Summary Table of Study Protocol

[This information is to be provided in a table on the title page of the study protocol. If any of the categories do not apply enter "NA".]

Title	*Persistence and compliance to anti-osteoporosis medications in the United Kingdom using the Clinical Practice Research Datalink (CPRD)*
Protocol version identifier	**20160192**
Date of last version of the protocol	*29th March 2017*
EU Post Authorisation Study (PAS) Register No	*NA*
Active Substance	Denosumab
Medicinal Product	Prolia
Product Reference	AMG162
Procedure Number	NA
Marketing Authorisation Holder(s)	Amgen Inc
Joint PASS	No
Research Question and Objectives	To assess the persistence and compliance of osteoporosis medications in postmenopausal women in the UK (period 2010-2015) including oral and parenteral therapies
Country(-ies) of Study	UK
Author	[redacted]

Marketing Authorisation Holder

Marketing authorisation holder(s)	Amgen B.V.
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Investigator's Agreement

I have read the attached protocol entitled Compliance and persistence to anti-osteoporosis medications in the United Kingdom using the Clinical Practice Research Datalink (CPRD) dated 22 September 2016, and agree to abide by all provisions set forth therein.

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- *my Subinvestigators (including, if applicable, their spouses [or legal partners] and dependent children)*

at the start of the study and for up to 1 year after the study is completed, if there are changes that affect my financial disclosure status.>>

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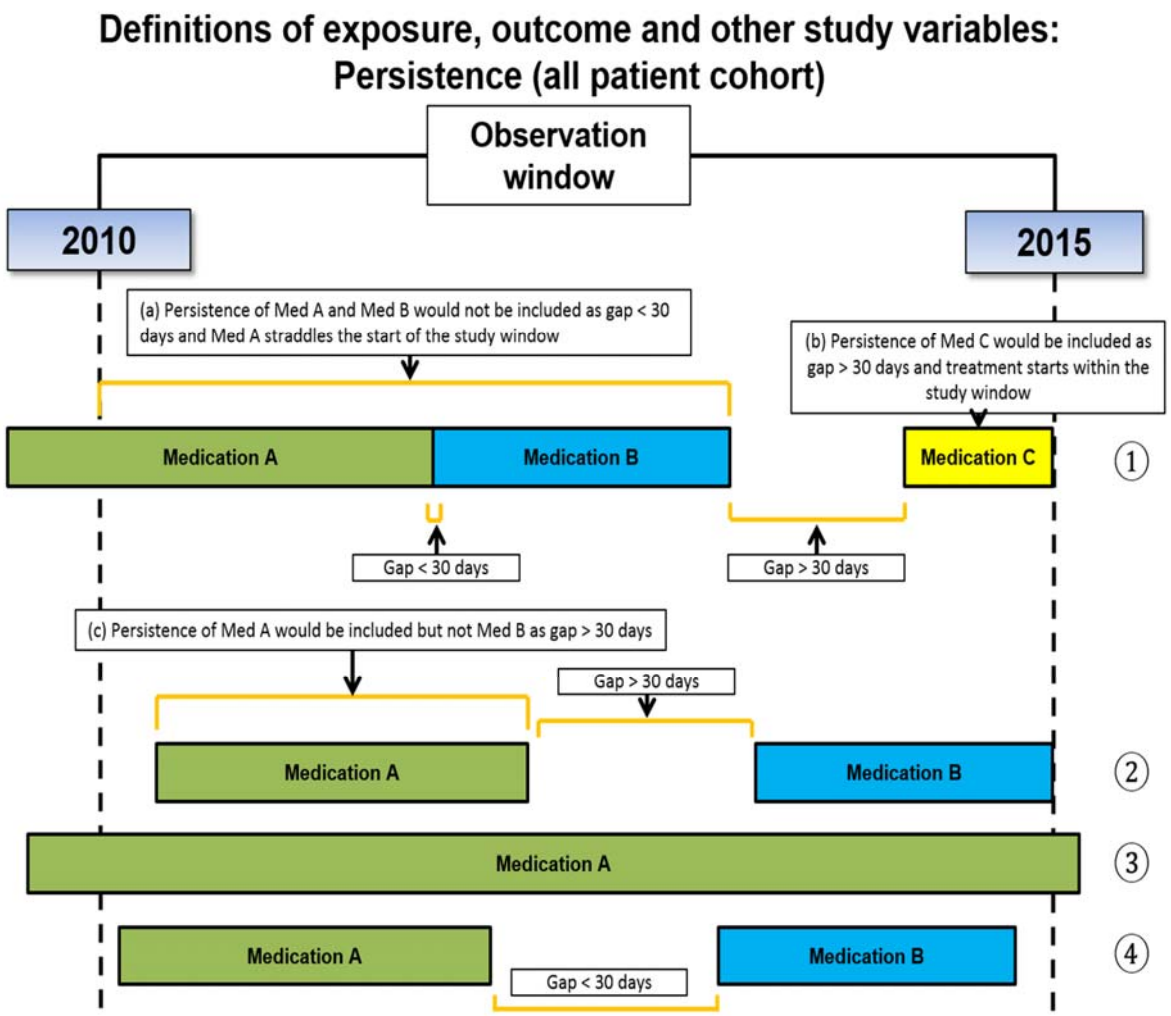
Signature	
Name of Investigator <<*Coordinating Investigator>>*	Date (DD Month YYYY)

Study Design Schema (1st January 2010 – 31st December 2015)

Three different schema as presented here, to show each cohort that will be evaluated.



(a) All patient cohort

Here we are evaluating the persistence overall by patient i.e. how long on average do they remain on treatment – the analysis is not by medication, but by patient. We are trying to ascertain the patient characteristics of those that persist on therapy irrespective of the medication that they are on.

Scenarios

Scenario 1:

a) Evaluating persistence on this patient is based starting therapy within the study window. Therefore for medication A which crosses over 2010 (i.e. was started prior to study window) and because the gap between Medication A and B is < 30 days then persistence for these is ignored.

