socioeconomic position (deprivation score for area or residence) and major chronic illness (including: diabetes, cancer, arthritis) using the Charlson index (27, 28). Relevant Read codes will be identified either by validated code lists or by searching for each of these events in the Read code dictionaries to identify any missing Read codes. Collider bias could occur if we conditioned on events that happened as a result of the prescription the patient was issued. To prevent this bias from affecting our results, we will define each covariate using data inputted prior to the first prescription (29). If there are missing data in the covariates we will consider using multiple imputation.

Statistical Analysis

For investigating the effects of varenicline use on each outcome (long-term smoking cessation, frequency of GP and hospital attendance, all-cause and cause-specific mortality, primary care diagnosis of respiratory illness, myocardial infarction, depression or anxiety), we will report a conventional multivariable-adjusted Cox regression, propensity score regression and instrumental variable analysis.

Analysis 1: Conventional Cox regression

In our first analysis, a conventional observational analysis, we will estimate hazard ratios of the outcomes using Cox-proportional hazards models and the actual prescriptions issued to the patients (30). Each patient's date of entry into the cohort will be the date they were first prescribed a smoking cessation therapy. The date of exit for each outcome will be the date on which they first have an event, or are censored due to end of follow-up or death or leaving the practice. We will report these associations adjusted for basic confounders (age and gender), and results adjusted for all measured covariates described above.

Analysis 2: Propensity score regression

In our second analysis we will construct a sample of patients balanced on covariates and risk factors using a propensity score (31–34). We will construct propensity scores using a logistic regression of the actual treatment received on the covariates described above. Therefore, each participant's propensity score will be their conditional probability (odds) of receiving varenicline versus nicotine replacement therapy. We will match each patient receiving varenicline to another patient receiving nicotine replacement therapy with the closest propensity score on a ratio of 1:1 using a nearest neighbour algorithm with no replacement, and matching will be restricted to the common support region. Patients outside the common support region are those prescribed varenicline with propensity scores higher than any patient prescribed nicotine replacement therapy and vice versa. We will estimate hazard ratios of the outcomes using the propensity score matched sample using Cox regressions using the same entry and exit information as the conventional Cox regression analysis described above.

Analysis 3: Instrumental variable analysis

In our third analysis, we will estimate the effects of smoking cessation therapies on the outcomes using physicians' prescribing preferences as instruments for the prescriptions the GPs issue to their patients. We cannot directly measure the physicians' preferences; therefore, we will use the prescriptions they issued to their previous patients as a proxy for their preferences. For example, if the instrument was based on just one previous prescription, physicians who previously prescribed varenicline would be categorised as a varenicline prescriber. As with our previous studies we will use seven prior prescriptions to improve the strength of the instruments (14, 35, 36). Using multiple prior prescriptions will maximise power. We will report risk differences in the outcomes using additive structural mean models estimated via the generalised method of moments (37–39).

We will categorise each of the adverse event outcomes as occurring within 3, 6, 9, 12, 24 and 48 months of first prescription. We will do this because methods for conducting survival analysis using instrumental variables are not well developed. We will use Stata 13.1 SE to generate all results. The instrumental variable analysis will be conducted using the `ivreg2` command and `psmatch2` will be used to construct the propensity score (32, 40, 41). All standard errors will be estimated using cluster robust standard errors, which account for clustering of patients within practices.

Socio-economic variation in effectiveness of smoking cessation treatments

This project will use the entire sample of patients indicated as a smoker at any point after 1st September 2006. We will assign a measure of area level deprivation to each patient using their home address postcode and to each GP using the GP postcode. Deprivation levels will be based on the Indices of Multiple Deprivation (IMD), which are available from the ONS

and are updated every two years. We will use the most recent IMD statistics preceding the date of entry into the study for each patient. Although area level deprivation statistics will only be a proxy for individual level deprivation, these demonstrate the expected associations with smoking prevalence (42). We will investigate whether the proportion of smokers who attend their GP for smoking cessation treatment differs by IMD, and whether there are any differences in prescribing of varenicline versus nicotine replacement products between areas of high and low deprivation.

By using both individual and GP level IMD codes, we will investigate whether the effects of smoking cessation therapies differ by IMD at both the level of GPs and at the individual level. We will investigate treatment compliance by reporting the total number of prescriptions issued after the initial prescription. We will estimate the effects of smoking cessation therapies within sub-groups defined by IMD level both at the individual and GP level using the three methods described above, multivariable-adjusted Cox regression, propensity score regression and instrumental variable analysis (30, 33, 43). The cohort of patients will be defined as described above. We will report these associations adjusted for basic confounders (age and gender), and results adjusted for all measured covariates described above. Analyses will account for clustering of patients by GPs.

Ethics approval, peer review, data curation and dissemination

Access to the CPRD data is governed by its Independent Scientific Advisory Committee (ISAC). The empirical research described in this proposal significantly expands on our existing work. We have received approval for this project protocol from ISAC (protocol number 15_107). We will comply with all requirements of ISAC requirements for publications based on CPRD data, for example including the ISAC study protocol as an appendix to published papers. This protocol has been peer reviewed separately as part of the NIHR Health Technology Assessment board's efficient study designs call (proposal ID 14/49/94) and the ISAC expert advisory board. The data produced as part of this study will be made available via a system of managed open access – interested researchers who obtain necessary approvals from ISAC will be permitted access to the data generated during this study.

Key findings will be collated to form evidence-based recommendations which will be communicated to relevant groups, with the aim of improving the evidence base to inform advice to prescribers and patients. We will also aim to publish findings in peer-reviewed journals and present our work at national and international conferences.

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What are the effects of varenicline compared with nicotine replacement therapy on long term smoking cessation and clinically important outcomes? Protocol for a prospective cohort study

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3 **Title: What are the effects of varenicline compared with nicotine replacement therapy**
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5 **prospective cohort study**
6

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Abstract

Introduction

Smoking is a major avoidable cause of ill-health and premature death. Treatments that help patients successfully quit smoking have an important effect on health and life expectancy. Varenicline is a medication that can help smokers successfully quit smoking. However, there are concerns that it may cause adverse effects, such as increase in the occurrence of depression, self-harm and suicide, and cardiovascular disease. In this study we aim to examine the effects of varenicline versus other smoking cessation pharmacotherapies on smoking cessation, health service use, all-cause and cause-specific mortality, and physical and mental health conditions.

Methods

In this project we will investigate the effects of varenicline compared to nicotine replacement therapies on: i) long-term smoking cessation and whether these effects differ by area level deprivation; and ii) the following clinically-important outcomes: rate of General Practice (GP) and hospital attendance; all-cause mortality and death due to diseases of the respiratory system and cardiovascular disease; and a primary care diagnosis of respiratory illness, myocardial infarction or depression and anxiety. The study is based on a cohort of patients prescribed these smoking cessation medications from the Clinical Practice Research Datalink (CPRD). We will use three methods to overcome confounding: multivariable adjusted Cox regression, propensity score matched Cox regression, and instrumental variable regression. The total expected sample size for analysis will be at least 180,000. Follow-up will end with the earliest of either an “event” or censoring due to the end of registration or death.

