ISAC APPLICATION FORM

PROTOCOLS FOR RESEARCH USING THE CLINICAL PRACTICE RESEARCH DATALINK (CPRD)

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| ISAC use only:  Protocol Number  Date submitted | .............................  ............................. | **IMPORTANT**  **If you have any queries, please contact ISAC Secretariat:** ISAC[@cprd.com](mailto:Annalisa.Rubino@gprd.com) |

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| **Section A: The study** |
| 1. **Study Title**   Investigating the effects of commonly prescribed drugs on the prevention and treatment of Alzheimer’s and other neurodegenerative diseases: are there drugs already available that can be repurposed? |
| 1. **Has any part of this research proposal or a related proposal been previously submitted to ISAC?**   Yes No  *If Yes, please provide previous protocol numbers*: 08\_101 and 08\_101A |
| 1. **Has this protocol been peer reviewed by another Committee? (e.g. grant award or ethics committee)**   Yes No  *If Yes, please state the name of the reviewing Committee(s) and provide an outline of the review process and outcome:* |
| 1. **Type of Study** (please tick all the relevant boxes which apply)   Adverse Drug Reaction/Drug Safety Drug Utilisation  Disease Epidemiology  Drug Effectiveness  Pharmacoeconomics  Methodological  Health/Public Health Services Research  Post-authorisation Safety  **Other\***  \*Please specify the type of study in the lay summary |
| 1. **This study is intended for** (please tick all the relevant boxes which apply)**:**   Publication in peer reviewed journals  Presentation at scientific conference  Presentation at company/institutional meetings  Regulatory purposes  Other: PhD qualification |
| **Section B: The Investigators** |
| 1. **Chief Investigator** (full name, job title, organisation name & e-mail address for correspondence- see guidance notes for eligibility)   Professor Patrick Kehoe, Gestetner Professor of Translational Dementia Research, University of Bristol, Patrick.Kehoe@bristol.ac.uk  CV has been previously submitted to ISAC  **CV number:** 388\_15  A new CV is being submitted with this protocol  An updated CV is being submitted with this protocol |
| 1. **Affiliation** (full address)   Dementia Research Group, School of Clinical Sciences, University of Bristol, Level 1, Learning & Research, Southmead Hospital, Bristol, BS10 5NB  Tel: [0117 4147821](tel:0117%204147821) |
| 1. **Corresponding Applicant**     Same as chief investigator  CV has been previously submitted to ISAC  **CV number:** 388\_15  A new CV is being submitted with this protocol  An updated CV is being submitted with this protocol |

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| 1. **List of all investigators/collaborators** (*please list the full names, affiliations and e-mail addresses\* of all collaborators*, *other than the Chief Investigator*)   Other investigator: Professor Richard Martin, School of Social and Community Medicine, University of Bristol, [Richard.Martin@bristol.ac.uk](mailto:Richard.Martin@bristol.ac.uk)  CV has been previously submitted to ISAC  **CV number:**  A new CV is being submitted with this protocol  An updated CV is being submitted with this protocol  Other investigator: Dr Neil Davies, School of Social and Community Medicine, University of Bristol, Neil.Davies@bristol.ac.uk  CV has been previously submitted to ISAC  **CV number:**  A new CV is being submitted with this protocol  An updated CV is being submitted with this protocol  Other investigator: Venexia Walker, School of Social and Community Medicine, University of Bristol, Venexia.Walker@bristol.ac.uk  CV has been previously submitted to ISAC  **CV number:** 389\_15  A new CV is being submitted with this protocol  An updated CV is being submitted with this protocol  [Please add more investigators as necessary]*\*Please note that your ISAC application form and protocol* ***must*** *be copied to all e-mail addresses listed above at the time of submission of your application to the ISAC mailbox. Failure to do so will result in delays in the processing of your application.* | | |
| 1. **Conflict of interest statement**\* (please provide a draft of the conflict (or competing) of interest (COI) statement that you intend to include in any publication which might result from this work)   All of the authors confirm they have no interests, commercial or otherwise, that would conflict with the motivations or data generated for this study.  *\*Please refer to the International Committee of Medical Journal Editors (ICMJE) for guidance on what constitutes a COI* | | |
| 1. **Experience/expertise available** (please complete the following questions to indicate the experience/expertise available within the team of investigators/collaborators actively involved in the proposed research, including the analysis of data and interpretation of results   **Previous GPRD/CPRD Studies** **Publications using GPRD/CPRD data**  None  1-3  > 3 | | |
|  | **Yes** | **No** |
| **Is statistical expertise available within the research team?**  *If yes, please indicate the name(s) of the relevant investigator(s)*  Professor Richard Martin and Dr Neil Davies. |  |  |
| **Is experience of handling large data sets (>1 million records) available within the research team?**  *If yes, please indicate the name(s) of the relevant investigator(s)*  Professor Richard Martin and Dr Neil Davies |  |  |
| **Is experience of practising in UK primary care available within the research team?**  *If yes, please indicate the name(s) of the relevant investigator(s)*  Professor Richard Martin |  |  |