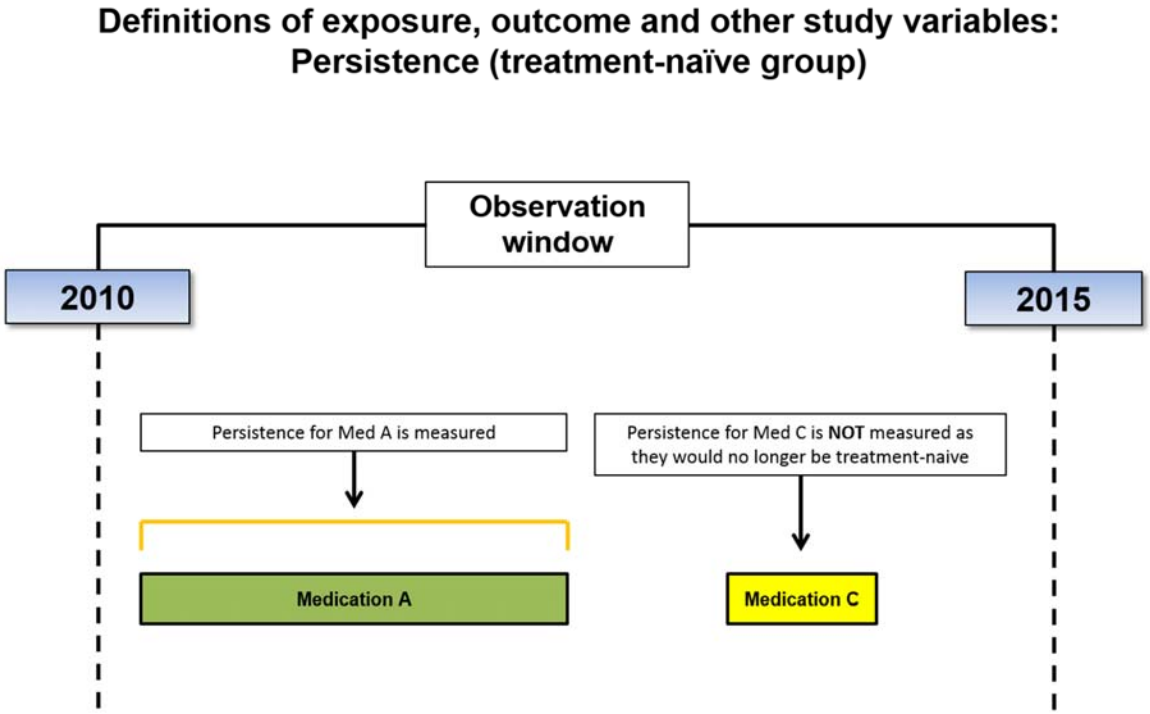
b) If the gap in between therapies is > 30 days, then persistence for Medication C would be included.

Scenario 2:

c) Persistence in this patient is measured as in observation window. As the treatment gap in this example is > 30 days, the persistence is calculated using medication A and medication B would be omitted.

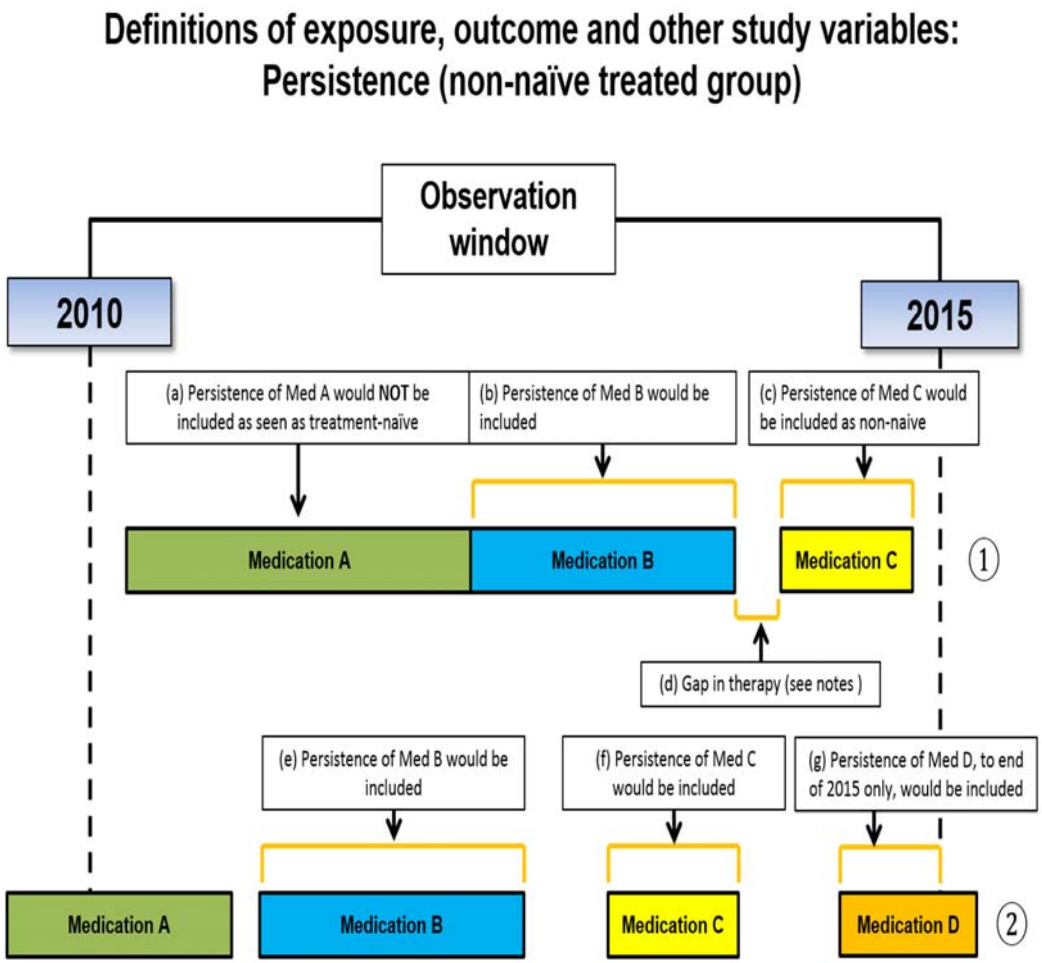
Scenario 3: Persistence for Medication A, would not be calculated as it would have been started prior to study window.