Ethics and dissemination

Ethics approval was not required for this study. This project has been approved by the CPRD’s Independent Scientific Advisory Committee (ISAC). We will disseminate our findings via publications in international peer-reviewed journals and presentations at international conferences.

Strengths and limitations of this study

- We will use data from a large sample of patients prescribed smoking cessation treatment in UK general practices. This means we will have substantial power to detect even relatively small effects, or effects on rare outcomes.
- We will use three statistical approaches to overcome confounding. These approaches depend on distinct assumptions. Triangulating across different methods will help provide more robust evidence about the effects of these medications.
- Our study will use observational data and so results can suffer from unobserved confounding. We will report in detail the confounding structure, and detail the methods we used to overcome this limitation.
- The outcomes used in this study will be defined using diagnoses and interactions that occur as part of the patients' routine care. Different GPs may use a range of Read codes to record diagnoses. We will mitigate this limitation by using validated code lists, where available, to ensure the algorithms we use accurately capture the diagnoses and events of interest.

Introduction

Smoking is the major cause of preventable morbidity and mortality in the UK and internationally (1,2). Smoking is also the principal cause of health inequalities and is responsible for most of the difference in healthy life-expectancy between the richest and poorest in our society (3) and those with and without mental health problems (4,5). Smoking-related illnesses are estimated to cost the NHS approximately £5bn per year (6). Varenicline has been shown to be the most clinically effective smoking cessation medicine for short-term abstinence in randomized controlled trials (RCTs) (7). However, there is relatively little evidence for its long-term effectiveness and impact on clinical outcomes.

Concerns have been raised that varenicline may be associated with a higher risk of adverse events, including suicide and self-harm and cardiovascular events, than other smoking cessation interventions (8–11). In 2009, the US Food and Drug Administration (FDA) mandated that varenicline carry a black box warning (the agency's strongest safety warning) highlighting the increased risk of suicidal ideation and depression in patients prescribed varenicline. This was based on spontaneous reports to the FDA Adverse Events Reporting (FDA AERS) database (12). These warnings are meant to indicate causal effects of pharmaceuticals. However, there are an increasing number of experimental and observational studies that suggest there is little difference in risk of adverse neuropsychiatric effects of varenicline compared to nicotine replacement products (11,13). In October 2014, the FDA decided that the black box warning on varenicline should remain; it is expected that this guidance will be updated after publication of the results of the EAGLES randomised trial in late 2015 (14,15).

The committees decided that the black box warning on varenicline should remain, and expect to update their guidance after publication of the results of the EAGLES randomised trial in late 2015 (14,15). Much of the evidence about the potential adverse effects of varenicline comes from observational studies, which are prone to confounding. We will add to the evidence base about the possible adverse and beneficial effects of prescribing different smoking cessation medications using three statistical approaches to overcome confounding: multivariable adjusted regression, propensity score regression and instrumental variable analysis. Using these three approaches we aim to examine the effects of varenicline versus other smoking cessation pharmacotherapies on smoking cessation, health service use, all-cause and cause-specific mortality, and physical and mental health conditions. Follow-up will end with the earliest of either an "event" or censoring due to the end of registration or death. We will not investigate bupropion because it is rarely prescribed and systematic reviews have found that it is less effective than varenicline for smoking cessation (7).

Study Aims:

1. What is the effect of varenicline on smoking abstinence? We will investigate the effects of varenicline on smoking abstinence because existing evidence from randomised controlled trials typically only followed participants for one year, and are not informative about long-term outcomes.

2. What are the effects of varenicline on NHS service use? We will investigate the effects of varenicline prescriptions on all-cause primary and secondary care utilization because smoking increases morbidity and imposes major costs on the health care services (16).

3. What are the effects of varenicline on all-cause and cause-specific mortality? We will investigate the incidence illnesses in the Clinical Practice Research Database (CPRD) using primary care diagnoses, admission to secondary care using ICD-10 codes, and Office of National Statistics (ONS) mortality records to maximise the number of events detected.

4. What are the effects of varenicline on common physical and mental health conditions?

We will investigate the effects of varenicline on rates of cardiovascular outcomes and respiratory illnesses, as previous research has suggested that patients prescribed varenicline may have different rates of these outcomes (9,10). Second, we will investigate the effects of varenicline on rates of depression and anxiety because there has been some reports that varenicline may reduce the risk of these outcomes (13).

5. We will also examine differences in smoking cessation medication effectiveness by socio-economic position. A recent systematic review reported that stop-smoking services may be helping to reduce inequalities in smoking prevalence by preferentially targeting smokers of lower socio-economic position (SEP). Data from primary care records (THIN) show that between 2008 and 2010, smokers in more deprived groups were more likely to receive smoking cessation interventions (17).

Methods and analysis

We will conduct a prospective cohort study of all patients prescribed varenicline or nicotine replacement products in the CPRD. Variables will be defined using “Read codes” which are clinical encoding of patient phenomena, for example a patient’s: occupation, demographic information, social circumstances, clinical symptoms and observations, laboratory tests and results, and diagnoses.

Inclusion and Exclusion Criteria

We will include patients who were older than 18 and were prescribed medicines in British National Formulary (BNF) category 4.10.2 (Nicotine Dependence) from 1st September 2006, when varenicline was introduced to the UK, to the present. We will use patients prescribed other smoking cessation products (nicotine patches, gum, lozenges, and inhalers) as controls for patients prescribed varenicline. We will include patients whose records were classified as ‘acceptable’ by the CPRD from all ‘up to standard’ GPs at least 18 months prior to date of entry of each cohort (1st March 2005). Up to standard GPs are practices that have submitted data that meets the CPRD quality control thresholds. Patient data are defined as “acceptable” by the CPRD if they meet minimum quality control standards, for example their registration period with their GP is valid.

We will exclude patients who registered at a GP less than 365 days before the first recorded prescription, to allow for high quality assessment of baseline data and possible confounders. Patients prescribed bupropion in the year before their index prescription of varenicline or nicotine replacement therapy will be excluded from the analysis. In the primary analysis we will exclude patients initially prescribed both nicotine replacement therapies and varenicline together, although in our previous analysis this only occurred for 0.25% of all prescriptions (13).