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| 1. **References relating to your study**   Please list up to 3 references (most relevant) relating to your proposed study:  Davies NM, Kehoe PG, Ben-Shlomo Y, Martin RM. Associations of anti-hypertensive treatments with Alzheimer’s disease, vascular dementia, and other dementias. J Alzheimers Dis. 2011 Jan 1;26(4):699–708.  Kehoe PG, Davies NM, Martin RM, Ben-Shlomo Y. Associations of Angiotensin Targeting Antihypertensive Drugs with Mortality and Hospitalization in Primary Care Patients with Dementia. J Alzheimers Dis. 2013;33(4):999–1008.  Corbett A, Pickett J, Burns A, Corcoran J, Dunnett SB, Edison P, et al. Drug repositioning for Alzheimer’s disease. Nature Reviews Drug Discovery. 2012 Nov 5;11(11):833–46. |
| **Section C: Access to the data** |
| 1. **Financial Sponsor of study**   Pharmaceutical Industry  *Please specify:*      Academia  *Please specify:* University of Bristol  Government / NHS  *Please specify:*      Charity *Please specify:* Perros Trust (A University of Bristol Campaigns and Alumni donor)  Other  *Please specify:*      None |
| 1. **Type of Institution carrying out the analyses**   Pharmaceutical Industry *Please specify:*      Academia *Please specify:* University of Bristol  Government Department *Please specify:*      Research Service Provider *Please specify:*  NHS *Please specify:*      Other  *Please specify:* |
| 1. **Data source**   The sponsor has direct access to CPRD GOLD and will extract the relevant data\*    A data set will be supplied by CPRD\*\*  CPRD has been commissioned to extract the relevant data and to perform the analyses  Other *Please specify:*    \*If data sources other than CPRD GOLD are required, these will be supplied by CPRD. The School of Social and Community Medicine is currently finalising a contract for CPRD GOLD access.  \*\* Please note that datasets provided by CPRD are limited in size. Applicants should contact CPRD ([KC@CPRD.com](mailto:KC@CPRD.com)) if a dataset of >300,000 patients is required. |
| 1. **Primary care data** (please specify which primary care data set(s) are required)   Vision only (Default for CPRD studies)  EMIS® only\*  Both Vision and EMIS®\*  *Note: Vision and EMIS are different clinical systems, Vision data has traditionally been used for CPRD, EMIS is currently undergoing beta-testing.*  *\*Investigators requiring the use of EMIS data must discuss the study with a member of CPRD staff before submitting an ISAC application*  Please list below the name of the person/s at the CPRD with whom you have discussed your request for EMIS data: |

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| **Section D: Data linkage** |
| 1. **Does this protocol also seek access to data held under the CPRD Data Linkage Scheme?**   Yes\*  No  If No, please move to section E.  *\*Investigators requiring linked data must discuss the study with a member of CPRD staff. It is important to be aware that linked data are not available for all patients in CPRD GOLD, the coverage periods for each data source may differ and charges may be applied. Please contact the CPRD Research Team on +44 (20) 3080 6383 or email* [*kc@cprd.com*](mailto:kc@cprd.com) *to discuss your requirements before submitting your application.*  Please list below the name of the person/s at the CPRD with whom you have discussed your request:  Daniel Dedman  *Please note that as part of the ISAC review of linkages, the protocol may be shared - in confidence - with a representative of the requested linked data set(s) and summary details may be shared - in confidence - with the Confidentiality Advisory Group of the Health Research Authority.* |
| 1. **Please select the source(s) of linked data being requested:**   ONS Mortality Data  NCDR Cancer Registry Data\*  Inpatient Hospital Episode Statistics  MINAP  Outpatient Hospital Episode Statistics  Mother Baby Link    Index of Multiple Deprivation  Townsend Score  Other\*\* *Please specify:*  *\*Please note that applicants seeking access to cancer registry data must provide consent for publication of their study title and study institution on the UK Cancer Registry website. They must also complete a* ***Cancer Dataset Agreement Form*** *(available from CPRD) and provide a* ***System level Security Policy*** *for each organisation involved in the study.*  *\*\* If “Other” is specified, please name an individual in CPRD that this linage has been discussed with.* |
| 1. **Total number of linked datasets requested including CPRD GOLD**:   4 |
| 1. **Is linkage to a local dataset with <1 million patients being requested?**   Yes\*  No  *\* If yes, please provide further details:* |
| 1. **If you have requested linked data sets, please indicate whether the Chief Investigator or any of the collaborators listed in response to question 5 above, have access to any of the linked datasets in a patient identifiable form, or associated with a patient index.**   Yes\*  No  *\* If yes, please provide further details:* |
| 1. **Does this study involve linking to patient *identifiable* data from other sources?**   Yes  No |

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| **Section E: Validation/verification** |
| 1. **Does this protocol describe a purely observational study using CPRD data (this may include the review of anonymised free text)?**   Yes\*  No\*\*  *\* Yes: If you will be using data obtained from the CPRD Group, this study does not require separate ethics approval from an NHS Research Ethics Committee.*  *\*\* No: You may need to seek separate ethics approval from an NHS Research Ethics Committee for this study. The ISAC will provide advice on whether this may be needed.* |
| 1. **Does this study require anonymised free text?**   Yes\*  No  *\*Please note that work involving free text can only be performed on the July 2013 CPRD GOLD database build or earlier versions. CPRD can provide further advice on the use of anonymised free text.* |
| 1. **Does this protocol involve requesting any additional information from GPs?**   Yes\*  No  \* *Please indicate what will be required:*  Completion of questionnaires by the GP*ψ* Yes  No  Provision of anonymised records (e.g. hospital discharge summaries) Yes  No  Other (please describe)  *ψ Any questionnaire for completion by GPs or other health care professional must be approved by ISAC before circulation for completion.* |
| 1. **Does this study require contact with patients in order for them to complete a questionnaire?**   Yes\*  No  *\*Please note that any questionnaire for completion by patients must be approved by ISAC before circulation for completion.* |
| 1. **Does this study require contact with patients in order to collect a sample?**   Yes\*  No  *\* Please state what will be collected:* |
| **Section F: Signatures** |
| 1. **Signature from the Chief Investigator**   I confirm that the above information is to the best of my knowledge accurate, and I have read and understood the guidance to applicants.  Name: Professor Patrick Kehoe Date: 10/12/15 E. signature (type name):Pat Kehoe |

**Protocol Information**

In order to help ensure that protocols submitted for review contain adequate information for protocol evaluation, ISAC have produced guidance on the content of protocols for research using CPRD data. This guidance is available on the CPRD website ([www.cprd.com/ISAC](http://www.cprd.com/ISAC)). All protocols using CPRD data which are submitted for review by ISAC must contain information on all the areas detailed below. If a specific area required by ISAC is not applicable to your protocol, please provide the justification underneath the relevant heading.

The protocol section (next page) has pre-defined headings and the protocol must be written using these headings. Additional headings are not acceptable; however, supplementary information may be placed in one or more of the appendices providing this information is essential and an appropriate reference to it is made within the protocol. Unless very short, codes lists should be placed in an Appendix. Applications will be regarded as invalid and returned to the applicant if any of the headings below are missing or if additional sections are included.

