ZED study protocol

Study name:

Intended and unintended effects of Z-drug use for sleep disturbance in people with dementia – 'Z-drug Evaluation in Dementia' (ZED)

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Contents

Glossary of abbreviations and terms

ADAS-COG	Alzheimer's Disease Assessment Scale – Cognitive
ADL	Activities of daily living
ADCS	The Alzheimer's Disease Cooperative Study
BADL	Bristol Activities of Daily Living
BZD	Benzodiazepine
CAG	Confidentiality Advisory Group
CALM-AD	Trial of a Cholinesterase Inhibitor and Atypical Neuroleptic in the Management of Agitation in Alzheimer's Disease
CDR	Clinical Dementia Rating
CESD	Centre for Epidemiologic Studies Depression scale
CPRD	Clinical Practice Research Datalink
DEMQOL	Dementia Quality of Life measure
DDD	Defined daily doses
DOMINO-AD	Donepezil and memantine in moderate to severe Alzheimer's disease study
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EQ-5D EuroQOL	Quality of life measure
GABA	Quality of life measure
HR	Gamma-aminobutyric acid Hazard ratio
HES	Hospital Episode Statistics
ICD	International Classification of Diseases
IRR	Incidence rate ratio
ISAC	CPRD's Independent Scientific Advisory Committee
Inspire	Organisation supporting patient and public involvement in Research
MAGD	Memantine for Agitation in Dementia study
MMSE	Mini-mental state examination
NACC	National Alzheimer's Coordinating Centre
NPI	Neuropsychiatric Inventory
NNH	Number needed to harm
ONS	Office for National Statistics

PwD	People with dementia
PPI	Patient and Public Involvement
PPV	Positive predictive value
QOL	Quality of life
QOL-AD	Quality of Life – AD
QUALID	Quality of Life in Late Stage Dementia
REDIC	Resource Use and Disease Course in Dementia study
SIB	Severe Impairment Battery
UTS	Up-to-standard
WHELD	Improving Well-being and HEaLth for people with Dementia study
Z	Z-drug
ZED	Z-drug Evaluation in Dementia Study

Roles and responsibilities

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1 Abstract:

Background

Sleep disturbance is common in dementia, and can severely affect patient and carer quality of life. Z-drugs (zolpidem, zaleplon and zopiclone) are sedating hypnotics that are used for insomnia in older people and in people with dementia. Current guidance suggests Z-drugs or short acting benzodiazepines (BZD) can relive sleep disturbance and can provide respite for carers. Nevertheless there are concerns about tolerance, addiction and the safety of Z-drugs, with adverse effects including increases in falls and fracture risk, impaired daytime cognition, and higher risks of infections. Other sedating neuroleptics are known to increase stroke risk and mortality, with mediating pathways including dehydration and over-sedation and it is important to confirm whether Z-drugs confer similar risks.

Aims

Our aim is to understand the benefits and harms of using Z-drugs for people with dementia who have trouble sleeping. Using existing data we will look at whether Z-drugs improve sleep, whether they improve quality of life for people with dementia and their carers and how they affect memory and thinking during the day or other behavioural problems. We will also look at whether people who take Z-drugs fall more often, have more infections or are taken to hospital more often.

We will compare Z-drugs to other sleep drugs prescribed to people with dementia, and to people who do not use any sleep medication at all.

Methods

As specified in our NIHR commissioning brief this study will use existing data only.

Work package 1

We will conduct a prospective cohort study of anonymised data from the Clinical Practice Research Datalink (CPRD). We will identify a cohort of older people with sleep disorders, and estimate the risk of pre-specified health outcomes as a function of their (possibly changing) medication use.

Work package 2

In WP2 we will use anonymised data from existing research studies (RCTs and cohort studies) involving people with dementia. Many studies ask their participants about sleeping problems and about medicines that they use. They also test changes in quality of life, memory and health. This data will be used to estimate how Z-drugs affect sleep disturbance, markers of cognitive function and patient reported outcomes quality of life for patients and carers.

2 Background and Introduction

2.1.1.1 Epidemiology and impact of sleep disturbance in dementia

Dementia is a syndrome of progressive decline in cognitive and daily function. There are over 800,000 people with dementia (PwD) in the UK (1). Around 60% are affected by sleep disturbance (2,3) including insomnia, night-time wandering, or excessive day sleep (4). Sleep disturbance affects the quality of life (QOL) of PwD, their families and carers, and in healthcare settings can be detrimental to the wellbeing of other patients. Sleep disturbance is multi-factorial with causes including effects of the dementia, medical or psychiatric comorbidity, medications, environment or lifestyle.

Carers of people with dementia are particularly affected by sleep disturbance of those they care for, and play a vital role in the decision to medicate the condition. Sleep disturbance contributes to significant decrements to the sleep of carers, poorer physical health outcomes, limits the carers ability to care, and reduces health-related quality of life (5). Carer depression is also associated with sleep disturbance in the PwD (6).

2.1.1.2 Treatment and management of sleep disturbance

Benzodiazepines (BZD) are often used for insomnia in older people. BZDs act on gamma-aminobutyric acid (GABA), an inhibitory neurotransmitter, by binding to GABA receptors causing a sedative effect. BZD are still regularly used, often long-term, despite concerns about their side effects, tolerance and dependence and withdrawal effects.

In the late 1980s a class of non-benzodiazepine GABA agonists were introduced. These include zaleplon, zopiclone and zolpidem and are collectively known as Z-drugs (Zs). Zs were originally believed to be safer than BZDs, but addiction and tolerance are increasingly recognised.

National Institute for Health and Care Excellence (NICE) guidance on the use of Zs recommends that non-pharmacological approaches are considered to manage insomnia, but that short acting BZD or Z should be used for up to four weeks if considered appropriate (7). The most recent evidence has suggested that melatonin can be used in those aged 55 years and older for up to ten weeks. In practice, Zs, BZD and other medications including sedating antidepressants, sedating antihistamines, and antipsychotics, are used to manage sleep disturbance in the older population and in PwD.

2.1.1.3 Potential benefits and harms of Z-drug use

BZDs and Z-drugs can improve sleep quality, but cause clinically relevant adverse events (8). Risks in people with dementia are largely unknown, but findings in the general older population are likely to apply or to be exacerbated in PwD:

Falls and injuries. Between 36% and 66% of PwD experience a fall annually (9,10). Fall related injuries have an enormous impact on quality of life, are an important cause of death and institutionalisation, and cause a substantial cost to the NHS (£581 million in 1999 in the over 60s) (11–13). BZD are consistently associated with a 20% increased risk of falls in older people (14), and increase the risk of hip fractures in PwD (15). Zs were originally claimed to cause fewer falls (16), but recent observational studies have found Z use associated with a four-fold increase in falls (17), and an increased risk of fractures (18–23). These effects have been particularly associated with new Z use (20,21,23), although no studies have been specifically conducted in dementia (24,25).