Scenario 4: Persistence for medication A and medication B would be measured as both started in the study window with a gap < 30 days



(b) For the treatment-naïve group:

Persistence measured for Medication A as initiated during the observation window and stopped in observation window. Medication C would not be measured as they would have already received a prior medication (i.e. Medication A) and therefore would not be termed as treatment-naïve



(c) For the non-naïve treated group:

Scenario 1:

a) Persistence measured for Medication A would not be included as this is seen as a naïve-treatment period.

b) Persistence measured for Medication B, as initiated during the observation window and stopped in observation window. Furthermore, the patient would be non-naïve and be included on this basis

c) Persistence measured for Medication C, as initiated during the observation window as non-naïve treated.

d) If there is a gap in therapy of less than 30 days, then the persistence of Medication B would be measured and then the persistence of Medication C

Scenario 2

e) Persistence of Medication B would be measured as non-naïve treated and within the observation window

f) Persistence of Medication C would be measured as non-naïve treated and within the observation window gap?

g) Persistence of Medication D would be measured as non-naïve treated but only up until the end of the observation window (i.e. 31st Dec 2015) and not beyond this gap

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2. List of Abbreviations

Abbreviation/acronym	Definition
SERM	Selective Estrogen Receptor Modulator
Persistence	The accumulation of time from treatment initiation to discontinuation of therapy.
Refill Compliance	The extent to which a patient acts in accordance with the prescribed interval, and dose of a dosing regimen. This is specific to refill compliance where only the act of refilling the prescription is evaluated.
BMD	Bone Mineral Density
BMI	Body Mass Index
DXA	Dual X-ray Absorptiometry
FLS	Fracture Liaison Service
GI	Gastrointestinal
GP	General Practitioner
CPRD	Clinical Practice Research Datalink
HRT	Hormonal Replacement Therapy
MHRA	Medicines and Healthcare Product Regulatory Agency
NHS	National Health Service
NIHR	National Institute for Health Research
PPI	Proton Pump Inhibitor
PTH	Parathyroid Hormone
RANKL	Receptor Activator of Nuclear Kappa B

3. Responsible Parties

Amgen Ltd

4. Abstract

Study Title: Persistence and compliance to anti-osteoporosis medications in the United Kingdom using the Clinical Practice Research Datalink (CPRD)

Indication: Postmenopausal osteoporosis

Study Background and Rationale: Whilst the efficacy of osteoporosis therapies has been demonstrated in multiple randomised clinical trials, poor persistence and compliance to these therapies in the 'real-world' still remains a particular problem for patients who receive them. In the UK, a number of studies have evaluated compliance and persistence of anti-osteoporotic therapies. However, the focus has been on commonly prescribed oral bisphosphonates, specifically alendronate and risedronate. All

of these studies utilize study periods (up until the end of 2006) where newly introduced medications including ibandronate, zoledronate, denosumab and strontium ranelate (where the dose frequency and mode of administration vary from the traditional bisphosphonate therapy) could not be evaluated.

Study Objectives:

Primary Objective

To estimate persistence and refill compliance to osteoporosis therapies (both oral and parenteral) in a real-world setting over 6, 12, 18, 24 month follow-up periods in postmenopausal women.

Secondary Objectives

To estimate persistence and refill compliance to osteoporosis therapies (both oral and parenteral) in a real-world setting over 6, 12, 18, 24 month follow-up periods in postmenopausal women who are treatment-naïve and also in those who are non-naïve treated.

Exploratory Objectives

- To describe persistence of denosumab and oral bisphosphonates over 6, 12, 18, 24 months, 3 and 5 years in postmenopausal women
- To describe persistence of denosumab and oral bisphosphonates by dosing frequency (i.e. daily, weekly, monthly) over 6, 12, 18, 24 months, 3 and 5 years in postmenopausal women
- To describe persistence of denosumab and IV bisphosphonates over 6, 12, 18, 24 months, 3 and 5 years in postmenopausal women
- To describe demographic and clinical characteristics in relation to the estimated levels of persistence and refill compliance to osteoporosis therapies (both oral and parenteral) in postmenopausal women
- To describe changes in persistence at key regulatory changes for selected osteoporosis medications

Hypothesis(es)/Estimation: The study will be descriptive in nature with no formal hypothesis being tested. The aim is to provide statistical estimates of persistence and refill compliance along with 95% confidence intervals.

Study Design/Type

A retrospective database analysis of the Clinical Practice Research Data link (CPRD) to evaluate the persistence and compliance of osteoporosis therapies between 2010-2015.

Study Population or Data Resource: The study will be conducted using primary care medical records data from the CPRD database in the UK between the 1st January 2010 to 31st December 2015. The CPRD covers approximately 11.3 million patients from 674 practices in the UK are included in the database. *(Herrett 2015)*

Index date: An index date will be identified for each cohort of interest. It will be defined as the first day of osteoporosis therapy within the observational window determined by the definition for the cohort. A subject's index date will vary depending on the cohort of interest.

Summary of patient Eligibility Criteria: Patients who meet all of the following characteristics will be eligible for inclusion in the study:

Inclusion criteria:

- Women aged 50 years and over or women aged under 50 experiencing a premature (incl. surgery-induced) menopause and who receive at least one prescription for any licensed osteoporosis therapy * on or after January 1st 2010.

***** Osteoporosis therapy includes:

- Oral bisphosphonates (e.g. risedronate, alendronate, ibandronate, etidronate)
- Parenteral bisphosphonates (e.g. zoledronate, ibandronate)
- Selective oestrogen receptor modulators (SERMs; e.g. raloxifene)
- Parathyroid hormone (e.g. teriparatide, 1-84 PTH)
- Strontium ranelate
- Denosumab

Subjects taking or about to take calcium and/or vitamin D (singly or in combination) and HRT or related molecules such as tibolone or sex steroid derivatives are not eligible if these are taken as a sole therapy for the treatment of osteoporosis. However, if these are taken in combination with one of the included therapies then the subject is eligible for the study.

Exclusion Criteria:

- History of cancer (except non-melanoma skin cancer) before or on the index date
- Metabolic bone disease (including rickets or osteomalacia, hyperparathyroidism, and Paget's disease of bone) before or on the index date.
- Less than 12 months of medical history in the CPRD before the index date
- Less than six months of medical records in the CPRD after the index date

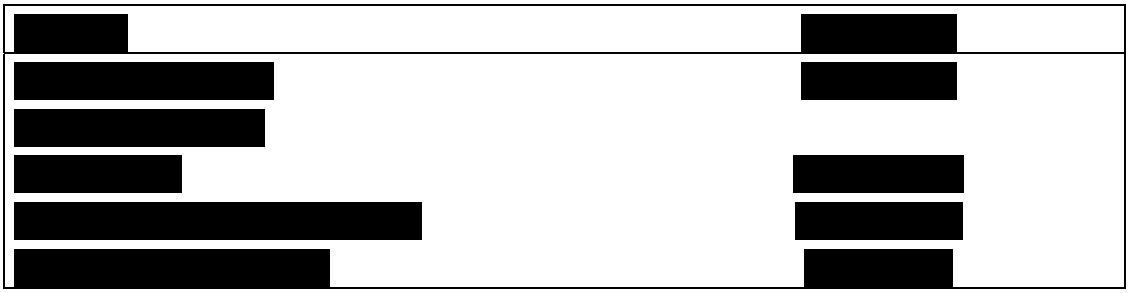
Sample Size

The sample size for the study is estimated to be approximately 60000 patients initiating osteoporosis therapy during the period of 2010 to 2015. As such, the available sample size should be large enough to allow estimation with a good precision for the estimation of overall persistence and refill compliance to osteoporosis therapies as well as within the targeted cohorts treatment naïve and non-naïve treated. Assuming that the expected rate is 50%, the maximum half width will vary from 5% when the sample size is approximately 390 to less than 1% when the sample size is approximately 10,000 or larger.