Power calculations

The following power calculations are based on effect sizes and confidence intervals observed in our previously published results, which used data from 110,000 individuals prescribed

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3 either varenicline or nicotine replacement therapy (13). Based on the rate of 18,000 new
4 prescriptions per year observed in the CPRD from 2006 to 2011 (13), we estimate that with a
5 further 4 years of follow-up the number of patients prescribed either varenicline or nicotine
6 replacement therapy will have increased by 72,000. Therefore the total expected sample size
7 for analysis will be around 180,000.
8

9
10 In our previous analysis using CPRD data the age- and sex-adjusted hazard ratio for self-
11 harm/suicide for varenicline vs. nicotine replacement therapy at nine months was 0.73 (95%
12 CI: 0.54 to 0.99); after adjusting for possible confounders this became 0.90 (95% CI: 0.66 to
13 1.22) (13). A 70% increase in sample size would lead to a reduction of the standard error by a
14 factor of 1.3, reducing the breadth of the above confidence interval in the adjusted analysis
15 from 0.56 to 0.43.
16

17
18 Rare outcomes, such as self-harm and suicide were used in previous analyses; in this project
19 we will have greater power to explore more common outcome measures. For example, in the
20 previous analysis the nine-month age- and sex-adjusted hazard ratio for all-cause mortality
21 nine months after first prescription for varenicline vs. nicotine replacement therapy was 0.43
22 (95% CI: 0.35 to 0.53); after controlling for possible confounders this became 0.49 (95% CI:
23 0.40 to 0.61). A 70% increase in sample size would lead to a reduction of the standard error
24 by a factor of 1.3, reducing the breadth of the above confidence interval in the adjusted
25 analysis from 0.21 to 0.16.
26

27
28 For the effects of varenicline versus nicotine replacement therapy on all-cause mortality,
29 instrumental variable analysis found a risk difference of 0.7 (95% CI: -3.3 to 4.7) per 1,000
30 patients treated after nine months. We estimate that a 70% increase in sample size would
31 narrow the confidence intervals from 8.0 to 6.2.
32

33
34 Using data from our previous project, within two years of first prescription, we found 2,517
35 admissions for respiratory disease amongst 1,374 patients; 3,144 admissions for
36 cardiovascular disease amongst 1,022 patients; and 3,277 admissions for depression or
37 anxiety amongst 213 patients. This is more events than we found for suicide and self-harm in
38 our previous study; therefore we believe that there will be enough events for this analysis.
39

40
41 To investigate differences in health care seeking behaviour of smokers by socioeconomic
42 position we will combine the sample used for the health outcomes described above with a
43 sample of all other patients indicated as a current smoker after the 1st of September 2006.
44

45 **Data collection and linkage**

46 We will use linked Hospital Episodes Statistics (HES) and ONS mortality data to define
47 frequency of GP and hospital attendance, frequency of all-cause and cause-specific
48 hospitalization and all-cause and cause-specific mortality. We will test these hypotheses
49 using data from GP practices linked to external datasets only.
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51
52 These are important hard outcomes for our study. We have already established that for certain
53 outcomes, such as cause specific mortality the linked ONS data are more accurate (18).
54 Whilst it is possible to investigate these outcomes using CPRD data from GPs, the data are
55 less precise and consistently recorded (18). Thus analyses using linked data are likely to be
56 more precise. Furthermore, the linked data provide direct evidence about secondary care
57 attendance of patients via the HES data. Again, whilst there are some data about referrals to
58 secondary care in the main tables of the CPRD, the data are not as comprehensive as HES
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3 data. Our outcomes of interest occur after September 2006; therefore, we believe that both the
4 linked HES and ONS data will provide sufficient coverage for these outcomes.
5

6 7 **Data analysis**

8 9 **Exposure measures**

10
11 First time users of the smoking cessation therapies (varenicline or nicotine replacement
12 therapy) will be defined as people who received at least one prescription of the product after
13 the 1st of September 2006 but with no use of a related product during the 12 months before
14 the index date (the first date on which a prescription was issued). Langley and colleagues
15 found the smoking cessation prescription data in the THIN database, which is closely related
16 to the CPRD, to be highly comparable to national dispensing data (19). The analysis will be
17 limited to the first treatment episode. This will mimic an intention-to-treat analysis in a RCT
18 (20). This ensures that the target parameter estimated in the observational study will be
19 comparable to the parameter estimated by a RCT. The prescriptions will be defined by the
20 therapy file in the CPRD, which contains a list of all prescriptions issued to patients by their
21 GP. Each therapy record records the date a prescription was issued, the quantity of drug
22 prescribed and the dosage.
23

24
25 To mimic an intention-to-treat analysis in an RCT, in our primary analysis patients who are
26 initially prescribed nicotine replacement therapy, but later switch to varenicline, will be
27 allocated to nicotine replacement therapy and vice-versa. We will use an intention-to-treat
28 design for two reasons. First, whilst there are theoretical statistical models for estimating the
29 effects of treatment switching such as marginal structural models, these methods require the
30 strong assumption that there are no unmeasured confounders and typically require detailed
31 data on time-varying confounders, which are unlikely to be available in the CPRD. Second,
32 to our knowledge there are no instrumental variable methods to estimate the effects of
33 switching treatment.
34
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36 37 **Outcome measures**

38 39 **Outcome 1: Smoking abstinence**

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41 In the CPRD smoking status is indicated by whether the patient is a current, former or never
42 smoker. As GPs are paid to record smoking status smoking behaviour is robustly recorded in
43 the CPRD (21). Marston and colleagues found that 84% of patients had smoking status
44 recorded within a year of registering at a GP, and that smoking prevalence rates by age were
45 similar in CPRD and the Health Survey of England (21). Booth and colleagues found that the
46 difference in prevalence of smoking estimate between the CPRD and the Health Survey for
47 England was less than 1%, and the mean difference was 0.1% (95% CI: -1.5% to 1.7%) (22).
48 Using unpublished data from CPRD sampled as part of the research reported in Thomas et al.
49 (2013) we found that 74% of patients prescribed smoking cessation medication had a
50 subsequent record indicating smoking status (13). Of these 66% were indicated as current
51 smokers and 33% as ex-smokers. We will initially define a patient as relapsed if they have
52 any record indicating that the patient is a current smoker after their first prescription of a
53 smoking cessation therapy. We will not be able to determine the smoking status of patients
54 who do not return to the GP. Therefore, we will perform sensitivity analyses to examine
55 whether the assumptions made about the smoking status of individuals who are not observed
56 affect the results. For example, we will conduct a sensitivity analysis to see if the results are
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3 altered by assuming that patients with missing data have relapsed, or by assuming that
4 patients with missing outcome data have achieved abstinence.
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7 **Outcome 2: Frequency of GP and hospital attendance**

8 We will define service use as the number of visits to GP and hospitals in the 3, 6, 9, 12, 24
9 and 48 months after first prescription. We will define GP appointments using the clinical data
10 file of the CPRD. This includes all the diagnoses and symptoms that GPs record about all of
11 their patients. As with the other outcomes, the vast majority of diagnoses and symptoms
12 include the date on which the data were added to the database. We will use these dates to
13 calculate the number of times each patient attends primary care. We will define the hospital
14 visits outcome using the linked HES data. We will investigate all-cause hospitalisation and
15 three specific causes of hospitalisation: 1) diseases of respiratory system (ICD-10=J00-J99),
16 2) cardiovascular disease (ICD-10=I00-I52) and 3) anxiety and depression (ICD-10=F31.3,
17 F31.4, F31.5, F32, F40-F48). Causes of hospitalisation are available for approximately half of
18 the sample. Again these data contain the date on which the event occurred, which we will use
19 to define attendance to secondary care within 3, 6, 9, 12, 24 and 48 months after first
20 prescription.
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23 **Outcome 3: All-cause and cause-specific mortality**