Please note that ISAC will not consider any application where the protocol exceeds 12 pages (excluding sections A-F of the application form and annexes). Annexes should be kept to a minimum and contain only vital information that could not be provided in the main protocol section. A font-size of at least 12 should be used. Protocols not exceeding 15 pages would be acceptable if ISAC has required a resubmission where additional information is requested.

Please note, your protocol will not be reviewed by ISAC if it falls short of the above requirements. You are advised to speak to the Secretariat if you have any queries.

Voluntary registration of ISAC approved studies:

Epidemiological studies are increasingly being included in registries of research around the world, including those primarily set up for clinical trials. To increase awareness amongst researchers of ongoing research, ISAC encourages voluntary registration of epidemiological research conducted using MHRA databases. This will not replace information on ISAC approved protocols that may be published on the CPRD website. It is for the applicant to determine the most appropriate registry for their study. Please inform the ISAC secretariat that you have registered a protocol and provide the location.

**Protocol Section**

The following headings **must** be used to form the basis of the protocol. Pages should be numbered. All abbreviations must be defined on first use.

1. **Lay Summary (Max. 200 words)**

Please provide a succinct overview of your proposed research in plain English i.e. non-technical language. This should cover the background, purpose of the study and the potential importance of the findings. References and abbreviations should be avoided. If you have ticked the "other" box in response to question 4 on the application form, up to an additional 100 words should be used to describe the benefit to public health expected from the study.

1. **Technical Summary (Max. 200 words)**

Please provide a succinct overview of the objectives, methods and data analysis for the proposed research. Avoid the use of references in this section.

1. **Objectives, Specific Aims and Rationale**

Please include:

(i) The broad research objectives

(ii) The specific aims; any hypotheses to be tested should be stated here.

(iii) An explanation of how achievement of the specific aims will further the research objectives

1. **Background**

Please provide a succinct review of the relevant background literature with references so as to explain the purpose of the study. Please ensure that you refer to any previous research in CPRD that is related, providing published references and, when known, the ISAC Protocol Number

1. **Study Type**

Specify whether the study will be primarily descriptive, exploratory, hypothesis testing or a methodological piece of research.

1. **Study Design**

Describe the overall research design (for example, case-control, cohort) and reasons for choosing the proposed study design.

1. **Sample Size**

Please provide an estimate of sample size, and, where possible, a formal power calculation. An estimate of the expected number of patients available in the CPRD database should normally be included.

1. **Data Linkage Required (if applicable)**

Please provide a synopsis of the purpose(s) for which the each of the linkages requested in section 18 of the application form is required.

1. **Study Population**

Define the source and study population, in terms of persons, place, time period, and listing the criteria which will be used to select the study population from the CPRD, i.e any inclusion or exclusion criteria. Please make clear any restrictions imposed by the use of linked datasets.

1. **Selection of comparison group(s) or controls**

Describe the criteria for eligibility and the procedure for control selection.

1. **Exposures, Outcomes and Covariates**

For exposures and outcomes operational definitions (or procedures for developing them) must be provided, supported by preliminary code lists placed in an Annex. A comprehensive list of covariates should also be provided for any study which is not purely descriptive.

1. **Data/ Statistical analysis**

This section should cover both the analytic methods and also the analyses which are to be performed to meet all the specific aims listed earlier. It is important to ensure that this section is clear and specific about any comparisons which will be made.

1. **Plan for addressing confounding**

Purely descriptive studies are exempt from this requirement. All other studies should here provide some discussion of what they are doing in the design and/or analysis to control for confounding.

1. **Plan for addressing missing data**

The potential for missing data should be identified and how it will be addressed discussed here.

1. **Limitations of the study design, data sources and analytical methods**

The general limitations of the databases and observational research are well-known. Specific consideration of the potential impact of such limitations should be provided in the context of the proposed study.

1. **Patient or user group involvement (if applicable)**

Please indicate whether you have or intend to involve patient groups in your study. Such involvement is encouraged by ISAC and required for studies which directly involve patients.

1. **Plans for disseminating and communicating study results, including the presence or absence of any restrictions on the extent and timing of publication**

ISAC expects most studies that it approves to be published in the scientific literature and considers it an ethical obligation for any study with potential public health implications. In cases where multiple publications are likely to arise, a publication plan should be provided in this section.

1. **References**

Please provide a numbered list of references at the end of the protocol.

**Appendices**

Appendices should be used for essential supporting information only (e.g. code-lists) and they must be cited within the body of the protocol.

Investigating the effects of commonly prescribed drugs on the prevention and treatment of Alzheimer’s and other neurodegenerative diseases: are there drugs already available that can be repurposed?

Investigators

Venexia Walker, Patrick Kehoe, Neil Davies and Richard Martin.

1. Lay summary

Alzheimer’s disease is a progressive disease affecting brain function and independent living, and eventually requires full-time care. There are only a few treatments that temporarily help symptoms such as memory loss; however, these eventually become ineffective as the underlying disease progresses unabated. Part of the difficulty of treating Alzheimer’s disease is that it involves the activation of many destructive processes in the brain, each of which needs treatment simultaneously if the progression of the disease is to be halted. We hope to investigate the possibility of using a more time- and cost-effective method to reposition new drugs for the prevention or treatment of the disease. Drug development can take over 20 years and cost up to £1billion per eventually licensed drug. We wish to investigate the potential of using a number of existing drugs, already prescribed for other conditions that may offer protection to the brain, as a cheaper and more rapid method of identifying new drugs. To explore this we will test whether these treatments protect against or increase the risk of other neurodegenerative diseases, and to what extent this effect is further enhanced when existing dementia therapies are co-administered. This could then help to prioritise groups of drugs that may be beneficial in the treatment of a number of neurological conditions and therefore accelerate the formal testing of recognised safe and cost-effective drugs as new potential approaches for preventing or treating Alzheimer’s and other neurodegenerative diseases.