Statistical Considerations

Analyses supporting the primary and secondary objectives will describe persistence and compliance among patients starting and finishing any new osteoporosis therapy during 2010-2015. Outcomes will be assessed for the entire study population and separately, for the cohorts of interest, treatment naïve and non-naïve treated patients. Persistence and compliance with osteoporosis therapies will be assessed over 6, 12, 18, 24 months, 3 and 5 years of follow-up. All summaries of the data will be descriptive in nature. For categorical variables (including the primary outcome measure), the frequency and percentage, with 95% confidence interval, will be given. Summary statistics for continuous variables will include the number of subjects, mean, median, standard deviation or standard error, 25th percentile (Q1), 75th percentile (Q3), minimum, and maximum. Time to non-persistence will be performed using Kaplan-Meier methodology.

5. Milestones



[redacted] Rationale and Background

Persistence

Persistence is defined as “the duration of time from initiation to discontinuation of therapy.” Persistence is often presented as the number of days on treatment, or as the percentage of the cohort still on treatment at the end of a specified time frame (e.g. one year). *(Cramer 2008)* Low persistence with prescribed medication regimens is regarded as a major problem in the treatment of many illnesses, *(Vermiere 2001)* especially chronic diseases *(Lam 2015, Iglay 2015)* including osteoporosis. *(Compston 2006, Karlsson 2015, Li 2012)* Numerous studies have shown that up to 50% of patients drop out of treatment of osteoporosis during the first year. *(Li 2012, Cramer 2006)*

The consequence of low persistence is increased morbidity and mortality since patients fail to receive the drug benefit and this can lead to a greater risk of osteoporotic fracture. *(Siris 2009, Huybrechts 2006, Imaz 2010, Choddick 2016)* Furthermore, an analysis from the Clinical Practice Research Datalink (CPRD) (period between 2000-2007), has shown that in patients with poor persistence, there was a trend towards an increase in healthcare resource utilisation and higher fracture rates, compared with those that had longer persistence. *(Ferguson 2015)*

The determinants of low persistence with treatment of osteoporosis are not very well understood. Studies suggest that multiple factors are involved with adherence to medications, including but not limited to: special and complex dosing requirements, healthy adherer bias, medication dosing interval, cost of medication, drug-related side effects, the patient-physician relationship, depression and difficulties for patients to detect improvements in a disease that is largely asymptomatic. *(Lindsay 2016, Silverman 2010)* A previous analysis from the CPRD published in 2015 (covering the period 1993-2008) also showed that patient characteristics significantly associated with switching or discontinuation of therapy included age, occurrence of fracture,

glucocorticoid use, renal failure, liver disease, chronic obstructive pulmonary disease (COPD), gastrointestinal disease, heart disease, anticonvulsant use, and duration of osteoporosis. *(Feudjo-Tepie 2015)*

Retrospective investigations of persistence, like the one proposed in this study, utilize databases made up of patient records. These studies can be less expensive, and can also be less accurate than prospective data collection. In addition, there is an absence of prescription data for patients treated in secondary care. Determining persistence on basis of prescription records is not ideal because there is no information available whether the patient actually has consumed the drug. However, it can be assumed that patients would not continue to refill a prescription without the intention to continue to administer the medication. *(Dezii 2001)* Although persistence is fairly straightforward to quantify in a retrospective manner employing the second stated definition above, there are measurement problems with this notion.

The first problem concerns temporary versus permanent discontinuation of treatment. A patient may stop taking treatment temporarily, for say one month, but then continue to collect their medication. To determine which patients are to be regarded as persistent, the maximum allowed length of break from treatment, known as "grace period" *(Dezii 2001)* or "gap" *(Peterson 2007)*, must be specified. Not surprisingly, the length of the grace period will have a large impact on the estimated levels of persistence. The length of the grace period will be inversely related to the estimated medication possession ratio (MPR) in persistent patients since patients will be considered non-compliant rather than non-persistent if a longer grace period is adopted. *(Dezii 2001)*. Studying persistence is contingent on that the patient has initiated the treatment within the study period. The sample will otherwise contain patients that have been on treatment longer than perceived. Thus, a "washout period" is needed.

Compliance

Medication compliance refers to the extent the patient acts according to medical or health advice *(Cramer 2008)*. It incorporates many aspects of the relationship between the patient and health care in general, such as if the patient seeks medical care in time, participates in health care programs, and so forth. In the context of medical treatment of osteoporosis, compliance reflects how well patients take their medication as prescribed (i.e. according to treatment recommendations). *(Seeman 2007)* Naturally, treatment recommendations are different for different drugs, but can for example include the need

to fast overnight or to take the medication with water. It has been argued that poor compliance, together with low persistence, is the "Achilles heel" *(Seeman 2007),* of osteoporosis treatment.

Studies have shown that around 30% to 50% of patients fail to take their medication as directed. *(Cramer 2005)* The reduced efficiency of the treatment related to poor compliance is accompanied by increased morbidity costs due to, for example, a greater incidence of fractures. Poor compliance is therefore regarded a major public health issue, placing a significant economic burden on the health care sector. *(Vermiere 2001, Choddick 2016, Ferguson 2015)* The most common barriers include age, prior history of fracture, dosing frequency, and concomitant use of other medications. Other factors involved in maintaining osteoporosis therapy include the special dosing requirements, adverse events, low motivation due to the asymptomatic nature of the disease, and the physician-patient relationship. *(Silverman 2010)*

Investigating compliance is not an easy task. *(Vermiere 2001)* In retrospective studies, compliance is quantified as the number of days of medication available to the patient divided by the total number of days of medication prescribed. This measure is usually termed "medication possession ratio" (MPR). *(Cramer 2008)* This simplified measure is obviously far from perfect, since the definition does not assess if the patient takes the medication. Nonetheless, in the absence of a valid measure and to maintain consistency and comparability between studies of compliance of treatment of osteoporosis, the MPR will be used in this retrospective study specifically in relation to oral therapies.