24 We will define all-cause and cause-specific mortality using the linked ONS mortality dataset.
25 These include the date of death and cause of death using ICD-9 codes. We will investigate
26 three specific causes of mortality: 1) diseases of respiratory system (ICD-10=J00-J99), 2)
27 cardiovascular disease (ICD-10=I00-I52), and 3) anxiety and depression (ICD-10=F31.3,
28 F31.4, F31.5, F32, F40-F48). We will use validated code lists for each outcome.
29
30

31 **Outcome 4: Incident respiratory illness, myocardial infarction, depression or anxiety**

32 We will define the adverse event outcomes using the diagnosis records from the Clinical and
33 Referral files in the CPRD. These files record all the diagnoses that the GPs input into their
34 computer system. Each record in the table is given a diagnosis code based on the Read code
35 categorisation. We will use validated Read code lists, for the three adverse event outcomes,
36 respiratory illnesses, myocardial infarction or depression and anxiety, please see the cited
37 papers for Read code lists (23–25). For eligible patients we will extract all records from the
38 Clinical and Referral Tables that indicate the patient either received a specific diagnosis or
39 were referred for a specific diagnosis. As with the therapy records for prescriptions described
40 above, each Clinical and Referral Record indicates the date the information was inputted into
41 the system. We will use this date to define the date that the diagnosis was made. We will
42 define a set of outcomes within 3, 6, 9, 12, 24 and 48 months after first prescription.
43
44

45 **Confounding factors**

46
47 We will include gender, age in years at time of first prescription, previous psychiatric
48 illness/consultation, previous use of psychotropic medications such as hypnotics,
49 antipsychotics and antidepressants, previous self-harm, measures of alcohol consumption
50 where appropriate mean/median number of GP visits per year, body mass index,
51 socioeconomic position (deprivation score for area or residence) and major chronic illness
52 (including: diabetes, cancer, arthritis) using the Charlson index (26,27). Relevant Read codes
53 will be identified either by validated code lists or by searching for each of these events in the
54 Read code dictionaries to identify any missing Read codes. Collider bias is a potential threat
55 to the analysis; this type of bias occurs when the association between two variables changes
56 upon conditioning of a third variable if the third variable is affected by the first two variables.
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3 Collider bias could occur if we conditioned on events that happened as a result of the
4 prescription the patient was issued. To prevent this bias from affecting our results, we will
5 define each covariate using data inputted prior to the first prescription (28). If there are
6 missing data in the covariates we will consider using multiple imputation.
7

8 9 **Follow-up**

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11 Follow-up will end with the earliest of either an “event” or censoring due to the end of
12 registration or death.
13

14 15 **Statistical Analysis**

16
17 For investigating the effects of varenicline use on each outcome (long-term smoking
18 cessation, frequency of GP and hospital attendance, all-cause and cause-specific mortality,
19 primary care diagnosis of respiratory illness, myocardial infarction, depression or anxiety),
20 we will report a conventional multivariable-adjusted Cox regression, propensity score
21 regression and instrumental variable analysis.
22

23 24 **Analysis 1: Conventional Cox regression**

25 In our first analysis, a conventional observational analysis, we will estimate hazard ratios of
26 the outcomes using Cox-proportional hazards models and the actual prescriptions issued to
27 the patients (29). Each patient’s date of entry into the cohort will be the date they were first
28 prescribed a smoking cessation therapy. The date of exit for each outcome will be the date on
29 which they first have an event, or are censored due to end of follow-up or death or leaving the
30 practice. We will report these associations adjusted for basic confounders (age and gender),
31 and results adjusted for all measured covariates described above.
32

33 34 **Analysis 2: Propensity score regression**

35 In our second analysis we will construct a sample of patients balanced on covariates and risk
36 factors using a propensity score (30–33). We will construct propensity scores using a logistic
37 regression of the actual treatment received on the covariates described above. Therefore, each
38 participant’s propensity score will be their conditional probability (odds) of receiving
39 varenicline versus nicotine replacement therapy. We will match each patient receiving
40 varenicline to another patient receiving nicotine replacement therapy with the closest
41 propensity score on a ratio of 1:1 using a nearest neighbour algorithm with no replacement,
42 and matching will be restricted to the common support region. Patients outside the common
43 support region are those prescribed varenicline with propensity scores higher than any patient
44 prescribed nicotine replacement therapy and vice versa. We will estimate hazard ratios of the
45 outcomes using the propensity score matched sample using Cox regressions using the same
46 entry and exit information as the conventional Cox regression analysis described above.
47

48 49 **Analysis 3: Instrumental variable analysis**

50 In our third analysis, we will estimate the effects of smoking cessation therapies on the
51 outcomes using physicians’ prescribing preferences as instruments for the prescriptions the
52 GPs issue to their patients. We cannot directly measure the physicians’ preferences; therefore,
53 we will use the prescriptions they issued to their previous patients as a proxy for their
54 preferences. For example, if the instrument was based on just one previous prescription,
55 physicians who previously prescribed varenicline would be categorised as a varenicline
56 prescriber. As with our previous studies we will use seven prior prescriptions to improve the
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3 strength of the instruments (13,34,35). Using multiple prior prescriptions will maximise
4 power. We will report risk differences in the outcomes using additive structural mean models
5 estimated via the generalised method of moments (36–38).
6

7
8 We will categorise each of the adverse event outcomes as occurring within 3, 6, 9, 12, 24 and
9 48 months of first prescription. We will do this because methods for conducting survival
10 analysis using instrumental variables are not well developed. We will use Stata 13.1 SE to
11 generate all results. The instrumental variable analysis will be conducted using the `ivreg2`
12 command and `psmatch2` will be used to construct the propensity score (31,39,40). All
13 standard errors will be estimated using cluster robust standard errors, which account for
14 clustering of patients within practices.
15

16 17 **Socio-economic variation in effectiveness of smoking cessation treatments**