Cognitive impact and impact on daily activities. Older adults using BZD have greater risk of incident mobility and activities of daily living (ADL) disability (26). Short and long-acting benzodiazepines cause cognitive impairment in older adults, but studies are fewer for z-drugs and results less consistent (27).

Infections. Combined analysis of RCT data flagged a 1.4-2 fold increased risk of infections when taking z-drugs (28). Observational studies have supported this finding (29,30). The reason for this relationship is unknown, but benzodiazepines can reduce immune function, reduce respiration and may impair response to infection (28,30). Infections in PwD are a leading cause of mortality and hospitalisation, very costly to the NHS, and as such are an important outcome to assess.

Mortality. An increased risk of infection, fractures and injury suggests a potentially increased mortality risk. However studies on z-drug or benzodiazepine use and mortality have been conflicting (31), and reported associations may simply stem from confounding (32). In a US study, crude mortality rates were higher in PwD taking hypnotics, but the association was not tested statistically (33).

Cerebrovascular events. With increased cerebrovascular events suspected to contribute to the excess mortality observed in PwD taking antipsychotics, and zolpidem being associated with excess stroke risk in a case-control study, cerebrovascular events as a potential consequence of z-drug use warrant further investigation (34,35).

Other possible harms of Zs. Daytime drowsiness/fatigue, headache, nightmares, gastrointestinal disturbances, reflux, and incontinence have all been suggested as possible harms of Z use although evidence for these is inconsistent (8,36). Adverse neuropsychiatric reactions have been reported with the use of zolpidem, including hallucinations/sensory distortion, delirium and amnesia (37,38).

2.1.1.4 What is not known and why this research is needed now

Sleep disturbance is common in dementia, has a large impact on PwD and their families, health and social care services. The evidence base for sleep management in dementia is poor, particularly with respect to the safety and the effectiveness of pharmacological interventions, and many PwD and carers use Zs to manage sleep disturbance. In 2013 the NHS in spent £7.8m on Z (39), although it is unclear what proportion were in PwD.

Benefits and harms of Z use have a potentially large impact on NHS resources. Lower daytime cognitive function, an increase in falls, accidents or infection risk will lead to higher rates of hospitalisations and hasten institutionalisation. Conversely, alleviation of sleep disturbance might improve PwD and carer quality of life and delay institutional placement. It is important to quantify these potential benefits and harms.

This proposed research will use existing data to quantify the intended and unintended effects of different Zs in PwD with sleep disturbance, compared to use of other sleep drugs or no pharmacological treatment. Findings will help carers and clinicians to balance potential risks versus benefits, and support treatment decisions. The use of anti-psychotics in dementia has fallen rapidly in recent years mainly because of the strong evidence of the harms that they cause. This has also led to the developments of a more person centred approach to reducing agitation in dementia. If harms are associated with Zs then identifying these will have a similar effect on the development of alternative medicines and a person-centred non-pharmacological approach to sleep management in dementia.

3 Aims and objectives

3.1 Aims

Our broad aim is to estimate the benefits and harms of using Z-drugs for PwD by using data from primary care, hospital admission records and existing clinical research studies. We will estimate the impact of Z on cognitive function, QoL and functional ability in PwD, and QoL in their carers. We will also estimate how Zs affects the rates of falls and fractures, new infections, stroke, incident behavioural and psychiatric disturbance, healthcare utilisation and mortality.

To inform this analysis it is important to understand the ways in which Zs are used by PwD. Since there is little evidence on the use of Zs by PwD we will also describe the typical pattern of use and the relationship between Zs and other hypnotic use.

3.2 Definition of technology being assessed (Z-drugs) and comparisons of interest

To aid decision making and future research it is important to estimate the effects of Zs in comparison to currently used alternative treatments. Comparing Zs to all other alternatives combined would not be useful as other medications may also be harmful. Therefore it is important to compare the effects of Zs against a 'no-treatment' group, and to enable comparisons between Zs and other classes, in particular BZD where these are of interest.

Z-drugs prescribed in the UK are zopiclone, zolpidem and zaleplon. While comparisons between specific Zs might be of interest, there is little to suggest that their effects are different, and there are unlikely to be sufficient numbers to be able to make this comparison.

Hence in both workstreams we will classify exposure to 'medications used in sleep disturbance' in six groups: (i) BZD (ii) Z (iii) melatonin (iv) sedating antidepressants (v) sedating antihistamines, and (vi) antipsychotics. Our preliminary analysis suggests that there might be fewer people in groups (iii)-(vi), but it is important to document this use, to exclude such individuals from the main comparison and to be able to make comparisons between these groups and Zs if sufficient numbers do arise. These groups will be used for both workstreams. More detailed coding of dose, frequency and duration of Zs is discussed for workstream 1 below.

3.3 Specific objectives

Our specific objectives are as follows:

Workstream 1

1) Use data from the Clinical Practice Research Datalink (CPRD) to describe the treatment of sleep disturbance in PwD in the UK, including the:

a. Time between dementia diagnosis and first sleep disturbance

b. Distribution, frequency, dose and duration of first sleep disturbance treatment.

c. Concurrent or subsequent use of other hypnotics

2) Use data from CPRD to estimate the effects of first prescription of Z in PwD with sleep disturbance, compared with alternative treatments or with no treatment. Specific patient outcomes include:

a. The incidence of falls and fractures (including hip and forearm fracture)

b. Mortality

c. The incidence of infection

d. The incidence of stroke and venous thromboembolism

e. The incidence of behavioural and psychological symptoms

f. Additional medication use: (a) sedatives (b) antipsychotics, (c) antidepressants

g. Healthcare utilisation (GP visits, hospital admissions)

Workstream 2

3) Use data from existing clinical trials and observational studies to estimate the impact of Z on patient and carer reported outcomes. Specifically we will:

a. Harmonise data from clinical studies where participants included PwD

b. Use multilevel models to estimate how QOL, functional ability, cognitive function and sleep disturbance in PwD and carer QOL vary with the concurrent use of Z, adjusting for confounding factors in particular sleep disturbance.