Although MPR is a widely used measure for adherence of oral medication, there is limited information measuring MPR with injectable agents. *(Shi et al, 2007)*. Injectable agents, typically have a longer duration of effect and are more likely to be administered by a healthcare professional rather than the patient. This would then impact persistence and adherence to the medication, as deviations from dosing instructions would be reduced. *(Hadji 2015)*

Furthermore, the medication possession ratio (MPR; proportion of days for which a patient has an adequate supply of the medication over a defined time period) cannot be assessed for injectable agents, because the patient is covered therapeutically for a specific amount of time. Instead, the medication coverage ratio (MCR) can be calculated, which measures the percentage of days that the patient was covered by an injectable agent over a given time interval after receiving the injection. *(Hadji 2015)*

6.1 Diseases and Therapeutic Area

Osteoporosis is a systemic skeletal disorder characterized by low bone mass and micro-architectural deterioration of bone tissue, leading to enhanced bone fragility and consequent susceptibility to fracture. *(NIH consensus document 2001)* It most commonly occurs in postmenopausal women owing to a loss of oestrogen around and after the menopause. This leads to accelerated bone loss and is exacerbated by further age related bone loss, and other conditions or therapies that exacerbate bone loss and reduce bone quality. *(Drake 2015)* Osteoporosis is considered a “silent disease” until a fracture occurs.

Fractures as a result of osteoporosis are one of the most disabling consequences of aging in women since they are associated with significant morbidity and mortality and a reduction in quality of life. *(Hernlund 2013)* Across the EU, at the age of 50 years, the remaining lifetime probability of women or men experiencing a hip, spine, or wrist fracture is estimated at 46% and 22% respectively. *(Hernlund 2013)* The impact of fractures as a result of osteoporosis is far-reaching not only for the individuals themselves, but for the health service, economy, and population as a whole. *(Hernlund 2013)*

There are several effective pharmacological interventions approved for use in both men and women with osteoporosis, including bisphosphonates, strontium ranelate, selective oestrogen receptor modulators (SERMs), parathyroid hormone peptides and receptor activator of NF-κB (RANKL) inhibitors. Most have shown efficacy in preventing or treating osteoporosis in men and women to reduce the risk of fracture resulting from osteoporosis. As part of effective pharmacological interventions, adherence to such regimens is necessary to achieve the full potential benefit. *(Hernlund 2013)*

6.2 Rationale

Despite the efficacy of pharmacological therapies demonstrated in clinical trials, poor compliance and persistence in the ‘real-world’ are particular problems for patients who receive treatment for osteoporosis. *(Iglay 2015)* For example, a significant number of patients who receive treatment fail to remain on treatment for >1 year, *(Li 2010)* in part due to side effects of available medications, difficulties taking the medications (such as complicated dosing requirements for bisphosphonates), or in relation to characteristics of osteoporosis itself which remains asymptomatic for long periods. *(Silverman 2010)* Failure to follow treatment guidelines not only leaves patients exposed to a higher risk of

fracture as a result of osteoporosis *(Siris 2009)* but also is associated with significant healthcare costs *(Choddick 2016, Ferguson 2015)*. Consequently, strategies to improve compliance and persistence with treatment together with lifestyle changes must be considered from the start.

Several studies have investigated the level of adherence in treatment of osteoporosis, in particular treatment with oral bisphosphonates. *(Choddick 2016)* The share of patients persisting with therapy (either daily or weekly) for one-year range between approx. 46% to 80% and the average level of compliance (MPR) have been estimated to lie between 60% and 70%. *(Choddick 2016)*

In addition, some patients end up 'cycling' through multiple osteoporosis therapies and this can affect persistence still further. In some studies this has meant that after therapy initiation the duration of use can range from only 56 days on therapy to 184 days. *(Li 2014, Choddick 2016)* The variability in the results is likely attributed to different assumptions regarding the notions of persistence and compliance, different statistical methods employed and different populations studied. Even so, persistence to osteoporosis therapies remains poor.

In the UK, a number of studies have evaluated compliance and persistence of anti-osteoporotic therapies using database analyses. *(Brankin 2006, Gallagher 2008, Li 2012, Li 2014).*

Brankin et al evaluated bisphosphonate therapies including alendronate and risendronate from 2001 to 2005 assessing the difference in compliance and persistence between weekly and daily regimens across three different UK datasets. *(Brankin 2006)* Results from the GPRD [CPRD] dataset showed that those on weekly regimens had a higher compliance (MPR) than those on daily regimens (GPRD [CPRD] 76.2%, 95% CI, 75.4–77.0 vs. 63.5%, 95% CI 61.2–65.8; $p < 0.0001$) and persisted longer with treatment (GPRD 249 days, 95% CI 246–253 vs. 208 days, 95% CI 199– 217; $p < 0.0001$).

A second study using the GPRD by Gallagher et al evaluated the persistence of bisphosphonate therapy including alendronate and risedronate from 1987 to 2006. *(Gallagher 2008)* Results showed that 58.3% of the patients continued bisphosphonate treatment for >1 year and 23.6% for > 5 years. A third study by Rietbrock et al using data from GPRD [CPRD], modelled the 1-year persistence for weekly bisphosphonate and found in the model it was 56.7% with a 3-year persistence of 35.3%. *(Rietbrock 2009)*

Finally a study by Li et al using data from the UK CPRD over the period (1995-2008)

found that persistence to osteoporosis therapies was still poor. *(Li 2012)* Approximately 18% of daily alendronate users were persistent at one year, with a similarly poor rate of around 41% of weekly alendronate users being persistent after this time. By three and five years of follow up non-persistence rates were over 90% for most of the osteoporosis therapies studied. *(Li 2012)*

One way of improving persistence and adherence to osteoporosis treatment is by the use of parenteral therapies. As these have a longer duration of action, this should reduce the dependency on taking a tablet every day or week, and thereby improve adherence and persistence. *(Hadji 2015)*

Denosumab was approved in the UK for use in postmenopausal women with osteoporosis in in 2010. It is a fully human monoclonal antibody with affinity and specificity for RANK ligand (RANKL), an important factor for the formation, function and survival of osteoclasts. *(Lacey 2012)*

Since this date, persistence studies with denosumab have been published in the literature including the crossover-designed clinical trial (DAPS) from the USA *(Freemantle 2012)*, a prospective observational trial from the USA and Canada *(Silverman 2015)*, a retrospective database study from Germany *(Hadji 2016 GRAND-4)*, a patient-support program analysis from Canada *(Papaioannou 2015)*, a prescription-base database analysis from the Czech republic *(Fuksa 2015)*, and Sweden *(Karlsson 2015)* and a retrospective longitudinal database study from Hungary *(Lakatos 2016)*.