1. Technical summary

There is urgent need for new evidence about medications that could influence the incidence and progression of neurodegenerative diseases. One promising approach is to investigate drug repositioning1, which offers a time- and cost-effective alternative to traditional drug development. A recent consensus study of dementia experts identified a short-list of individual and classes of prescribed drugs that may be repurposed as novel treatments for dementia.2 The short-list included compounds used to treat hypertension, hypercholesterolemia and type 2 diabetes, all of which could be classed as having ‘cerebroprotective’ properties and have variable levels of pre-clinical evidence that suggest they may have beneficial effects for various aspects of dementia pathology. However as yet there is limited pharmacoepidemiological data to support their effects in human populations.

Our primary aim, therefore, is to investigate whether these existing medications, previously identified as potentially cerebroprotective, could be repurposed to prevent or treat Alzheimer’s disease and other types of dementia, amyotrophic lateral sclerosis and Parkinson’s disease. We will conduct an observational cohort study to investigate the relationship of these medications with incidence and post-diagnosis survival of patients and at the same time identify to what extent any observed associations are altered when existing dementia therapies are co-administered. Collectively these findings will allow the prioritisation of drugs to be tested as repurposed treatments in clinical trials of these conditions in the future.

1. Objectives, specific aims and rationale
   1. Research objectives

The objective of our research is to investigate drug effects on the prevention and treatment of Alzheimer’s disease and the neurodegenerative diseases Parkinson’s disease and amyotrophic lateral sclerosis. This will be done by considering the following specific aims.

* 1. Specific aims

1. To investigate whether commonly prescribed medications, previously identified as potentially cerebroprotective, are associated with the incidence of neurodegenerative disease.
2. To investigate whether commonly prescribed medications, previously identified as potentially cerebroprotective, are associated with the post-diagnosis survival of people with neurodegenerative disease.
3. To investigate the additional effects of commonly prescribed medications, previously identified as potentially cerebroprotective, when co-administered with drugs for dementia in relation to post diagnosis survival of patients with dementia, and test whether there is evidence of: a) dose and duration responses; and b) interaction with the drugs described in aims 1 and 2.
4. To investigate whether the withdrawal of support for the prescription of cholinesterase inhibitors is associated with a reduced rate of prescription of these drugs and, if so, a change in the survival or service use of patients with Alzheimer’s disease and to inform potential use in other neurodegenerative conditions with dementia.

Our investigations will focus on the following commonly prescribed medications:

1. Treatments for hypertension
2. Treatments for hypercholesterolemia
3. Treatments for type 2 diabetes

Along with the following neurodegenerative diseases:

1. Alzheimer’s disease
2. Other dementia
3. Amyotrophic lateral sclerosis
4. Parkinson’s disease
   1. Rationale

In aims 1 and 2 we will identify whether specific drugs identified as potentially cerebroprotective may, in addition to improving the condition they are intended for, also be associated with changes to the incidence and survival in dementia and other neurodegenerative diseases. If we find robust evidence of differences in incidence or survival between patients prescribed different medications then this would provide evidence to support the potential of these drugs towards repurposing that would need to be formally tested by clinical trials of patients at risk of, or with these conditions. Drug repurposing (also referred to as drug repositioning) has been the basis of successful therapies in many clinical areas including cancer, stress incontinence, irritable bowel syndrome, obesity, smoking cessation, psychosis and attention deficit disorder.1,3

Aims 3 and 4 will explore the level of interaction when the proposed cerebroprotective drugs are co-administered with dementia medications. This may identify additive interaction effects with respect to rates of survival of patients in general practice4–6. We are conscious that the analysis of interaction may be limited by the temporary withdrawal of support by NICE for the prescription of cholinesterase inhibitors, resulting from a perceived lack of cost-effectiveness in dementia. The true extent to which the withdrawal of support affected prescription rates for these drugs remains unknown, however new data will naturally emerge as a result of this analysis. This could provide important secondary insights into the potential impact of this temporary change on rates of prescription, survival and service use.7

1. Background

Epidemiological evidence links cardio-metabolic diseases, including hypertension, hypercholesterolemia, cardio-thrombosis and diabetes to the aetiology of Alzheimer’s disease.8–10 Furthermore, Alzheimer’s disease prognosis is associated with drugs prescribed for mental health problems, cardiovascular diseases and hypertension.11,12

Although the cause of Alzheimer’s disease is still unknown, the level of knowledge of the epidemiology of Alzheimer’s disease contrasts markedly with that of some other less common forms of dementia or neurodegenerative disease. Alzheimer’s disease is the most common form of neurodegenerative disease.13,14 There are no known cures for any form of dementia or neurodegenerative disease. Alzheimer’s disease also has similar neuropathology to other forms of neurodegenerative disease, such as Parkinson’s disease dementia, Lewy body dementia, and amyotrophic lateral sclerosis. There is some evidence that there are common risk factors across different forms of neurodegenerative disease. For instance hypertension appears to be a risk factor for Alzheimer’s disease and vascular dementia but also possibly Parkinson’s disease15–17 and amyotrophic lateral sclerosis.18 Furthermore hypertensive patients prescribed angiotensin converting enzyme inhibitors or angiotensin receptor blockers, have been reported to have a lower risk of Alzheimer’s disease.19–21 The reported evidence-base includes our own previous study using CPRD data (ISAC 08\_101).21 Anti-hypertensive medications have also been implicated in amyotrophic lateral sclerosis22 and Parkinson’s disease.17 Yet there are no associations between hypertension and frontotemporal dementia23 or progressive supranuclear palsy.24 Diabetes is a risk factor for Alzheimer’s disease, frontotemporal dementia23 and Parkinson’s disease,25 whereas diabetes may protect against amyotrophic lateral sclerosis.26

The overlap of different forms of neurodegenerative disease, seemingly dependent on the sharing of various risk factors, would suggest that there may be scope to translate existing or newly identified interventions for testing in neurodegenerative diseases where similarities exist. Indeed there is evidence that various cardio-metabolic diseases such as hypertension, hypercholesterolemia, cardio-thrombosis and diabetes contribute to the pathogenesis of Alzheimer’s disease, while there is also some evidence that effective treatment of these may also have some ‘cerebroprotective’ (protective to the brain and its vasculature) benefit with respect to Alzheimer’s disease. Since Alzheimer’s disease is the most common form of neurodegenerative disease, it can act as the basis by which we can explore the existence of currently available drugs, ordinarily prescribed for other conditions, that may serve to modify the development (e.g. delay or bring forward the onset) and/or progression (e.g. decrease or increase the rate) of Alzheimer’s disease mortality. The potential impact of these could then also be explored in other forms of neurodegenerative disease, to test: (i) the specificity of any observed associations; (ii) whether any candidate drugs have previously unrecognised broader neuroprotective effects; or (iii) identify certain types of drug that may adversely affect other forms of neurodegenerative disease that would themselves represent a modifiable risk factor.