18
19 This project will use the entire sample of patients indicated as a smoker at any point after 1st
20 September 2006. We will assign a measure of area level deprivation to each patient using
21 their home address postcode and to each GP using the GP postcode. Deprivation levels will
22 be based on the Indices of Multiple Deprivation (IMD), which are available from the ONS
23 and are updated every two years. We will use the most recent IMD statistics preceding the
24 date of entry into the study for each patient. Although area level deprivation statistics will
25 only be a proxy for individual level deprivation, these demonstrate the expected associations
26 with smoking prevalence (41). We will investigate whether the proportion of smokers who
27 attend their GP for smoking cessation treatment differs by IMD, and whether there are any
28 differences in prescribing of varenicline versus nicotine replacement products between areas
29 of high and low deprivation.
30
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32
33 By using both individual and GP level IMD codes, we will investigate whether the effects of
34 smoking cessation therapies differ by IMD at both the level of GPs and at the individual
35 level. We will investigate treatment compliance by reporting the total number of prescriptions
36 issued after the initial prescription. We will estimate the effects of smoking cessation
37 therapies within sub-groups defined by IMD level both at the individual and GP level using
38 the three methods described above, multivariable-adjusted Cox regression, propensity score
39 regression and instrumental variable analysis (29,32,42). The cohort of patients will be
40 defined as described above. We will report these associations adjusted for basic confounders
41 (age and gender), and results adjusted for all measured covariates described above. Analyses
42 will account for clustering of patients by GPs.
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45 46 **Ethics approval, peer review, data curation and dissemination**

47
48 Access to the CPRD data is governed by its Independent Scientific Advisory Committee
49 (ISAC). The empirical research described in this proposal significantly expands on our
50 existing work. We have received approval for this project protocol from ISAC (protocol
51 number 15_107). We will comply with all requirements of ISAC requirements for
52 publications based on CPRD data, for example including the ISAC study protocol as an
53 appendix to published papers. This protocol has been peer reviewed separately as part of the
54 NIHR Health Technology Assessment board's efficient study designs call (proposal ID
55 14/49/94) and the ISAC expert advisory board. The data produced as part of this study will be
56 made available via a system of managed open access – interested researchers who obtain
57 necessary approvals from ISAC will be permitted access to the data generated during this
58 study.
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Data sharing: Additional data is available by emailing the corresponding author.

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22 Key findings will be collated to form evidence-based recommendations which will be
23 communicated to the FDA and the Medicines and Healthcare Products Regulatory Agency
24 (MHRA), with the aim of improving the evidence base to inform advice to prescribers and
25 patients. We will also aim to publish findings in peer-reviewed journals and present our work
26 at national and international conferences.
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BMJ Open

What are the effects of varenicline compared with nicotine replacement therapy on long term smoking cessation and clinically important outcomes? Protocol for a prospective cohort study

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Manuscripts

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3 **Title: What are the effects of varenicline compared with nicotine replacement therapy**
4 **on long term smoking cessation and clinically important outcomes? Protocol for a**
5 **prospective cohort study**
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Abstract

Introduction

Smoking is a major avoidable cause of ill-health and premature death. Treatments that help patients successfully quit smoking have an important effect on health and life expectancy. Varenicline is a medication that can help smokers successfully quit smoking. However, there are concerns that it may cause adverse effects, such as increase in the occurrence of depression, self-harm and suicide, and cardiovascular disease. In this study we aim to examine the effects of varenicline versus other smoking cessation pharmacotherapies on smoking cessation, health service use, all-cause and cause-specific mortality, and physical and mental health conditions.

Methods

In this project we will investigate the effects of varenicline compared to nicotine replacement therapies on: i) long-term smoking cessation and whether these effects differ by area level deprivation; and ii) the following clinically-important outcomes: rate of General Practice (GP) and hospital attendance; all-cause mortality and death due to diseases of the respiratory system and cardiovascular disease; and a primary care diagnosis of respiratory illness, myocardial infarction or depression and anxiety. The study is based on a cohort of patients prescribed these smoking cessation medications from the Clinical Practice Research Datalink (CPRD). We will use three methods to overcome confounding: multivariable adjusted Cox regression, propensity score matched Cox regression, and instrumental variable regression. The total expected sample size for analysis will be at least 180,000. Follow-up will end with the earliest of either an “event” or censoring due to the end of registration or death.

Ethics and dissemination

Ethics approval was not required for this study. This project has been approved by the CPRD’s Independent Scientific Advisory Committee (ISAC). We will disseminate our findings via publications in international peer-reviewed journals and presentations at international conferences.

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1 Strengths and limitations of this study

- 2 • We will use data from a large sample of patients prescribed smoking cessation
3 treatment in UK general practices. This means we will have substantial power to detect even
4 relatively small effects, or effects on rare outcomes.
- 5 • We will use three statistical approaches to overcome confounding. These approaches
6 depend on distinct assumptions. Triangulating across different methods will help provide
7 more robust evidence about the effects of these medications.
- 8 • Our study will use observational data and so results can suffer from unobserved
9 confounding. We will report in detail the confounding structure, and detail the methods we
10 used to overcome this limitation.
- 11 • The outcomes used in this study will be defined using diagnoses and interactions that
12 occur as part of the patients' routine care. Different GPs may use a range of Read codes to
13 record diagnoses. We will mitigate this limitation by using validated code lists, where
14 available, to ensure the algorithms we use accurately capture the diagnoses and events of
15 interest.

peer review only

1 Introduction

2 Smoking is the major cause of preventable morbidity and mortality in the UK and
3 internationally (1,2). Smoking is also the principal cause of health inequalities and is
4 responsible for most of the difference in healthy life-expectancy between the richest and
5 poorest in our society (3) and those with and without mental health problems (4,5). Smoking-
6 related illnesses are estimated to cost the NHS approximately £5bn per year (6). Varenicline
7 has been shown to be the most clinically effective smoking cessation medicine for short-term
8 abstinence in randomized controlled trials (RCTs) (7). However, there is relatively little
9 evidence for its long-term effectiveness and impact on clinical outcomes.

10
11 Concerns have been raised that varenicline may be associated with a higher risk of adverse
12 events, including suicide and self-harm and cardiovascular events, than other smoking
13 cessation interventions (8–11). In 2009, the US Food and Drug Administration (FDA)
14 mandated that varenicline carry a black box warning (the agency's strongest safety warning)
15 highlighting the increased risk of suicidal ideation and depression in patients prescribed
16 varenicline. This was based on spontaneous reports to the FDA Adverse Events Reporting
17 (FDA AERS) database (12). These warnings are meant to indicate causal effects of
18 pharmaceuticals. However, there are an increasing number of experimental and observational
19 studies that suggest there is little difference in risk of adverse neuropsychiatric effects of
20 varenicline compared to nicotine replacement products (11,13). In October 2014, the FDA
21 decided that the black box warning on varenicline should remain; it is expected that this
22 guidance will be updated after publication of the results of the EAGLES randomised trial in
23 late 2015 (14,15).