In these studies, 12 month persistence data for denosumab ranged between 55.9 – 90.5% and at 24 months between 34.8 – 92.5%. *(Freemantle 2012, Silverman 2015, Hadji 2016, Papaioannou 2015, Fuksa 2015, Karlsson 2015, Lakatos 2016)*

Conversely, for parenteral therapies and for oral BPs persistence at 12 months (where reported) ranged between 33.8 – 74.5% and 10 – 78%. *(Freemantle 2012, Hadji 2016, Karlsson 2015, Lakatos 2015)* At 24-months persistence ranged between 20.9 – 35.8% for parenteral therapies and between 15.9 – 63.5% for oral therapies. *(Freemantle 2012, Hadji 2016, Karlsson 2015, Lakatos 2015)*

Therefore, an analysis which is specific to the UK, using more recent data from the CPRD (period 2010-2015) which includes persistence data with denosumab and other parenteral therapies would be of benefit for prescribers to identify those patients that receive denosumab and identify ways in which persistence to therapies could be improved.

The variability in the results is likely attributed to different assumptions regarding the notions of persistence and compliance, different statistical methods employed and different populations studied. The studies are therefore not necessarily comparable. For example, the Denosumab Adherence and Persistence study (DAPS) may overestimate the persistence and adherence rates for alendronate on the basis that patients are in a clinical trial and hence would be followed more rigorously. It is known that when applied in the “real-world” setting outside of controlled clinical trials, persistence is much worse. *(Li 2012)* The analyses of these databases also vary owing to differences in grace periods for discontinuation of therapy. Ultimately, most studies with oral bisphosphonates show poor persistence at 1- or 2-years post therapy initiation.

The commonality of the studies evaluating compliance and persistence in UK data sources has focused on commonly prescribed bisphosphonates, specifically alendronate and risedronate. All of these studies utilize study periods (up until the end of 2006) where newly introduced medications including ibandronate, IV ibandronate, strontium ranelate, denosumab and IV zoledronate (where the dose frequency and mode of administration vary from the traditional bisphosphonate therapy) could not be evaluated.

Furthermore, the introduction of fracture liaison services (FLS) in the management of osteoporotic patients, both in the primary and secondary care settings, could also influence persistence and adherence to anti-osteoporosis therapies. In an FLS facilities audit recently completed by the Royal College of Physicians, it was shown that 82% (23 of 28 replies) of FLSs surveyed included medication adherence as part of their initial evaluation and re-evaluation of patients. However, there are two important aspects to consider:

(1) Services which delegate monitoring to primary care, means that follow up of these patients becomes more difficult

(2) Most FLSs (51%; 14/28) perform one evaluation around 6 months after therapy is initiated, but then fewer continue this to 12 months (39%; 11/28) *(FLS-DB audit report 2016)*

Therefore, the introduction of FLSs, whilst mainly based in secondary care, may have also influenced persistence with therapies within the primary care setting. *(FLS-DB audit report 2016)* Moreover, the introduction in April 2012 of a Quality Outcome Frameworks (QoF) domain for secondary fracture prevention within primary care, might also be expected to improve persistence.

Health economic evaluations based on mathematical models are commonly used to compare alternative treatment strategies in osteoporosis to support decision-makers and to provide information to treatment guidelines. *(Hiligsmann 2015)* The estimates of treatment effect employed in such economic evaluations are usually based on the efficacy results from randomized clinical trials (RCTs), and the efficacy observed therefore incorporates the adherence of the trial population. The benefits of treatments that offer better adherence in a real-world setting may be underestimated in cost-effectiveness models if the comparisons are based on clinical trial data.

To be able to include an adherence argument in modelling it is necessary to produce the necessary data to populate models and support modelling assumptions. *(Hiligsmann 2012)* A more accurate estimate of persistence and compliance will allow simulations of treatment and disease patterns that better reflect clinical practice. Additionally, more reliable data on persistence and compliance will support the overall argument of taking these treatment patterns characteristics into account in health economical evaluations.

The study outlined in this protocol will satisfy local data requirements and health economic model input needs. It will provide estimates of persistence and refill compliance with newer oral and parenteral medications, and try to characterise patients with prior fracture and co-morbidities to assess whether this affects persistence and compliance over the period of this study.

6.3 Statistical Inference (Estimation or Hypothesis[es])

The study is purely descriptive in nature with no formal hypothesis being tested. The study will provide an estimation of the proportion of patients who are persistent and compliant during the follow-up period. Point estimates and 95% confidence intervals will be provided. The sample size of the study will also allow sufficiently precise estimates to be obtained within each cohort of interest.

7. Research Question and Objectives

7.1 Primary Objective

To estimate persistence and refill compliance to osteoporosis therapies (both oral and parenteral) in a real-world setting over 6, 12, 18, 24 month follow-up periods in postmenopausal women.

7.2 Secondary Objectives

To estimate persistence and refill compliance to osteoporosis therapies (both oral and parenteral) in a real-world setting over 6, 12, 18, 24 month follow-up periods in

postmenopausal women who are treatment-naïve and also in those who are non-naïve treated.

7.3 Exploratory Objectives

- To describe persistence of denosumab and oral bisphosphonates over 6, 12, 18, 24 months, 3 and 5 years in postmenopausal women
- To describe persistence of denosumab and oral bisphosphonates by dosing frequency (i.e. daily, weekly, monthly) over 6, 12, 18, 24 months, 3 and 5 years in postmenopausal women
- To describe persistence of Denosumab and IV bisphosphonates over 6, 12, 18, 24 months, 3 and 5 years in postmenopausal women
- To describe demographic and clinical characteristics in relation to the estimated levels of persistence and refill compliance to osteoporosis therapies (both oral and parenteral) in postmenopausal women
- To describe changes in persistence at key regulatory changes for selected osteoporosis medications
- To estimate persistence and refill compliance to osteoporosis therapies (both oral and parenteral) in a real-world setting over 3 and 5 years follow-up periods in postmenopausal women.
- To estimate persistence and refill compliance to osteoporosis therapies (both oral and parenteral) in a real-world setting over 3 and 5 years follow-up periods in postmenopausal women who are treatment-naïve and also in those who are non-naïve treated.

8. Research Methods

8.1 Study Design

The study will be a retrospective database analysis based on data from the CPRD (for description see section 9.2) over the period 2010-2015 in postmenopausal women in the UK.

The data are collected from general practitioners and comprise a representative sample of the UK population. The database contains information on patient demographics, all outpatient medications received, diagnoses and symptoms, laboratory test results,

clinical details such as information on height, weight, smoking, and alcohol and drug abuse. The database does not contain information on diet and exercise. Smoking and BMI data are available in around 95% and 80% of patients respectively.