1. and F. Study type and design

We will conduct a hypothesis testing longitudinal observational cohort study of disease incidence and progression, driven by existing literature indicating the potential cerebroprotective benefits of our chosen commonly prescribed medications2,27–30. Our study will employ both conventional regression and more advanced causal analysis methods. For the statistical analysis of disease incidence we will use Cox-regression adjusted for a range of baseline confounders, propensity score matched regression, instrumental variable analysis, and marginal structural models. For survival analysis, we will use Cox-regression models adjusted for a range of baseline confounders and propensity score matched Cox-regression. We will evaluate physicians’ prescribing preferences as potential instrumental variable for the prescriptions issued31,32 and investigate whether marginal structural models can account for time dependent confounding and treatment switching.33

1. Sample Size

The table below (Table 1) details our estimates of the sample size and minimum detectable hazard ratio (alpha=0.05, beta=0.80) for cohorts B and C. The minimum detectable hazard ratio is taken to be the detectable hazard ratio for the smallest exposed group tested against the control group. It is difficult to provide sample size and minimum detectable hazard ratios for cohort A due to its novel design that includes patients who are ‘at risk of’ the condition the treatment is used for. We can however consider the sample size estimates for cohort B to be conservative estimates for cohort A as all patients in cohort B are included in cohort A by definition. Further details concerning the sample size and detectable hazard ratios (alpha=0.05, beta=0.80) for specific comparisons within cohorts B and C can be found in Appendices 6 and 7.

**Table 1: The sample size and minimum detectable hazard ratios for cohorts B and C.**

|  |  |  |  |
| --- | --- | --- | --- |
| **Cohort** | **Start of Follow Up** | **Sample Size** | **Detectable**  **Hazard Ratio** |
| B | Treatment for hypertension | 1,018,519 | 0.9676923 |
| Treatment for hypercholesterolaemia | 808,687 | 0.8436064 |
| Treatment for type 2 diabetes | 200,800 | 0.9432468 |

|  |  |  |  |
| --- | --- | --- | --- |
| C | Dementia | 105,471 | 0.9816402 |
| Parkinson’s disease | 20,686 | 0.9587554 |
| Amyotrophic lateral sclerosis | 2,227 | 0.600025 |

1. Data Linkage Required

Having established that for cause-specific mortality the linked Office of National Statistics (ONS) data are more accurate than CPRD data from general practices,34 we will use the ONS database to identify date and cause of death. We will, therefore, test our hypotheses relating to mortality using data from linked practices only. We will also be investigating differences in service use between individuals prescribed dementia drugs, and those who were not prescribed them. We will define ‘use’ as the number of visits to: i) primary care and ii) secondary care following diagnosis. To define this outcome we will use linked data from the Hospital Episodes Statistics (HES) database - specifically we are interested in the diagnoses and any dates relating to appointments or hospital admissions contained within the database.

1. Study population

**Inclusion criteria:** Men and women older than 40, with at least 12 consecutive months of records classified as ‘acceptable’ by the CPRD from **all** “up to standard” practices.

**Exclusion criteria:** Patients registered at a practice less than 365 days before their 40th birthday, or those with a first record of one of the index drug classes of interest before their 40th birthday. This will ensure high quality assessment of baseline data and possible confounders.

1. Selection of comparison group(s) or controls

We will investigate both the incidence and progression of Alzheimer’s disease, other dementia and other neurodegenerative disease. Our investigations into the incidence will focus on three treatments, which are potentially cerebroprotective, namely: treatments for hypertension29, treatments for hypercholesterolaemia27,30 and treatments for type 2 diabetes28. For each treatment, we will conduct two analyses. The first will compare treated to untreated individuals with similar indications – this is cohort A. The second will compare the outcomes of individuals given different sub-classes of specific medications – this is cohort B. Our investigations into progression will use a third cohort, cohort C. Using this cohort, we will look into the effects of the three possible new treatments in people diagnosed with at least one of the index neurodegenerative diseases of interest. To fully investigate the potential of these treatments, we will include both patients on these drugs at the time of diagnosis and those prescribed these drugs post-diagnosis. Cohort C will also be used to investigate the progression of dementia and service use of individuals prescribed the existing drugs for dementia. For all cohorts, individuals with less than 12 consecutive months of records prior to cohort entry will be excluded. All read code lists can be found in Appendices 1, 2 and 3 and all product code lists can be found in Appendices 4 and 5.

Cohort A

For each treatment, we will create a cohort of patients who are diagnosed with the condition the treatment is used for or ‘at risk of’ that condition. This will be determined by the indications and test results described in Table 2. We will split each cohort into ‘exposed’ and ‘unexposed’ groups. The ‘exposed’ group will consist of patients who received a treatment of interest within 6 months of initial diagnosis of the condition. The ‘unexposed’ group will consist of all others in the cohort. Patients will be identified as having received a treatment of interest by product codes (see Appendix 5). Therefore in this analysis we will compare an ‘exposed’ group of individuals who were prescribed the treatment to an ‘unexposed’ group of individuals who received similar test results, but did not receive the treatment, as illustrated in Figure 1. The aim of this approach is to address confounding by indication which could cause bias if the ‘unexposed’ group is drawn from the full population, who are likely to be healthier. We will also explore the effects of more complex treatment patterns using marginal structural models.