24
25 Much of the evidence about the potential adverse effects of varenicline comes from
26 observational studies, which are prone to confounding. We will add to the evidence base
27 about the possible adverse and beneficial effects of prescribing different smoking cessation
28 medications using three statistical approaches to overcome confounding: multivariable
29 adjusted regression, propensity score regression and instrumental variable analysis. Using
30 these three approaches we aim to examine the effects of varenicline versus other smoking
31 cessation pharmacotherapies on smoking cessation, health service use, all-cause and cause-
32 specific mortality, and physical and mental health conditions. Follow-up will end with the
33 earliest of either an "event" or censoring due to the end of registration or death. We will not
34 investigate bupropion because it is rarely prescribed and systematic reviews have found that
35 it is less effective than varenicline for smoking cessation (7).

36 Study Aims:

37
38
39 1. What is the effect of varenicline on smoking abstinence? We will investigate the effects of
40 varenicline on smoking abstinence because existing evidence from randomised controlled
41 trials typically only followed participants for one year, and are not informative about long-
42 term outcomes.

43
44 2. What are the effects of varenicline on NHS service use? We will investigate the effects of
45 varenicline prescriptions on all-cause primary and secondary care utilization because
46 smoking increases morbidity and imposes major costs on the health care services (16).

47
48
49 3. What are the effects of varenicline on all-cause and cause-specific mortality? We will
50 investigate the incidence illnesses in the Clinical Practice Research Database (CPRD) using

1 primary care diagnoses, admission to secondary care using ICD-10 codes, and Office of
2 National Statistics (ONS) mortality records to maximise the number of events detected.

3
4 4. What are the effects of varenicline on common physical and mental health conditions?

5 We will investigate the effects of varenicline on rates of cardiovascular outcomes and
6 respiratory illnesses, as previous research has suggested that patients prescribed varenicline
7 may have different rates of these outcomes (9,10). Second, we will investigate the effects of
8 varenicline on rates of depression and anxiety because there has been some reports that
9 varenicline may reduce the risk of these outcomes (13).

10
11 5. We will also examine differences in smoking cessation medication effectiveness by socio-
12 economic position. A recent systematic review reported that stop-smoking services may be
13 helping to reduce inequalities in smoking prevalence by preferentially targeting smokers of
14 lower socio-economic position (SEP). Data from primary care records (THIN) show that
15 between 2008 and 2010, smokers in more deprived groups were more likely to receive
16 smoking cessation interventions (17).

17 18 19 **Methods and analysis**

20
21 We will conduct a prospective cohort study of all patients prescribed varenicline or nicotine
22 replacement products in the CPRD. Variables will be defined using “Read codes” which are
23 clinical encoding of patient phenomena, for example a patient’s: occupation, demographic
24 information, social circumstances, clinical symptoms and observations, laboratory tests and
25 results, and diagnoses.

26 27 **Inclusion and Exclusion Criteria**

28 We will include patients who were older than 18 and were prescribed medicines in British
29 National Formulary (BNF) category 4.10.2 (Nicotine Dependence) from 1st September 2006,
30 when varenicline was introduced to the UK, to the present. We will use patients prescribed
31 other smoking cessation products (nicotine patches, gum, lozenges, and inhalers) as controls
32 for patients prescribed varenicline. We will include patients whose records were classified as
33 ‘acceptable’ by the CPRD from all ‘up to standard’ GPs at least 18 months prior to date of
34 entry of each cohort (1st March 2005). Up to standard GPs are practices that have submitted
35 data that meets the CPRD quality control thresholds. Patient data are defined as “acceptable”
36 by the CPRD if they meet minimum quality control standards, for example their registration
37 period with their GP is valid.

38
39 We will exclude patients who registered at a GP less than 365 days before the first recorded
40 prescription, to allow for high quality assessment of baseline data and possible confounders.
41 Patients prescribed bupropion in the year before their index prescription of varenicline or
42 nicotine replacement therapy will be excluded from the analysis. In the primary analysis we
43 will exclude patients initially prescribed both nicotine replacement therapies and varenicline
44 together, although in our previous analysis this only occurred for 0.25% of all prescriptions
45 (13).

46 47 **Power calculations**

48 The following power calculations are based on effect sizes and confidence intervals observed
49 in our previously published results, which used data from 110,000 individuals prescribed
50 either varenicline or nicotine replacement therapy (13). Based on the rate of 18,000 new

1 prescriptions per year observed in the CPRD from 2006 to 2011 (13), we estimate that with a
2 further 4 years of follow-up the number of patients prescribed either varenicline or nicotine
3 replacement therapy will have increased by 72,000. Therefore the total expected sample size
4 for analysis will be around 180,000.

5
6 In our previous analysis using CPRD data the age- and sex-adjusted hazard ratio for self-
7 harm/suicide for varenicline vs. nicotine replacement therapy at nine months was 0.73 (95%
8 CI: 0.54 to 0.99); after adjusting for possible confounders this became 0.90 (95% CI: 0.66 to
9 1.22) (13). A 70% increase in sample size would lead to a reduction of the standard error by a
10 factor of 1.3, reducing the breadth of the above confidence interval in the adjusted analysis
11 from 0.56 to 0.43.

12
13 Rare outcomes, such as self-harm and suicide were used in previous analyses; in this project
14 we will have greater power to explore more common outcome measures. For example, in the
15 previous analysis the nine-month age- and sex-adjusted hazard ratio for all-cause mortality
16 nine months after first prescription for varenicline vs. nicotine replacement therapy was 0.43
17 (95% CI: 0.35 to 0.53); after controlling for possible confounders this became 0.49 (95% CI:
18 0.40 to 0.61). A 70% increase in sample size would lead to a reduction of the standard error
19 by a factor of 1.3, reducing the breadth of the above confidence interval in the adjusted
20 analysis from 0.21 to 0.16.

21
22 For the effects of varenicline versus nicotine replacement therapy on all-cause mortality,
23 instrumental variable analysis found a risk difference of 0.7 (95% CI: -3.3 to 4.7) per 1,000
24 patients treated after nine months. We estimate that a 70% increase in sample size would
25 narrow the confidence intervals from 8.0 to 6.2.

26
27 Using data from our previous project, within two years of first prescription, we found 2,517
28 admissions for respiratory disease amongst 1,374 patients; 3,144 admissions for
29 cardiovascular disease amongst 1,022 patients; and 3,277 admissions for depression or
30 anxiety amongst 213 patients. This is more events than we found for suicide and self-harm in
31 our previous study; therefore we believe that there will be enough events for this analysis.

32
33 To investigate differences in health care seeking behaviour of smokers by socioeconomic
34 position we will combine the sample used for the health outcomes described above with a
35 sample of all other patients indicated as a current smoker after the 1st of September 2006.

36 37 **Data collection and linkage**

38 We will use linked Hospital Episodes Statistics (HES) and ONS mortality data to define
39 frequency of GP and hospital attendance, frequency of all-cause and cause-specific
40 hospitalization and all-cause and cause-specific mortality. We will test these hypotheses
41 using data from GP practices linked to external datasets only.