An index date will be identified for each cohort of interest. It will be defined as the first day of osteoporosis therapy within the observational window determined by the definition for the cohort. A subject's index date will vary depending on the cohort of interest.

8.2 Setting and Study Population

This study will be conducted using data from the UK Clinical Practice Research Datalink (CPRD). The CPRD is a dedicated multi-disciplinary team based at the Medicines & Healthcare products Regulatory Agency (MHRA) in London. It is a joint venture between the MHRA and National Health Service (NHS) National Intitute for Heath Research (NIHR). The CPRD takes on all the original work of UK General Practice Research Datatbase (GPRD) and the NIHR Research Capability Programme Pilots.

The CPRD is a longitudinal database of anonymised medical records from primary care, with coverage of over 11.3 million patients from 674 practices in the UK.

With 4.4 million active (alive, currently registered) patients meeting quality criteria (a combination of the "acceptable patient metric" and "up to standard [UTS] date", *(Herrett 2015)*), approximately 7% of the UK population are included and patients are broadly representative of the UK general population in terms of age, sex and ethnicity. General practitioners are the gatekeepers of primary care and specialist referrals in the UK. The CPRD primary care database is therefore a rich source of health data for research, including data on demographics, symptoms, tests, diagnoses, therapies, health-related behaviours and referrals to secondary care. For over half of patients, linkage with datasets from secondary care, disease-specific cohorts and mortality records enhance the range of data available for research. The CPRD is very widely used internationally for epidemiological research and has been used to produce over 1500 research studies, published in peer-reviewed journals across a broad range of health outcomes. However, researchers must be aware of the complexity of routinely collected electronic health records, including ways to manage variable completeness, misclassification and development of disease definitions for research. *(Herrett 2015)*

8.2.1 Study Period

The study period will consist of a 5 year observational period between 1st January 2010 to 31st December 2015 inclusive. The index date will be considered as the first day of

the osteoporosis therapy of interest within the observational window and will vary for a subject depending on the cohort of interest. Post-index periods will consist of 6, 12, 18 and 24 months following the start of the osteoporosis therapy of interest. Post-index periods beyond 24 months will be considered exploratory. Further details on the baseline period, cohorts of interest and index date defintions are found further in this section.

8.2.2 Subject/Patient/Healthcare Professional Eligibility

8.2.2.1 Inclusion Criteria

Women aged 50 years and over or women aged under 50 at index date experiencing a premature (including surgery-induced) menopause (see appendix 1) and who have received at least one prescription for any licensed osteoporosis therapy * on or after January 1st 2010.

***** Osteoporosis therapy includes:

- Oral bisphosphonates (e.g. risedronate, alendronate, ibandronate, etidronate)
- Parenteral bisphosphonates (e.g. zoledronate, ibandronate)
- Selective oestrogen receptor modulators (SERMs; e.g. raloxifene)
- Parathyroid hormone (e.g. teriparatide, 1-84 PTH)
- Strontium ranelate
- Denosumab

Subjects taking or about to take calcium and/or vitamin D (singly or in combination) and HRT or related molecules such as tibolone or sex steroid derivatives are not eligible if these are taken as a sole therapy for the treatment of osteoporosis. However, if these are taken in combination with one of the included therapies then the subject is eligible for the study.

8.2.2.2 Exclusion Criteria

- History of cancer (except non-melanoma skin cancer) before or on the index date
- Metabolic bone disease (including rickets or osteomalacia, hyperparathyroidism, and Paget's disease of bone) before or on the index date.
- Less than 12 months of medical history in the CPRD before the index date
- Less than six months of medical records in the CPRD after the index date

8.2.3 Baseline Period

The baseline period or pre-index period will consist of the 12 months prior to the patients index date and will differ for a patient depending on the cohort of interest. In order to calculate FRAX scores, fracture history (non-traumatic or pathologic) of each patient will be sought from medical records, from either entry in the CPRD, or at least 5 years prior to index date, whichever is sooner. FRAX defines prior fracture history as, "A previous fracture denotes more accurately a previous fracture in adult life occurring spontaneously, or a fracture arising from trauma which, in a healthy individual, would not have resulted in a fracture." As this definition includes any fracture as an adult (over the age of 18 years of age), there will be an exploratory analysis to assess FRAX by age group. The patient's demographic and clinical characteristics of the study, such as comorbidities and evidence of osteoporosis-related fracture will be assessed in this period.

8.2.4 Study Follow-up

The study will measure persistence and compliance between 1st January 2010 to 31st December 2015. The follow-up period will begin on the date of index (the start date of the osteoporosis therapy), and will end at 24 months post the index date. Follow-up beyond these dates will be considered exploratory. Per eligibility exclusion criteria, a minimum observational period will be 6 months.

8.3 Variables

8.3.1 Exposure Assessment

Exposure will be assessed for patients who start osteoporosis treatment, within the observation window 1st January 2010 to 31st December 2015. The exposure time will be defined as the time period from the index date (start of follow-up) to date of discontinuation of osteoporosis therapy or end of patient follow up whichever is earlier. Start and discontinuation of exposure time will be defined differently for a patient depending on the cohort of interest:

All patient cohort:

This cohort will consist of all patients intiating an osteoporosis therapy during the observational window. The exposure time will be from the index date of the first osteoporosis therapy to the date of discontinuation of osteopororosis therapy. A patient's exposure may include more than one therapy. Discontinuation/end of therapy

will be defined depending on the time interval between the adjacent prescriptions. If the gap (or grace period) between the expected end date of the previous prescription and the next prescription is greater than 30 days the patient will be assumed to have discontinued therapy and their end of therapy will be the end date of the previous prescription.

Treatment-naïve cohort:

This cohort will consist of patients initiating an osteoporosis therapy during the observational window with no prior osteoporosis therapy within 12 months of start of observational period. The exposure time will be from the index date of the first osteoporosis therapy to the end of the same osteoporosis therapy. A patient's exposure will only include one type of medication.

Non-naive treated cohort:

This cohort will consist of all patients intiating an osteoporosis therapy during the observational window after having received a prior osteoporosis therapy. The exposure time will be from the index date of the new osteoporosis therapy to the end of the osteoporosis therapy. A gap of less than 30 days will be required between the old and new therapy for the new therapy to be considered non-naïve. A patient's exposure may be calculated multiple times (for each non-naïve therapy received) if they receive more than one non-naïve therapy.