Follow-up for cohort A will start either when a patient is indicated as ‘at risk of condition’ or, in the case of no period ‘at risk’, diagnosed with the condition itself. The date from which a patient is considered ‘at risk’ will be determined by the first elevated test result (see Table 2) or read code indicating they are ‘at risk of’ the condition (see Appendix 2). If there is no period ‘at risk’, follow-up will start on the diagnosis date as determined by the first record of a relevant read code (see Appendix 3) or a test result indicating the condition (see Table 2). Follow-up will end with the earliest of a relevant neurodegenerative disease diagnosis or censoring due to the end of registration at a CPRD general practice. The diagnosis date of the neurodegenerative disease will be determined by the first record of a relevant read code (see Appendix 1).

**Table 2: The cohorts of type A, one for each treatment of interest.**

|  |  |
| --- | --- |
| **Treatment** | **Cohort** |
| Treatments for hypertension | Patients ‘at risk of hypertension’ as indicated by a read code (see Appendix 2.1) or blood pressure test result between 120/80 mm/Hg and 140/90 mm/Hg. In the case of no period ‘at risk’, patients with hypertension as indicated by a read code (see Appendix 3.1) or a blood pressure test result in excess of 140/90 mm/Hg. |
| Treatments for hypercholesterolaemia | Patients ‘at risk of hypercholesterolaemia’ as indicated by a read code (see Appendix 2.2) or a test result where total cholesterol level is between 4-5 mmol/L or LDL level is between 2-3 mmol/L. In the case of no period ‘at risk’, patients with hypercholesterolaemia as indicated by a read code (see Appendix 3.2) or a test result where total cholesterol level exceeds 5 mmol/L or LDL level exceeds 3 mmol/L. |
| Treatments for  type 2 diabetes | Patients with impaired glucose tolerance or ‘at risk of diabetes’ as indicated by a read code (see Appendix 2.3) or a test result where blood glucose level is 6-7 mmol/l before the test and 7.9-11mmol/l two hours after the test. In the case of no period ‘at risk’, patients with type 2 diabetes (see Appendix 3.3) or a test result where blood glucose level exceeds 7 mmol/l before the test and 11mmol/l two hours after the test. |

**Figure 1: The cohort construction for cohort type A, designed to eliminate immortal time bias. For those without a period ‘at risk’, cohort entry will occur when they are diagnosed with the condition.**

Exposed

Unexposed

Diagnosis of ‘precondition’

Outcome

Diagnosis of condition

Diagnosis of ‘precondition’

Outcome

Diagnosis of ‘precondition’

Outcome

Diagnosis of condition

First drug use

A patient will enter the cohort for a given treatment when they become ‘at risk of’ the condition the treatment is used for or, in the case of no period ‘at risk’, when they are diagnosed with the condition (see Table 2). We define cohort entry in this way to avoid excluded immortal time bias that can occur when cohort entry is determined by treatment variation over time.35,36 Immortal time is the period during follow-up when the outcome cannot occur. For example, suppose we started following patients from the date of their first prescription. This would make it impossible for patients to have an outcome prior to their first prescription. This means that patients in the ‘exposed’ group all have a period before treatment, when an event could not occur. This period is their immortal time, and it must be correctly attributed to the ‘unexposed’ group i.e. if they have an event prior to the first prescription, they should be allocated to the ‘unexposed’ group. To do this patients in the ‘exposed’ and ‘unexposed’ groups must be followed-up from the same start date. In this study we are following individuals either from first test result, first read code indicating ‘at risk of’ the condition or, in the case of no time spent ‘at risk’, first read code indicating the condition. Therefore, our results will not suffer from immortal time.

Cohort B

In this analysis we will compare different drug sub-classes that exist for a given treatment, as shown in Table 3. We will create a cohort of all patients who were prescribed the medication. We will categorise all the patients by the drug sub-class they initially received, and will compare the outcomes for each of these groups. For each medication, we have defined the most frequently prescribed sub-class as the control (indicated in Table 3). In the primary analysis of this cohort we will exclude patients initially prescribed the control sub-class if they receive another sub-class of the same treatment at the same time, although we anticipate this will be rare. We will explore the outcomes of individuals prescribed multiple sub-classes, other than that specified above, in a sensitivity analysis.

Exposure to multiple sub-classes of the same treatment can introduce immortal time bias if the time between medications is misclassified. We will be using an intention-to-treat analysis so individuals initially prescribed a non-control medication, who later stop that medication or switch to the control medication, will be allocated to the treatment group. Similarly, individuals initially prescribed the control medication will be allocated to the control group, regardless of what happens to them in the future. If we were to use other types of analysis, the time prior to receiving the second medication would become immortal as patients would need to survive long enough to change medications. Other analyses also have the potential for outcome-free follow-up for the first medication to be excluded from rate calculations. By using intention-to-treat, we will avoid this immortal time bias, regardless of treatment switching.

Follow-up for cohort B will start on the date of first eligible prescription (see Appendix 5). Follow-up will end with the earliest of a relevant neurodegenerative disease diagnosis or censoring due to the end of registration at a CPRD general practice. The diagnosis date of the neurodegenerative disease will be determined by the first record of a relevant read code (see Appendix 1).

**Table 3: The drug sub-classes of interest for each treatment group with the control treatments indicated.**

|  |  |
| --- | --- |
| **Treatments for hypertension**   * Beta-adrenoceptor blocking drugs (control) * Angiotensin-converting enzyme inhibitors * Thiazides and related diuretics * Calcium channel blockers * Loop diuretics * Alpha-adrenoceptor blocking drugs * Centrally acting antihypertensive drugs * Angiotensin-II receptor antagonists * Vasodilator antihypertensive drugs * Potassium-sparing diuretics and aldosterone antagonists | **Treatments for hypercholesterolaemia**   * Statins (control) * Fibrates * Bile acid sequestrants * Omega-3 fatty acid compounds * Ezetimibe * Nicotinic acid group |
| **Treatments for type 2 diabetes**   * Biguanides (control) * Sulphonylureas * Other antidiabetic drugs |

Cohort C

For each neurodegenerative disease of interest, we will create a cohort of individuals with a read code indicating this outcome (see Appendix 1). These cohorts will be used to investigate the association of neurodegenerative disease progression with exposure to one of the three treatment groups of interest: treatments for hypertension, treatments for hypercholesterolaemia and treatments for type 2 diabetes. To fully appreciate the potential of these treatments, we will consider both exposure before and after the diagnosis of a neurodegenerative disease. We will also use the cohorts relating to dementia to assess the progression of the disease after exposure to the existing treatments for dementia, as well as the service use of these individuals. We will define ‘service use’ by the number of visits to primary and secondary care following diagnosis. For all of the treatments we consider, each cohort will be split into ‘exposed’ and ‘unexposed’ groups. In the analysis, individuals in the ‘exposed’ group, i.e. those who were prescribed the treatment under investigation, will be compared with individuals in the ‘unexposed’ groups, i.e. those who did not receive the treatment.