4 Workstream 1: An inception cohort analysis of the Clinical Practice Research Datalink

4.1 Design and theoretical framework

Workstream 1 is based on the analysis of data from Clinical Practice Research Datalink GOLD database (henceforth CPRD). CPRD is the largest source of research quality longitudinal primary care medical records in the UK with records from over 14 million patients. CPRD is widely used for pharmacoepidemiological applications (40). We have established the feasibility of our proposed analyses in consultation with CPRD and by preliminary analysis of a sample dataset.

We will perform an *inception cohort study* using data extracted from CPRD (41). Patients will be followed from first recorded diagnosis of a sleep disorder and the rates of adverse events will be analysed with respect to the exposures described above.

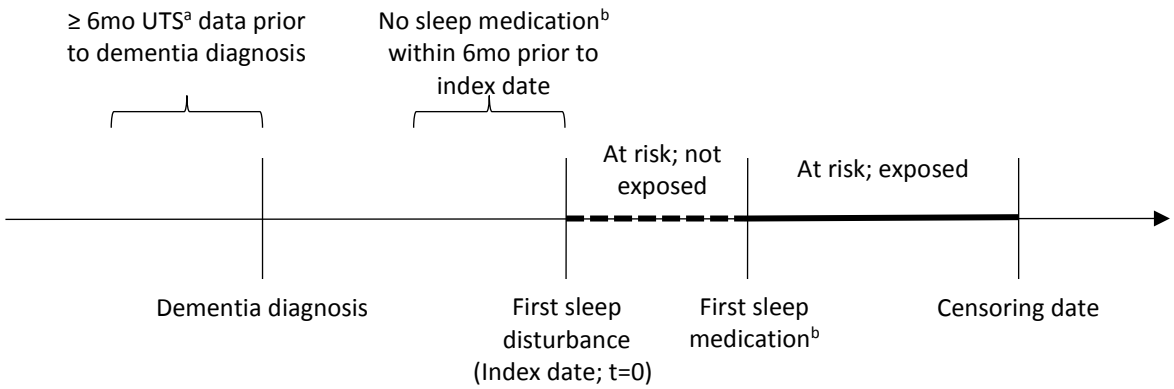

Figure 1 – Typical participant timeline. Participant is 'at risk' from the time of their first evidence of a sleep disturbance (diagnosis or z-drug or melatonin prescription) following dementia diagnosis.

Participant is 'exposed' from their first prescription of a 'sleep medication' following sleep disturbance. Participant is censored (at 'censoring date') the first of the: leaving practice date, death date, last practice extraction date, additional 'sleep medication' class, 2 years after first 'sleep medication' prescription.

Participants may be exposed for part of the at-risk period (as above), the whole of the at-risk period (if medication is prescribed concurrently with first sleep disturbance recorded), or none (if no medication is reported at all).

[a] UTS = 'Up-to-standard' (i.e. research quality data)

[b] Sleep medication = any Z, BZD, melatonin, sedating antidepressant, sedating antihistamine, or antipsychotic.

PwD will be followed from the inception of their first sleep disorder complaint and/or first initiation of a medication for sleep disturbance whilst being treatment naïve (see figure 1 for study design). PwD are censored when they switch therapy, to reduce a *channelling bias* whereby patients who switch therapy are different due to having probable treatment failure with their first sedative, and potentially a greater disease severity.

4.2 Target Population

- PwD in the UK with a first sleep disturbance reported to primary care.
- Not restricted by age or dementia subtype, and includes those living in the community and in residential care.
- We will not examine carer outcomes in this workstream because there are no sufficiently reliable methods to do so within CPRD. Instead, we will evaluate carer outcomes in workstream 2

4.2.1 Inclusion criteria

- **Diagnosis of dementia** defined by the first record of a dementia diagnosis *or* prescription of a cognitive enhancer (memantine, donepezil, rivastigmine, or galantamine) which is followed by a dementia code within a year. Dementia diagnosis using a very similar definition has been validated in CPRD with a positive predictive value (PPV) of 95% (42).
- A first date of **evidence of a sleep disorder** defined as either a diagnosis of sleep disorder or prescription of a Z-drug or melatonin (as medications with sleep disturbance as their *sole* indication) **on or after the dementia diagnosis date** and where this occurs after 1 Jan 2000. This date of first sleep disturbance defines the index date.
- Registration with a practice that provides **'up-to-standard' (research quality) data** for at least 6 months before the dementia diagnosis. This enables sufficient time to measure confounders, indications, and time since dementia diagnosis, and for recording to have stabilised for patients new to the practice (43).
- Practice **registration at least 12 months** before the index date.
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4.2.2 Exclusion criteria

- PwD with codes for sleep apnoea, sleep related respiratory failure, severe mental illness, Down syndrome, neuropathic pain (within 12 months) or alcohol abuse prior to the index date.
- PwD with prescription for a 'medication used in sleep disturbance' in the 12 months before the index date. This is to select treatment naïve patients.

4.3 Exposures

We will extract all prescriptions for sleep disturbance from primary care records. These will be defined using BNF codes that will be finalised during the development of the full protocol to be sent to ISAC. Extracted information will include the date of each prescription, the drug name, dosing instructions including the number of daily doses instructed, the dose and quantity prescribed. For each class of sleep medication, the primary comparison is the effect of any prescription in the class compared to no sleep medication.

To enable testing for a possible dose-response relationship, we will determine the average daily dose and the cumulative number of defined daily doses (DDD). We will calculate the total dose of each prescription by multiplying the dose of each tablet by the number of tablets prescribed. To enable comparison of doses across drug classes, we will convert the total dose for each medication to a number of DDDs. A DDD is defined as the assumed average maintenance dose per day for a drug based on its main indication in adults, using the DDD values assigned by the World Health Organisation's Collaborating Centre for Drug Statistics Methodology (www.whocc.no/atc_ddd_index).

Where a drug has multiple indications we will use the DDDs for the sedation indication. The average daily dose over the total treatment period will be estimated by dividing the total DDDs by the exposure duration.

We will consider exposure to be continuous where a prescription is made within 90 days of a preceding prescription. If no subsequent prescription is made within 90 days a participant will be considered exposed for the stated prescription duration, calculated as the quantity divided by the number of doses per day. Where number of doses per day is missing it will be assumed to be one. Where quantity is missing it will be assumed to be 28.

For Z-drugs and benzodiazepines we will also code the prescribing instructions as either being daily or 'as needed'.

4.4 Censoring

Patients will be censored at the earliest of: leaving practice date, death date, last practice extraction date, additional 'sleep drug' class prescription date, 2 years after the first 'sleep drug' prescription, or documented resolution of sleeping disturbance with no sleep drug prescription in the last 3 months.