42
43 These are important hard outcomes for our study. We have already established that for certain
44 outcomes, such as cause specific mortality the linked ONS data are more accurate (18).
45 Whilst it is possible to investigate these outcomes using CPRD data from GPs, the data are
46 less precise and consistently recorded (18). Thus analyses using linked data are likely to be
47 more precise. Furthermore, the linked data provide direct evidence about secondary care
48 attendance of patients via the HES data. Again, whilst there are some data about referrals to
49 secondary care in the main tables of the CPRD, the data are not as comprehensive as HES

1 data. Our outcomes of interest occur after September 2006; therefore, we believe that both the
2 linked HES and ONS data will provide sufficient coverage for these outcomes.

3 4 **Data analysis**

5 6 **Exposure measures**

7
8 First time users of the smoking cessation therapies (varenicline or nicotine replacement
9 therapy) will be defined as people who received at least one prescription of the product after
10 the 1st of September 2006 but with no use of a related product during the 12 months before
11 the index date (the first date on which a prescription was issued). Langley and colleagues
12 found the smoking cessation prescription data in the THIN database, which is closely related
13 to the CPRD, to be highly comparable to national dispensing data (19). The prescriptions will
14 be defined by the therapy file in the CPRD, which contains a list of all prescriptions issued to
15 patients by their GP. Each therapy record records the date a prescription was issued, the
16 quantity of drug prescribed and the dose.

17
18 The primary analysis will be limited to the first treatment episode. This is analogous to an
19 intention-to-treat analysis in a RCT (20). This ensures that the target parameter estimated in
20 the observational study will be comparable to the parameter estimated by a RCT. For
21 example, if patients' treatment adherence and duration is related to whether they experience
22 adverse events, then definitions of exposure which are based on treatment adherence may
23 provide unreliable evidence of the causal effect of the prescription on adverse outcomes. This
24 analysis framework was described in Hernán et al. (2008). The intuition is that most
25 randomized trials recruit individuals and then split participants into different treatment arms.
26 This means that comparison groups are implicitly from first treatment. The primary analysis
27 in an RCT typically reports an intention to treat estimate, which is the difference in allocation
28 between arms of the trial based on allocation, rather than the treatment the participant
29 received. To obtain results that are comparable to a randomized trial Hernán argued that
30 analysts need to construct cohorts that also follow up patients from first treatment, rather
31 using retrospectively defined exposures (e.g. retrospectively defining exposure as ever
32 exposed to varenicline).

33
34 To mimic an intention-to-treat analysis in an RCT, in our primary analysis patients who are
35 initially prescribed nicotine replacement therapy, but later switch to varenicline, will be
36 allocated to nicotine replacement therapy and vice-versa. We will use an intention-to-treat
37 design for two reasons. First, whilst there are theoretical statistical models for estimating the
38 effects of treatment switching such as marginal structural models, these methods require the
39 strong assumption that there are no unmeasured confounders and typically require detailed
40 data on time-varying confounders, which are unlikely to be available in the CPRD. Second,
41 to our knowledge there are no instrumental variable methods to estimate the effects of
42 switching treatment. However, we will investigate the number of participants who switch
43 treatment as a sensitivity analysis.

44 45 **Outcome measures**

46 47 **Outcome 1: Smoking abstinence**

48 In the CPRD smoking status is indicated by whether the patient is a current, former or never
49 smoker. As GPs are paid to record smoking status smoking behaviour is robustly recorded in

1 the CPRD (21). Marston and colleagues found that 84% of patients had smoking status
2 recorded within a year of registering at a GP, and that smoking prevalence rates by age were
3 similar in CPRD and the Health Survey of England (21). Booth and colleagues found that the
4 difference in prevalence of smoking estimate between the CPRD and the Health Survey for
5 England was less than 1%, and the mean difference was 0.1% (95% CI: -1.5% to 1.7%) (22).
6 Using unpublished data from CPRD sampled as part of the research reported in Thomas et al.
7 (2013) we found that 74% of patients prescribed smoking cessation medication had a
8 subsequent record indicating smoking status (13). Of these 66% were indicated as current
9 smokers and 33% as ex-smokers. We will initially define a patient as relapsed if they have
10 any record indicating that the patient is a current smoker after their first prescription of a
11 smoking cessation therapy. We will not be able to determine the smoking status of patients
12 who do not return to the GP. Therefore, we will perform sensitivity analyses to examine
13 whether the assumptions made about the smoking status of individuals who are not observed
14 affect the results. For example, we will conduct a sensitivity analysis to see if the results are
15 altered by assuming that patients with missing data have relapsed, or by assuming that
16 patients with missing outcome data have achieved abstinence.

18 **Outcome 2: Frequency of GP and hospital attendance**

19 We will define service use as the number of visits to GP and hospitals in the 3, 6, 9, 12, 24
20 and 48 months after first prescription. We will define GP appointments using the clinical data
21 file of the CPRD. This includes all the diagnoses and symptoms that GPs record about all of
22 their patients. As with the other outcomes, the vast majority of diagnoses and symptoms
23 include the date on which the data were added to the database. We will use these dates to
24 calculate the number of times each patient attends primary care. We will define the hospital
25 visits outcome using the linked HES data. We will investigate all-cause hospitalisation and
26 three specific causes of hospitalisation: 1) diseases of respiratory system (ICD-10=J00-J99),
27 2) cardiovascular disease (ICD-10=I00-I52) and 3) anxiety and depression (ICD-10=F31.3,
28 F31.4, F31.5, F32, F40-F48). Causes of hospitalisation are available for approximately half of
29 the sample. Again these data contain the date on which the event occurred, which we will use
30 to define attendance to secondary care within 3, 6, 9, 12, 24 and 48 months after first
31 prescription.

33 **Outcome 3: All-cause and cause-specific mortality**

34 We will define all-cause and cause-specific mortality using the linked ONS mortality dataset.
35 These include the date of death and cause of death using ICD-9 codes. We will investigate
36 three specific causes of mortality: 1) diseases of respiratory system (ICD-10=J00-J99), 2)
37 cardiovascular disease (ICD-10=I00-I52), and 3) anxiety and depression (ICD-10=F31.3,
38 F31.4, F31.5, F32, F40-F48). We will use validated code lists for each outcome.

40 **Outcome 4: Incident respiratory illness, myocardial infarction, depression or anxiety**

41 We will define the adverse event outcomes using the diagnosis records from the Clinical and
42 Referral files in the CPRD. These files record all the diagnoses that the GPs input into their
43 computer system. Each record in the table is given a diagnosis code based on the Read code
44 categorisation. We will use validated Read code lists, for the three adverse event outcomes,
45 respiratory illnesses, myocardial infarction or depression and anxiety, please see the cited
46 papers for Read code lists (23–25). For eligible patients we will extract all records from the
47 Clinical and Referral Tables that indicate the patient either received a specific diagnosis or
48 were referred for a specific diagnosis. As with the therapy records for prescriptions described
49 above, each Clinical and Referral Record indicates the date the information was inputted into

1 the system. We will use this date to define the date that the diagnosis was made. We will
2 define a set of outcomes within 3, 6, 9, 12, 24 and 48 months after first prescription.