Follow-up for cohort C will be the first recorded read code indicating Alzheimer’s disease, other dementia or other neurodegenerative disease (see Appendix 1). Follow-up will end with the earliest of death, as determined by linked Office of National Statistics data, or censoring due to the end of registration at a CPRD general practice.

Summary

We can summarize the three types of cohort we will consider in the following table.

**Table 4: Comparison of the three cohort types.**

|  |  |  |  |
| --- | --- | --- | --- |
|  | **Cohort A** | **Cohort B** | **Cohort C** |
| **Purpose** | To investigate incidence by comparing treated and untreated individuals. | To investigate incidence by comparing the different drug subclasses of each treatment. | To investigate the progression of neurodegenerative disease patients and the service use of dementia patients. |
| **Relevant Aims** | 1 | 1 | 2, 3, 4 |
| **Number of cohorts required** | There will be three cohorts of this type, one for each treatment of interest. | There will be three cohorts of this type, one for each treatment of interest. | There will be three cohorts of this type, one for each of dementia, Parkinson’s disease and amyotrophic lateral sclerosis. |
| **Exposures** | Treatments for hypertension, hypercholesterolaemia and type 2 diabetes. | Treatments for hypertension, hypercholesterolaemia and type 2 diabetes. | Treatments for hypertension, hypercholesterolaemia, type 2 diabetes and dementia. |
| **Start of**  **follow-up** | At risk of the condition the treatment is used for or the condition itself if there is no period at risk. | Prescription of a treatment of interest. | Diagnosis of neurodegenerative disease of interest. |
| **Outcome** | Diagnosis of neurodegenerative disease of interest. | Diagnosis of neurodegenerative disease of interest. | Death. |
| **Exclusion Criteria** | Individuals with less than 12 consecutive months of records prior to cohort entry. | Individuals prescribed both treatment and control medications at the same time or with less than 12 consecutive months of records prior to cohort entry. | Individuals with less than 12 consecutive months of records prior to cohort entry. |
| **Data Linkage** | ONS | ONS | ONS and HES |
| **Statistical Analysis** | Conventional regression, propensity score regression, instrumental variable analysis and marginal structural models. | Conventional regression, propensity score regression, instrumental variable analysis and marginal structural models. | Conventional regression, propensity score regression and marginal structural models. |

1. Exposures, outcomes and covariates

Exposures

For our primary analysis we will define all exposures based on the first prescription observed in the database.37 This is so that the target parameter estimated in the observational study will be comparable to that estimated by a randomised controlled trial (RCT). This, combined with analysing the data using an intention-to-treat (based on first test or recording of a relevant read code) will minimise the risk of immortal time-bias because all time at risk will be correctly allocated to exposed or unexposed patients.36 Immortal time bias cannot occur if all patients are followed up from consistent index date such as a test result.38 First time prescriptions of the medications of interest (treatment and control) will be defined as people who received at least one prescription of the product but who had no use of a related product during the 12 months before the start of follow-up. The prescriptions will be defined by the therapy file in the CPRD, which records the date each prescription was issued, the quantity of drug prescribed and the dosage. Patients initially receiving more than one prescription of a drug of interest will be included in our analysis in a group representing the specific combination of drugs they receive.

Analogous to an intention-to-treat analysis in a RCT, patients initially prescribed a treatment medication (exposed), but later stop that medication or switch to a control drug (unexposed), will be allocated to treatment (i.e. classified as exposed, irrespective of what happens in the future) and vice-versa. We will use an intention to treat analysis in our primary analysis for two reasons. First, whilst there are theoretical statistical models for estimating the effects of treatment switching such as marginal structural models, these methods require the strong assumption that there are no unmeasured confounders. Second, to our knowledge there are no instrumental variable methods for estimating the effects of switching treatment. We will investigate treatment switching using marginal structural models in a secondary analysis.

Outcomes

For incidence, we will identify the neurodegenerative disease outcomes (Alzheimer’s disease, other types of dementia, amyotrophic lateral sclerosis, Parkinson’s disease) using the code lists described in Appendix 1. For progression, we will identify the outcome death using the linked Office of National Statistics data. For the investigations into service use, we will define ‘use’ as the number of visits to: i) primary care and ii) secondary care following diagnosis. Secondary care visits will be identified via linked Hospital Episode Statistics data.

Covariates

We will include the following covariates matching on date of birth, sex, index date, general practice and years of recorded history in the database before the index date, we will control for the following factors: body mass index, smoking status, alcohol consumption, consultation rate, a postcode-based measure of socioeconomic position (a practice postcode-based indicator is available for all CPRD derived using the Index of Multiple Deprivation (IMD); a patient postcode-based indicator has been derived using Townsend scores and is available for patients registered with one of approximately 200 practices (50% of all) in England only), previous history of coronary-artery disease, previous coronary-bypass surgery and cerebrovascular disease including stroke. We will also control for other major chronic illness (including cancer, arthritis) using the Charlson index (for code lists see *25*, *26*). We will control for consultation rate because people who have more chronic conditions such as hypertension, diabetes or renal insufficiency may have higher rates of consultation,which may also increase the opportunity for recording otherdiagnoses such as dementia (‘ascertainment bias’). Consultation rate will be calculated by dividing thetotal number of clinic visits prior to the index date by thelength of each patient's follow-up. 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 41. If there are missing data in the covariates we will consider using multiple imputation.