4.5 Outcomes of interest

Outcomes are chosen based on the NIHR commissioning brief, with pharmacological plausibility, reasonable mechanistic hypotheses and previous support in the literature, suitability for inclusion (both occurring with sufficient frequency and validity of the recording in CPRD), and based on the views of family carers, care staff and clinicians. Read code lists for the outcomes will be finalised during the CPRD protocol development phase, but will be drawn, where applicable, from Quality of Outcomes Framework business rules, published studies with (or without) validated lists, keyword searches, and UK General Practitioner experience within the team.

CPRD recording of our outcomes has been well validated (40,44), but studies highlight additional need for hospital episode statistics (HES) linkage for recording of injuries and hospitalisation (45). For a sensitivity analysis to test whether limiting to CPRD is likely to introduce bias, we will restrict analysis to those with CPRD-HES data linkage and supplement the CPRD outcome with an occurrence of an ICD9 or ICD10 code for the admitting diagnosis or external cause in the HES inpatient data. For the mortality outcome, ONS data will be used instead for those with CPRD-HES linked data.

Specific outcomes of interest include:

1. Incident (a) fracture (any location) (b) hip fracture (c) forearm fracture. Hip fracture recording in CPRD has been well validated (PPV of 91%) (44).
2. Incident fall. GP records of falls may under-represent all falls that occur in the older population, but more accurately represent 'injurious falls requiring medical attention' (46).
3. Mortality
4. Infection. Respiratory tract infection has been validated in CPRD (PPV of 97%) (44).
5. Stroke. Stroke has been well validated in CPRD (44).
6. Venous thromboembolism. Diagnosis in CPRD has been validated (PPV of 94%) (47).
7. Incident behavioural and psychological symptoms – diagnosis of agitation/psychosis/delusions /wandering/anxiety. Psychosis diagnosis has been validated in CPRD (PPV of 93%), but the symptoms may be under-reported (44).
8. Additional medication use: (a) sedatives and other sleep medications, (b) antipsychotics, (c) antidepressants
9. Health care utilisation: number of GP visits; hospital admissions.

4.6 Potentially confounding covariates

Potentially confounding variables will be coded at the index date (date of first sleep disturbance) and at the start of new treatment where these are different. Covariates were selected on the basis of being potentially linked to sleep disturbance or hypnotic use and at least one of the outcomes, as well as the availability, completeness and reliability of data within CPRD.

Proxies for sleep disturbance severity: we are only including those with a new episode of sleep disturbance in the cohort, but to provide addition control for confounding by indication we will adjust for type of disturbance (insomnia, poor sleep pattern, nightmares, sleepwalking, other), time since sleep disturbance diagnosis, sleep disturbance diagnosis before dementia diagnosis and sleep medications used before dementia diagnosis.

Demographic factors: Age, sex, year, care home resident (where recorded), area level deprivation, GP practice

Lifestyle factors and cardiovascular health: Smoking, alcohol use, Body Mass Index, average systolic blood pressure (in mmHg, categorised).

Dementia subtype and proxies for dementia severity: time since dementia diagnosis, current or previous use and dose of cognitive enhancers, dementia sub-type, diagnoses since dementia diagnosis: wandering, agitation, psychosis, delusions.

Comorbidity and prior health: osteoporosis, anxiety, depression, Parkinson's disease, Epilepsy, urinary incontinence, age related macular degeneration, Glaucoma, Cataract, diabetes, dyslipidaemia, hypertension, ischemic heart disease, heart failure, atrial fibrillation, TIA, stroke, angina, Osteoarthritis, rheumatoid arthritis, chronic pain, cancer, Motor neuron disease, HIV/AIDS, Multiple sclerosis, pre-dementia sleep disorder/treatment. In the last 6 months: hospitalisation, a fall, fracture, pneumonia, upper respiratory tract infection, Urinary tract infection, number of GP visits.

Medication use at index date (ATC group): any prescription up to 90 days before index date of antiepileptic drugs (N03), drugs used in Parkinson's disease (N04), immunosuppressants (L04), antithrombotic agents (B01), vasodilators used in cardiac diseases (C01D), antihypertensives (C02), diuretics (C03), calcium channel blockers (C08), ACE inhibitors (C09A, C09B), angiotensin II receptor antagonists (ARBs) (C09C, C09D), beta blockers (C07), statins (C10AA), nonsteroidal anti-inflammatory drugs (M01A, M02A, N02BA), bisphosphonates (M05BA).

Previous sleep medication use (prior to 12 months before index date): z-drugs, benzodiazepines, melatonin, low dose TCAs.

4.7 Data analysis

We will estimate a multinomial regression model estimating the effect on initial treatment choice following sleep disturbance. Potential predictors in each case will be those identified as potential confounders, and measured at index date for the multinomial regression analysis. Predicted probabilities arising from the multinomial regression will be used to form a propensity score.

PwD will enter the study and be followed from the index date to the earliest of: leaving practice date, death date, one month before the last practice extraction date (48), additional 'sleep drug' class prescription date, 2 years after first sleep medicine prescription, or no sleep drug prescription in the last 3 months. Those never exposed will be followed for a maximum of 2 years from their sleep disturbance diagnosis date.

For the fracture, falls, stroke, and venous thromboembolism outcomes, we will examine the delay between events occurring in the linked HES data and recording in the primary care records. This delay will inform how long we will censor records before the last practice extraction date (48).

Additional exclusions will apply for different outcomes. For the fall and fracture outcomes, we will exclude PwD with a recorded fall or fracture in the 32 days before index date, due to the chance of repeated coding of the same event (46). For the antidepressant outcome we will exclude patients with a prescription for antidepressants in the 12 months before the index date. For the infections outcome we will exclude those with an infection or prescription for a medication for infection in the previous 30 days. For the analysis of other outcomes we will exclude patients who had already had the outcome at baseline.

Cox regression models will be used to estimate the hazard ratio (HR) for the effect of sleep medication class compared with no treatment on each binary outcome. Sleep medication exposure will be modelled as time-varying, such that PwD at the index date will be included for analysis in the 'no treatment' group until initiation of their first treatment and will re-enter the study at time 0 as exposed thereafter to avoid immortal time bias and reduce channelling bias. Robust standard errors, adjusting for the patients potentially appearing twice in the analysis (when not exposed and when exposed) will be used to calculate confidence intervals and p-values. The proportional hazards assumption may be violated since the risks associated with Z-drug might be highest with first use. We will check this using Schoenfeld residuals (49), and by dividing the exposure period and estimating separate HRs for the effects 1-90, 91-180, and 181-730 days since first use.