3 4 **Confounding factors**

5
6 We will include gender, age in years at time of first prescription, previous psychiatric
7 illness/consultation, previous use of psychotropic medications such as hypnotics,
8 antipsychotics and antidepressants, previous self-harm, measures of alcohol consumption
9 where appropriate mean/median number of GP visits per year, body mass index,
10 socioeconomic position (deprivation score for area or residence) and major chronic illness
11 (including: diabetes, cancer, arthritis) using the Charlson index (26,27). Relevant Read codes
12 will be identified either by validated code lists or by searching for each of these events in the
13 Read code dictionaries to identify any missing Read codes. Collider bias is a potential threat
14 to the analysis; this type of bias occurs when the association between two variables changes
15 upon conditioning of a third variable if the third variable is affected by the first two variables.
16 Collider bias could occur if we conditioned on events that happened as a result of the
17 prescription the patient was issued. To prevent this bias from affecting our results, we will
18 define each covariate using data inputted prior to the first prescription (28). If there are
19 missing data in the covariates we will consider using multiple imputation.

20 21 **Follow-up**

22
23 Follow-up will end with the earliest of either an “event” or censoring due to the end of
24 registration or death.

25 26 **Statistical Analysis**

27
28 For investigating the effects of varenicline use on each outcome (long-term smoking
29 cessation, frequency of GP and hospital attendance, all-cause and cause-specific mortality,
30 primary care diagnosis of respiratory illness, myocardial infarction, depression or anxiety),
31 we will report a conventional multivariable-adjusted Cox regression, propensity score
32 regression and instrumental variable analysis.

33 34 **Analysis 1: Conventional Cox regression**

35 In our first analysis, a conventional observational analysis, we will estimate hazard ratios of
36 the outcomes using Cox-proportional hazards models and the actual prescriptions issued to
37 the patients (29). Each patient’s date of entry into the cohort will be the date they were first
38 prescribed a smoking cessation therapy. The date of exit for each outcome will be the date on
39 which they first have an event, or are censored due to end of follow-up or death or leaving the
40 practice. We will report these associations adjusted for basic confounders (age and gender),
41 and results adjusted for all measured covariates described above.

42 43 **Analysis 2: Propensity score regression**

44 In our second analysis we will construct a sample of patients balanced on covariates and risk
45 factors using a propensity score (30–33). We will construct propensity scores using a logistic
46 regression of the actual treatment received on the covariates described above. Therefore, each
47 participant’s propensity score will be their conditional probability (odds) of receiving
48 varenicline versus nicotine replacement therapy. We will match each patient receiving
49 varenicline to another patient receiving nicotine replacement therapy with the closest

propensity score on a ratio of 1:1 using a nearest neighbour algorithm with no replacement, and matching will be restricted to the common support region. Patients outside the common support region are those prescribed varenicline with propensity scores higher than any patient prescribed nicotine replacement therapy and vice versa. We will estimate hazard ratios of the outcomes using the propensity score matched sample using Cox regressions using the same entry and exit information as the conventional Cox regression analysis described above.

Analysis 3: Instrumental variable analysis

In our third analysis, we will estimate the effects of smoking cessation therapies on the outcomes using physicians' prescribing preferences as instruments for the prescriptions the GPs issue to their patients. We cannot directly measure the physicians' preferences; therefore, we will use the prescriptions they issued to their previous patients as a proxy for their preferences. For example, if the instrument was based on just one previous prescription, physicians who previously prescribed varenicline would be categorised as a varenicline prescriber. As with our previous studies we will use seven prior prescriptions to improve the strength of the instruments (13,34,35). Using multiple prior prescriptions will maximise power. We will report risk differences in the outcomes using additive structural mean models estimated via the generalised method of moments (36–38).

We will categorise each of the adverse event outcomes as occurring within 3, 6, 9, 12, 24 and 48 months of first prescription. We will do this because methods for conducting survival analysis using instrumental variables are not well developed. We will use Stata 13.1 SE to generate all results. The instrumental variable analysis will be conducted using the `ivreg2` command and `psmatch2` will be used to construct the propensity score (31,39,40). All standard errors will be estimated using cluster robust standard errors, which account for clustering of patients within practices.

Socio-economic variation in effectiveness of smoking cessation treatments

This project will use the entire sample of patients indicated as a smoker at any point after 1st September 2006. We will assign a measure of area level deprivation to each patient using their home address postcode and to each GP using the GP postcode. Deprivation levels will be based on the Indices of Multiple Deprivation (IMD), which are available from the ONS and are updated every two years. We will use the most recent IMD statistics preceding the date of entry into the study for each patient. Although area level deprivation statistics will only be a proxy for individual level deprivation, these demonstrate the expected associations with smoking prevalence (41). We will investigate whether the proportion of smokers who attend their GP for smoking cessation treatment differs by IMD, and whether there are any differences in prescribing of varenicline versus nicotine replacement products between areas of high and low deprivation.

By using both individual and GP level IMD codes, we will investigate whether the effects of smoking cessation therapies differ by IMD at both the level of GPs and at the individual level. We will investigate treatment compliance by reporting the total number of prescriptions issued after the initial prescription. We will estimate the effects of smoking cessation therapies within sub-groups defined by IMD level both at the individual and GP level using the three methods described above, multivariable-adjusted Cox regression, propensity score regression and instrumental variable analysis (29,32,42). The cohort of patients will be defined as described above. We will report these associations adjusted for basic confounders

1 (age and gender), and results adjusted for all measured covariates described above. Analyses
2 will account for clustering of patients by GPs.

4 **Ethics approval, peer review, data curation and dissemination**

5
6 Access to the CPRD data is governed by its Independent Scientific Advisory Committee
7 (ISAC). The empirical research described in this proposal significantly expands on our
8 existing work. We have received approval for this project protocol from ISAC (protocol
9 number 15_107). We will comply with all requirements of ISAC requirements for
10 publications based on CPRD data, for example including the ISAC study protocol as an
11 appendix to published papers. This protocol has been peer reviewed separately as part of the
12 NIHR Health Technology Assessment board's efficient study designs call (proposal ID
13 14/49/94) and the ISAC expert advisory board. The data produced as part of this study will be
14 made available via a system of managed open access – interested researchers who obtain
15 necessary approvals from ISAC will be permitted access to the data generated during this
16 study.

17
18 Key findings will be collated to form evidence-based recommendations which will be
19 communicated to the FDA and the Medicines and Healthcare Products Regulatory Agency
20 (MHRA), with the aim of improving the evidence base to inform advice to prescribers and
21 patients. We will also aim to publish findings in peer-reviewed journals and present our work
22 at national and international conferences.

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39 this paper.

41 **Data sharing:**

42 Additional data is available by emailing the corresponding author.

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