1. Statistical analysis

We will use the following four statistical approaches to address confounding. We are committed to presenting the findings from all our analyses, irrespective of the direction of findings, and will handle discrepancies between them by assessing the merits of each method in the given situation. This project will involve a large sample of data and has considerable power to detect even relatively small effects. Therefore our statistical power will be more than adequate to test our proposed hypotheses, even under highly conservative Bonferroni corrections. We will account for multiple testing within each paper using permutation analysis where appropriate.

Conventional regression

In our first analyses, a conventional observational analysis, we will estimate the hazard ratios of incidence and survival using Cox-proportional hazards models. Both analyses will use the actual prescriptions issued to the patients.42 We will report these associations adjusted for basic confounders (age and gender), and results adjusted for all measured covariates described above.

Propensity score regression

In our second analysis we will construct a sample of patients balanced on covariates and risk factors using a propensity score.43–46 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 treatment or not (Cohort types A and C), or receiving treatment versus control therapy (Cohort type B). We will match each patient receiving one treatment to another patient receiving the control treatment 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 the treatment therapy with propensity scores higher than any patient prescribed the control treatment and vice versa. We will estimate odds-ratios and hazard ratios of the outcomes using the propensity score matched sample using logistic and Cox-regressions.

Instrumental variable analysis

In our third analysis, we will estimate the effects i) treatment or no treatment, and ii) the specific sub-class of medication prescribed 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 were based on just one previous prescription, physicians who previously prescribed the treatment therapy would be categorised as a “treatment” prescriber otherwise they would be categorised as “control”. As with our previous studies we will use seven prior prescriptions to improve the strength of the instruments.32,47,48 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.49–51 We will categorise each of the adverse event outcomes as occurring within 3, 6, 9, 12, 24 and 48 months of index date. Methods for estimating survival models using instrumental variables are not well developed. Therefore we will explore potential instrumental variable survival models in a secondary analysis.52

Marginal structural models

In our fourth analysis, we will estimate the effects of each treatment using marginal structural models.33 We will use these models to account for time dependent confounding and treatment switching. We will construct inverse probability weights for each treatment based on the patients’ observed characteristics such as: gender, age, comorbidities and concurrent treatments. We will use these models to estimate the odds and hazard ratios of disease incidence and progression.

1. Plan for addressing confounding

We plan to address confounding by using four different statistical approaches in our analysis. Specifically we have identified two key sources of confounding: confounding by indication and time dependent confounding. To address confounding by indication, we will explore the different approaches for modelling it. Through examination of these approaches, we hope to highlight any uncontrolled confounding that may be leading to false conclusions about drug effect. We will also account for confounding by indication in the construction of our cohorts. Consider cohort A, where we compare ‘exposed’ and ‘unexposed’ groups of individuals. Drawing the ‘unexposed’ group from the full population can introduce bias as they are likely to be in better health. We will avoid this by defining cohort entry on the basis of first test or recording of a relevant read code so the ‘exposed’ and ‘unexposed’ groups will have more in common, reducing bias. In addition to this, we will address time dependent confounding in our study. This will be done by using statistical methods that can account for it, such as marginal structural models. By taking these measures to allow for time dependent confounding we hope to reduce concerns about switching between products.

1. Plan for addressing missing data

We will investigate the extent of missing data in our exposures, outcomes and covariates and use multiple imputation to impute missing data where appropriate.53–55

1. Limitations of the study design, data sources and analytical methods

This analysis has the following limitations:

1. This is an observational study – any difference between products could arise because of uncontrolled confounding. We will investigate such effects by comparing the characteristics of those prescribed different products and adjusting for any differences in multivariable models and exploring different approaches for modelling confounding by indication.
2. It is possible that some patients are prescribed different medications within the study period. Furthermore, there may be a hierarchy of treatment, for example if patients being prescribed angiotensin-converting enzyme inhibitors first and only if this fails to control their hypertension they would be moved onto angiotensin-II receptor antagonists. Thus patients prescribed ARBs may represent treatment resistant hypertension, who in turn may be at higher risk of adverse outcomes. We will explore methods to model the effects of time dependent switching between products.
3. Prescribing patterns may have changed following specific drug scares. For example, a drug scare may push GPs towards prescribing alternative therapies for high-risk patients, introducing selection bias.
4. Dementia is a heterogeneous outcome, and codes used to define cases in primary care may not be as accurate as cases in clinical cohorts. However, we do not expect miss-diagnosis to differ by the type of medication prescribed. We will explore sensitivity analyses to see how this may affect our results.
5. It may not be realistic to assume information is missing at random for some of our covariates such as BMI and smoking. We will assess the effect of this assumption on our results via sensitivity analyses.
6. Patient or user group involvement

This study does not directly involve patients, however the topic of identifying new repurposable drug candidates for a number of neurodegenerative diseases is becoming widely supported by patient and user groups from various communities. In the event that we progress any drug candidates identified from this study into a formal clinical trial, as we have direct experience in with the current underway NIHR funded RADAR trial, the case for which was supported by work undertaken under ISAC Protocol 08\_101, then we will, as we did with RADAR consult with relevant representatives in the design of that study.

1. Plans for disseminating and communicating study results

This study will form the core of a funded 3-year PhD project (for Venexia Walker). We will publish the results of the study as open-access peer-reviewed publications. Our results will be disseminated in up to five papers (depending on findings linked papers may be merged into one) as detailed below:

* The association of treatments for cardiovascular disease (hypertension and hypercholesterolaemia) and the incidence of neurodegenerative disease
* The association of treatments for cardiovascular diseases (hypertension and hypercholesterolaemia) and the progression of neurodegenerative disease
* The association of treatments for type 2 diabetes and the incidence of neurodegenerative disease
* The association of treatments for type 2 diabetes and the progression of neurodegenerative disease
* The association of co-administration of the potentially cerebroprotective drugs with dementia drugs and the post-diagnosis survival of patients with dementia

We will disseminate findings through national and international conferences as are appropriate. Depending on the findings we would also explore additional options for focussed dissemination within appropriate communities, e.g. via an Alzheimer’s Society dissemination grant and/or via CLAHRC structures.

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