Negative binomial regression will be used to calculate incidence rate ratios (IRR) for the effect of sleep medication class on number of GP visits and hospital visits in the two years after index date.

We will carefully control for potential confounders, allowing for non-linear effects, and time-varying coding where confounders differ when the first sleep drug is after the first sleep disturbance diagnosis.

For common outcomes, interactions between Z-drug and age and sex will be tested.

The absolute risks of the adverse events and numbers needed to harm (NNH) will be estimated using a standard formula for NNH in time to event analysis (50).

We will test for a potential dose-response relationship by examining exposure according to both cumulative DDDs, average daily dose and by dosing instructions.

The primary analysis will report associations relative to no sleep medication use, but as secondary analysis, we shall report associations for the effect of Z-drug use compared to benzodiazepines, melatonin, and to low dose TCAs. We will also report associations for individual z-drugs, benzodiazepines, Amitriptyline, and Trazodone where the numbers are sufficient.

Stata (version 14) will be used for data management and statistical analysis. Due to examining 9 outcome domains, we will set a critical p-value threshold to control the false discovery rate at 5% (51).

4.8 Missing data

We expect incomplete recording of variables such as smoking and BMI (52). In the primary analyses, patients with missing covariate data will be coded in a missing data category. For covariates with at least 10% of patients with missing data, we will summarise the characteristics of those with and without missing data, and perform sensitivity analyses including restricting (i) to GPs/index dates with more complete data, and (ii) to those with complete data (53). As there is often a delay between secondary care medical events and their recording in the patient's primary data, we will censor our analyses 1 month before the last collection date to minimise this missing data (48).

4.9 Sensitivity analyses

It is always important in pharmacoepidemiological studies to conduct a range of sensitivity analyses to ensure that findings are robust to modelling assumptions, data quality, inclusion criteria and the choice of methods for confounding control. If results are substantially different using any of these methods the

underlying reason will be fully explored. Sensitivity analyses will be finalised during ISAC protocol development stage but may include:

1) **Recording of outcomes.** As a sensitivity analysis to assess the completeness of our outcome data, we will compare results when also including hospital admission data in the outcome definitions (and restricting to those patients with HES data available). HES records diagnosis and external cause for admissions to NHS hospitals (www.hesonline.nhs.uk). CPRD-HES linkage is available for about 55% of patients and is well validated (45,54–56). CPRD-HES linked data also includes date and cause of death from ONS (Office for National Statistics) records.

2) **Inclusion of prevalent users**. As our cohort is reduced by excluding those with prevalent sleep drug use, we will examine if the characteristics of those with prevalent sleep drug use differ and examine whether outcomes differ.
3) **Investigation of channelling bias.** We suspect that GPs will preferentially prescribe sleep treatments to certain patient groups, e.g. avoid Z-drugs in patients with a greater falls risk. This will be explored when we examine propensity scores for first sleep treatment (see confounding section M). We will also define high risk groups for the outcomes of falls, fractures, infection, stroke, and venous thromboembolism (defined by a recent history of these, age and relevant comorbidities) and examine whether there is an interaction between sleep drug use and this high risk group membership.

4) **Additional exclusions**
   a) Excluding those with additional comorbidities that *may* be the underlying cause of the sleep disorder on the index date, e.g. infection, asthma/allergies, pain, depression/anxiety (these will be controlled for in primary analyses).
   b) Excluding those with a first Z or melatonin prescription, but no diagnosis of a sleep disturbance. That is, restricting the definition of sleep disturbance to only those with a diagnosis.

Confounding control.

For the main analyses, all the covariates listed above will be adjusted for in the primary multivariable regression models. As sensitivity analysis, for comparison of first sleep drug prescriptions, the propensity for sleep medication class relative to no treatment will be estimated using multinomial logistic regression and will include all the covariates listed above (57). This will enable direct comparison of patient characteristics of those prescribed each sleep treatment. We will examine both adjusting for the propensity score in the regression models and matching on the propensity score split into deciles.

As further sensitivity analysis, we will investigate the feasibility of using GP's prescribing preferences as an instrumental variable. Instrumental variables have been used in routinely collected primary care data and offer a potentially powerful approach to confounding control but it is not clear that there is a feasible instrument to use in this situation. Instrumental variable analysis is useful to address confounding when an instrument *I* can be identified such that:

(i) *I* predicts the exposure of interest *Z* but is
(ii) not associated with the outcome *Y*, conditional on the exposure and other covariates.

The instrument that will be tested is the GP practice propensity to prescribe Z-drugs or other pharmacological treatment for a patient with sleep disturbance and dementia. For each participant we will create instrumental variables corresponding to the preference of the practice with respect to the prescription of Z-drugs or another medication at the time of the patient's presentation. This will be

estimated as the proportion of previous patients with dementia who were prescribed a Z-drug initially on presenting with a sleep disturbance (i) in the past calendar year, (ii) among the previous 10 eligible cases or (iii) for the previous case only.

We will conduct a two-stage predictor substitution analysis. First we will estimate a multinomial regression model individual treatment decisions (no treatment, Z-drug or other pharmacological treatment) for each patient based on the IV and individual patient level covariates.

The predicted probabilities of Z or other treatment will then be entered into a Cox proportional hazards regression for the outcomes of a fall, fracture and mortality. This will not be time varying but follow-up is restricted to two years as per the main analysis. Bootstrapping will be used to find the precision of resultant estimates.

The feasibility of each IV will necessarily be made subjectively but will be judged on

(i) the strength of the relationship between each IV and the exposure, measured by the pseudo R-squared
(ii) the balance between patient level covariates and dichotomised instrumental variable, and
(iii) the precision of the resultant estimates of the effect of Z-drugs on each binary outcome

If estimates of effects from any sensitivity analysis are substantially different to estimates from our main analysis this will be discussed in the context of the limitations of each analysis.

5)

4.10 Sample size calculation

A CPRD feasibility query in 2014 revealed at least 14,480 participants with sleep disturbance and dementia in CPRD GOLD. Preliminary analysis of a small sample of CPRD patients suggests that an equal number receive a Z, BZD, other sleep drug, or no treatment. Assuming 70% remain after applying the exclusion criteria (58), we expect 2534 patients in each group. When comparing Zs to no treatment for a common outcome over 2 years (e.g. falls at 36% per year (9)) we can detect a hazard ratio (HR) of 1.08 with 90% power. For rare outcomes, such as hip fractures at 1.7% per year (59), we can detect a HR of 1.56 with 90% power.

4.11 Target population (sleep disturbance) validation study

4.11.1 Rationale

We will validate the reporting of sleep disorders within dementia patients in CPRD using a validation study running in parallel with our main analysis.

Those with sleep disorders not prescribed sleep medications will form the reference group for all of our risk estimates, therefore we need to be confident they do in fact have sleep disturbance rather than are healthier individuals. This validation study will be used to guide our sensitivity analyses and will be reported alongside our main findings. This study will test the reliability of codes that we classify as ‘definite’ or ‘probable’ sleep disorder codes.

4.11.2 Objectives

To validate the sleep disorder diagnosis of patients identified by different sets of codes related to sleep in CPRD data.

4.11.3 Method

A process for validation studies in CPRD is well established and the administration of this study will be managed by CPRD.

A questionnaire will be developed by the research team in collaboration with CPRD Validation Services to be sent to selected GPs.

This will request confirmation of the sleep disturbance and dementia status of 100 selected patients.

4.11.4 Participants for validation study

Selected patients meeting our inclusion criteria will be stratified by sleep disturbance ('definite' sleep disturbance vs 'probable' sleep disturbance and Z prescription (Z vs other).

4.11.5 Analysis

The proportion that are confirmed as having a sleep disturbance will be reported, and if this is substantially lower in the group with 'probable' sleep disturbance then we will include a sensitivity analysis restricting the sample to include only those with a 'definite' code.

This validation study will be written into our main study protocol and will be conducted during the period of data definition and extraction ahead of the main WP1 analysis of CPRD data.

We have discussed this study with CPRD who have confirmed that this study is feasible, falls under the CPRD remit and hence NRES ethical approval, and that it will be completed within our main study timelines.

5 Workstream 2: Repurposing RCT and cohort study data

5.1 Study design

Data from clinical research studies including trials of other interventions and cohort studies will be used to estimate how patient and carer reported outcomes are affected by whether or not a participant was using a Z at each assessment. We will incorporate data from both prevalent and incident Z users.

Power and confounding control will be improved by restricting to data with repeat assessments and analyses that take advantage of within patient comparisons. This will allow patient level variation to be accounted for and the trajectories of cognitive function and quality of life to be taken into account. Guidelines recommend that treatment with Zs is restricted to four weeks. Given the range of follow-up regimens specified by each trial it is likely that we will see sufficient within-person variation in Z use to be able to make these comparisons.

Data will be drawn from studies reflecting the diversity of living situations and clinical characteristics of people with dementia. Data from several studies will be needed as no single source will include the numbers of participants and the diversity of PwD to be able to address the commissioning brief.

5.2 Target population and data sources

The target population for this analysis includes all PwD and their informal carers if living at home. Carers will be defined according to the definitions employed by the included studies. Data are collected from memory clinics, home and long-term institutional care. We have not considered data from hospital care, as both medication use and outcomes are likely to be severely affected by the condition that led to hospitalisation. We assessed clinical research studies on the basis of:

- Validated dementia diagnosis
- Specific assessment of sleep disturbance for all participants.
- At least two assessments per participant, with assessments separated by six months or less
- At least one key primary outcome included.
- Systematic assessment of participant medication use with a documented protocol for ascertainment.
- A well characterised sample, recruited from a defined population with clear inclusion/exclusion criteria.
- Sufficient sample size, or data that is readily harmonisable with other studies.

The studies from which we have secured access to data are described in table 1 below:

Study name	Study design and location	Participants and setting	N at baseline	Follow-up regimen	Sleep variable	Outcomes
DOMINO-AD (60)	RCT – AD drug, UK	Mod/sev AD in community taking donepezil	295	6, 18, 30, 52 weeks	NPI	MMSE, DEMQOL, BADLS, Carer GHQ, Carer EQ-5D

ADCS (www.adcs.org)	Harmonised data from 9 US drug or dietary supplement RCTs	Typically community living mild/mod AD	2,609	Varies across studies: typically 3,6,12,15, 18 months	NPI	MMSE, ADAS-Cog, ADCS-ADL, for most: CDR, QoL-AD, carer QoL-AD
WHELD (61)	RCT – training intervention, UK	All dementia in care homes	960	9 months	NPI	CDR, GDS, DEMQOL, QUALID, CANE
CALM-AD (62)	RCT - psychological intervention, UK	Poss/prob AD with agitation in care homes	272	4, 12 weeks	NPI	MMSE, SIB
MAGD (63)	RCT – AD drug, UK	Mod/sev AD with agitation in care homes	149	2,4,6,12 weeks	NPI	MMSE, SIB, QoL-AD
REDIC (64)	Clinical cohort study, Norway	PwD admitted to care homes. High prevalence of Z use	691	6,12,18,24,30,36 months	NPI	MMSE, SIB, CDR, QoL-AD, QUALID, EQ5D, ADL
NACC	Clinical research database of Alzheimer's Disease Patients in the US	All diagnosed with Alzheimer's disease attending one of the NACC clinics	Up to 35,000 patients	Yearly, up to 14 years data for some patients	NPI – only from later waves	MMSE, neuropsych battery

NPI – Neuropsychiatric Inventory; MMSE – Mini-mental state examination; ADAS-COG – Alzheimer's Disease Assessment Scale – Cognitive; CDR – Clinical Dementia Rating; DEMQOL – Dementia Quality of Life measure; SIB – Severe Impairment Battery; QOL-AD – Quality of Life – AD; CESD – Centre for Epidemiologic Studies Depression scale; QUALID – Quality of Life in Late Stage Dementia; EQ-5D (EuroQOL EQ-5D quality of life measure); BADL – Bristol Activities of Daily Living

In total these studies include 4976 people with dementia. Exploration and negotiation with other potential data sources is ongoing and would further strengthen our analysis.

Inclusion / exclusion criteria. Patients will be included if they have a dementia diagnosis made according to a recognised validated definition, and excluded if there is a reported diagnosis of sleep apnoea, alcoholism or severe mental illness at any assessment.

5.3 Combining data sources.

Data will be harmonised across studies. This is likely to be possible across RCTs, where standardised outcomes, methods for ascertainment of concomitant medications and similar follow-up times are commonly used.

5.4 Exposures

The presence or absence of each medication group (as defined above) at each time point will be coded as a binary variable, and these will each be independently entered into regression models. As with workstream 1, Z use compared to no Z use (adjusted for other sleep medicines) is the primary comparison of interest. Comparisons between Zs other classes will be made using linear combinations of coefficients where numbers are large enough for the comparison to be of clinical interest.

5.5 Outcomes

Outcomes will include cognitive function, QoL, functional ability and sleep disturbance in the PwD, and QoL in the carer. Studies will each have assessed these using a number of instruments as described below:

- Carer's Quality of Life (EQ-5D)
- PwD Cognitive function (ADAS-COG / MMSE)
- PwD Functional ability (Bristol ADL index)
- PwD Quality of Life (DEMQOL / QOL-AD)
- PwD Behavioural and psychological symptoms (Sum of NPI items excluding sleep)
- PwD Sleep disturbance (0-12 scale corresponding to severity and frequency of NPI sleep questions)

5.6 Covariates

Potentially confounding variables include study characteristics, patient characteristics and patient health. These might vary between assessments and will be coded at each follow-up. Potential confounders will be operationalised and carefully selected for inclusion depending on the outcome variable being tested. Common core covariates from clinical studies include:

- Age, sex, year, ethnicity, setting (care home or community)
- Carer characteristics
- Smoking, alcohol use
- Baseline dementia severity and subtype, behavioural and psychological symptoms.
- Comorbidity including anxiety, depression, diabetes, cardiovascular disease, cerebrovascular disease, arthritis, chronic pain.
- Other medication use, cognitive enhancer use
- Study characteristics (location, start year, specific intervention being tested, study arm)

5.7 Confounding by indication

To control for confounding by indication we will adjust each analysis for NPI-sleep questions, and recent insomnia diagnosis. The NPI is included in all but one of the studies and includes a detailed assessment of sleep disturbance. Specifically, the NPI includes

(i) Eight questions on the presence or absence of specific sleep disturbances
(ii) Frequency of overall sleep disturbance (Rarely/Sometimes/Often/Very Often)
(iii) Severity of sleep disturbance (Mild/Moderate/Severe)

(iv) Carer distress related to sleep disturbance (Not at all / Minimally / Mildly / Moderately / Severely / Extremely)

This will allow us to control for the nature, frequency, severity and burden of sleep disturbance for each participant at each time point.

5.8 Data analysis

For non-sleep outcomes, **mixed effects multilevel regression models** will be used to estimate the effect of Zs on each patient and carer outcome, adjusting for covariates as described above. A directed acyclic graph (DAG) illustrating a simple example of this model is shown in figure 2 below. Models will be iteratively developed (65); but at a minimum we will include main effects of exposures, confounding factors ascertained at each time point and random effects corresponding intercept and slope of individual patients outcomes. A separate model will be developed for each outcome variable. Non-linear effects, latent classes, and interaction effects will be tested for inclusion.

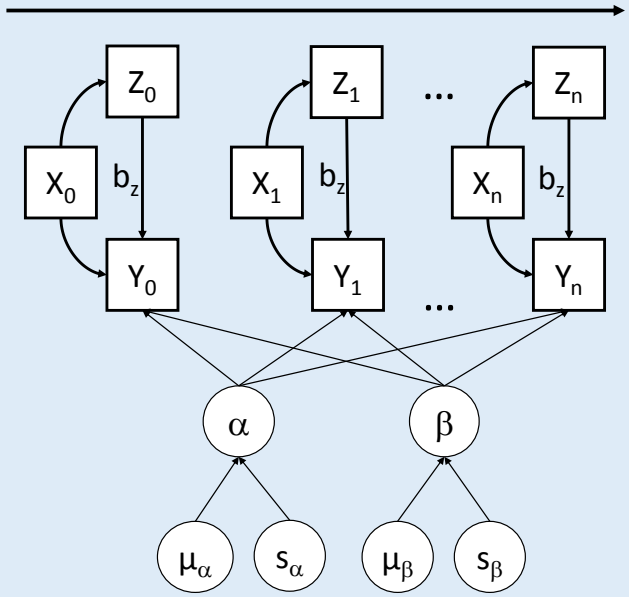

Figure 2. Basic multilevel model representing the effect of Z on an outcome across study follow-ups.

The effect of Z on the outcome Y is estimated by b_z, controlling for covariates X.

$Y_t = \alpha + \beta t + b_x X_i + b_z Z_t + e$

For each participant, a and b are random effects representing the intercept and slope of the outcome trajectory. α and β each have a study specific mean and variance.

Potential confounders will be carefully selected on an empirical and theoretical basis. Confounding by indication will be controlled for by including the full spectrum of responses on the NPI-sleep at the present assessment and previous assessment. Each of the outcomes is measured continuously. Distributional assumptions will be tested and transformation applied where necessary.

5.9 Sample size calculation for workstream 2

Although this study is based on existing data a power calculation is provided to illustrate the feasibility of estimating small to medium effects of Zs on main outcomes.

Preliminary analysis suggests that 5-10% of participants will be using a Z at some point, depending on the study. Our confirmed datasets so far include almost 5000 people with dementia.

Power calculations for multilevel models require estimates of the variance of outcome measures across first and second level units, in this case corresponding to the variance of an outcome between and within individuals. Preliminary analysis of DOMINO dataset suggests MMSE has a between person standard deviation of around 3.7 points and a within person standard deviation of 2.5 points after controlling for cognitive decline during the study. We assume a (conservative) prevalence of Z use of

2% at each assessment, and that there will be an average of three assessments per person with 20% of assessments missing at random. Then with 5000 participants we have 90% power to detect an effect of 0.5 MMSE points, or 0.2 standard deviations.

Power calculations were conducted by simulation using MLPowSim version 1.0 beta 1 (66).

6 Data collection and management

6.1 General principles of data management

All data will be held at the University of East Anglia on the central file store. No potentially identifying information will be transmitted to the research team at UEA or will be held at any time by the research team at UEA. Data will be transferred electronically to the study team. Access to all data will be restricted to research team members.

The source code used to derive analysis datasets and to conduct our analysis will be held alongside data (where permitted by individual studies) for at least ten years after our study conclusion.

6.2 Workstream 1 – CPRD, HES and Validation Questionnaire data

CPRD data will be held according to the terms of UEA's CPRD site licence. We will download anonymised primary care records from CPRD's server. We will abide by CPRD's security requirements by ensuring that data only remains within the UEA password protected file store.

Once we have our extracted patient IDs, CPRD will send us the associated anonymised HES and ONS data.

For the validation study, we will identify a set of patient IDs, transmit these to CPRD who will then administer the validation study, will collate and transmit GP questionnaire data to the study team. The anonymised results of the questionnaire data will be kept alongside other study data on the UEA filestore.

Full data will be deleted in line with CPRD requirements twelve months after extraction (or later should this be required and negotiated with CPRD).

6.3 Workstream 2 – Clinical Study data

Anonymised data from each study will be transmitted to the study team and will be held on the UEA filestore for analysis. Harmonised or derived datasets will be held for at least ten years alongside the source code used in their generation.

7 Study administration

7.1 Safeguarding of patient's interests

This study will rely on the analysis of anonymised data collected for research. We will not receive any patient identifiers, will securely store this data and screen outputs to ensure that no possible identification of participants could take place through for example small cell counts in tables. As such there are no potential harms to patients associated with this study.

7.1.1 CPRD (Clinical Practice Research Datalink)

CPRD only release data upon approval of a full study protocol by the Independent Scientific Advisory Committee (ISAC), an independent expert advisory body established by the Secretary of State to advise on research related requests for data.

The CPRD Group has obtained National Research Ethics Committee (NRES) approval for all observational medical and health research studies undertaken using the CPRD database. ISAC review

ensures that studies using the CPRD are of an appropriately high scientific standard and fit within CPRDs remit of medical and health research.

7.1.2 Clinical Study Data

Each of the studies from which we will use data we will use in WP2 was collected for research, and access to this data has been confirmed by representatives from the respective studies. Each study has appropriate ethical approval.

The relevant Regional Committee of Ethics (South-East A) in Norway has approved our application to receive and use REDIC data for the purpose of this study.

ADCS steering group has approved the use of their data for our research, and confirmed that their expectation is that findings from ADCS studies will be published.

7.2 Protocol registration and transparency

Before the start of workstream 1 analysis phase we will submit a protocol to the ENCePP (European Network of Centres for Pharmacoepidemiology and Pharmacovigilance; www.encepp.eu) to ensure that our research plan is transparent and that our results can be compared to the original protocol.

7.3 Day to day management of the study

Day to day management of the study will be coordinated by the study manager.

A management group will meet every two months or an *ad hoc* basis if needed to resolve day to day issues.

A steering group will meet four times during the course of the study.

7.4 Timelines

The study will begin on 1 June 2016 and continue 30 Jun 2018. Full details are attached as an appendix.

7.5 User involvement in the study design and in ongoing study development

In developing this proposal we worked with the Alzheimer's Society Research Network Volunteers and have met with a Patient and Public Involvement (PPI) panel from INSPIRE, a group of adults and older people with interest and experience relevant to mental health research (http://www.nsft.nhs.uk/Getinvolved/Pages/research.aspx).

PPI will help us to understand the motivation for seeking treatment, the ways in which Zs are used, the perceptions of benefits and harms of Zs, outcomes of interest to patients and carers and with how we should disseminate our findings to this group.

We will engage a local PPI advisory group of people affected by dementia (recruited from INSPIRE members) to get a broad spectrum of opinion and experience. Two members of this group will join our steering group to represent these views while contributing to the finalisation of analysis plans, study protocol and dissemination activity.

8 Dissemination

Our dissemination plan is designed to reach all relevant stakeholders to inform the policy debate around medication prescribing in dementia. This will include peer reviewed academic papers, conference presentations and presentations and outputs targeting stakeholder groups.

The full dissemination plan will be designed by the research team with input from the steering group and advisory groups during the course of the study.

Our sleep disturbance validation study will also be published to strengthen future work on sleep disturbance and dementia within CPRD.

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Appendix 1 – ZED Study timelines

	Phase	PHASE 1 - pre-star					PHASE 2 - Data collectior							PHASE 3 - Analysis													4 - Dissem		
	Project Month	-5	-4	-3	-2	-1	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24	25
	Calendar Month	Jan-16	Feb-16	Mar-16	Apr-16	May-16	Jun-16	Jul-16	Aug-16	Sep-16	Oct-16	Nov-16	Dec-16	Jan-17	Feb-17	Mar-17	Apr-17	May-17	Jun-17	Jul-17	Aug-17	Sep-17	Oct-17	Nov-17	Dec-17	Jan-18	Feb-18	Mar-18	Apr-18	May-18	Jun-18
Administration / meetings	Job description and advert for RA written	x																												
	Job description and advert for administrator		x																											
	RA post advertised		x																											
	Administrator post advertised			x																										
	RA/administrator interviewed / recruited				x																									
	RA starts										x																			
	Research fellow on maternity leave										x	x	x	x	x	x	x													
	UEA application for ethics approval		x	x																										
	All ethical approvals and permissions				x																									
	Project protocol written and documents				x	x																								
	Recruit PPI steering group members, PPI advisory group and healthcare professional		x	x				x																						
	Advisory group meet to discuss protocol						x																							
	Steering group agree protocol ahead of ISAC							x																						
	Steering group approve GP questionnaires																		x											
	Steering group meeting ahead of analysis													x																
	Steering group comment on early RCT																			x										
	Steering group comment on early CPRD																				x									
	Steering group approve RCT manuscripts																										x			
	Steering group approve CPRD manuscript																											x		
	Advsiory group meeting 2 - dissemination																											x		
	Steering group meeting ahead of																												x	
RCT data analysis	Collect RCT data				x	x	x					x																		
	RA training course																					x								
	Search for new RCTs											x	x																	
	Update RCT analysis protocol/analysis plan													x																
	Collect new RCT data														x	x														
	Code, clean and compile data																x	x	x											
	RCT data analysis																		x	x	x	x	x	x						
	Write publication(s)																								x	x	x	x		
	Submit publication(s)																												x	
CPRD analysis	Prepare CPRD ISAC protocol		x	x	x	x	x	x																						
	Submit CPRD ISAC protocol								x	x																				
	ISAC protocol approved									x																				
	Describe and extract data											x																		
	Aim 1 - Code, clean and compile data											x	x	x	x															
	Aim 1 - CPRD data analysis															x	x	x	x											
	Aim 1 - Write publication																			x	x	x	x							
	Aim 1 - submit publication																							x						
	Aim 2 - Code, clean and compile data																	x	x	x	x	x								
	Aim 2 - Collect HES data																		x											
	Aim 2 - CPRD data analysis																				x	x	x	x	x	x				
	Write publication																										x	x	x	
	Submit publication																													x
	Contact CPRD regarding GP questionnaires		x				x																							
	Draft GP questionnaires				x		x	x																						
	Get ISAC questionnaire approval																		x											
	Mail questionnaires																			x										
	Receive responses																				x									
	Analyse questionnaire responses																					x								
Dissemination	Preparation of interm reports										x	x						x	x											
	Preparation of findings report																									x	x	x	x	
	Dissemination event (London)																												x	
	Webinar																												x	
	Final Report Write-up and submission																												x	x