8.3.2 Outcome Assessment

Primary Outomes

The following outcomes will be examined for the all patient cohort:

- Persistence at 6, 12, 18, 24 months follow-up
- Time to non-peristence/discontinuation
- Refill compliance at 6, 12, 18, 24 months follow-up

Secondary Outcomes

The following outcomes by therapy will be examined for both the treatment-naïve and naïve-treated cohorts:

- Persistence at 6, 12, 18, 24 months follow-up
- Time to non-persistence/discontinuation

- Refill compliance at 6, 12, 18, 24 months follow-up

Exploratory Outcomes (in non-naïve treated and naïve-treated groups)

- Persistence and compliance of denosumab and persistence of oral bisphosphonates at 6, 12, 18, 24 months, 3 and 5 years follow-up
- Persistence and compliance of denosumab and persistence of oral bisphosphonates by their dosing frequency (i.e. daily, weekly, monthly, three-monthly) at 6, 12, 18, 24 months, 3 and 5 years follow-up
- Persistence and compliance of denosumab and persistence of IV bisphosphonates at 6, 12, 18, 24 months, 3 and 5 years follow-up
- Age, FRAX score (the age range between 40-90 years), prior fracture history, number of prior osteoporosis therapies, type of prior osteoporosis therapies (BPs, SERM, HRT, RANKL), number of co-morbid conditions,types of co-morbid conditions (SLE, RA, IBD, diabetes, heart disease, CKD status, GERD), number of other concomitant medications (not osteoporosis therapies), types of concomitant medications (HRT, other hormonal therapy, calcium, and vitamin D, systemic glucocorticoid therapy, TNFi, anakinra, disease modifying anti-rheumatic drugs (DMARDs), proton pump inhibitors (PPIs) and H_2 blockers, degree of renal impairment (CKD status by eGFR band (i.e. G1, G2, G3a, G3b, G4 and G5), that are diagnosed prior to the index date)

- Persistence (for non-naïve treated and naïve-treated groups):
    - Denosumab pre/post 2014 (ONJ warnings)
    - Strontium pre/post 2014 (Cardiovascular warnings)
    - Bisphosphonates pre/post 2014 (atypical femoral fractures)
    - Denosumab pre/post 2013 (atypical femoral fractures)
    - Strontium pre/post 2012 (akin reactions (Stevens Johnson syndrome and/or toxic epidermal necrolysis)
    - Alendronate pre/post 2012 (akin reactions (Stevens Johnson syndrome and/or toxic epidermal necrolysis)
    - Strontium pre/post 2012 (venous thromboembolis)

8.3.3 Validity and Reliability

Persistence is defined as "the duration of time from initiation to discontinuation of therapy." Persistence is often presented as the number of days on treatment, or as the percentage of the cohort still on treatment at the end of a specified time frame (e.g. one year). *(Cramer 2008)*

In retrospective studies, compliance is quantified as the number of days of medication available to the patient divided by the total number of days of medication prescribed. This measure is usually termed "medication possession ratio" (MPR). *(Cramer 2008)* This simplified measure is obviously far from perfect, since the definition does not assess if the patient takes the medication. Nonetheless, in the absence of a valid measure and to maintain consistency and comparability between studies of compliance of treatment of osteoporosis, the MPR will be used in this retrospective study specifically in relation to oral therapies and medication possession ratio (MCR) for parenteral therapies.

8.4 Data Sources

Data will be derived from the Clinical Practice Research Datalink (CPRD) as detailed in Section 9.2.

The CPRD has a number of strengths in the data that it collects. The CPRD is one of a few large databases that include daya on morbidity and life-style variables with linkage to secondary care and mortality data. The database, whilst it does not cover the entireity of the UK population, still has approximately 11.3 million patient's medical histories as detailed in section 9.2. Data quality is enhanced further by the Quality and Outcome

Framework (QoF) that was introduced to GPs in 2004, which encourages recording of key data items in relation to these QoFs. As a consequence, recording of these key data variables has improved following their introduction. *(Herrett 2015)* The QoF for osteoporosis was not included until April 2012. *(HSCIC 2012)*

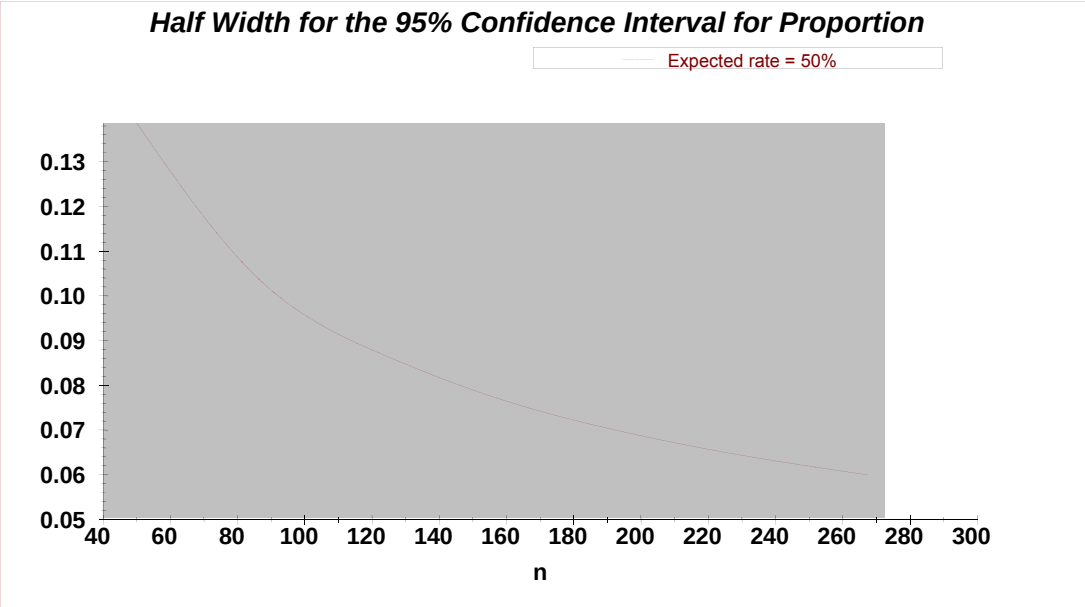
8.5 Study Size

The CPRD database available for this analysis contains approximately 75,000 postmenopausal women patients of which about 60,000 have received at least one prescription of osteoporosis medication. As such, the available sample size should be large enough to allow estimation with a good precision for the estimate of overall persistence and refill compliance to osteoporosis therapies and also the targeted cohorts of interest treatment naïve and non-naïve treated, as illustrated by the table below.

Table Half Width of the 95% CI

Sample size	Half width
150	8%
196	7%
270	6%
390	5%
600	4%
1070	3%
2400	2%
9600	1%
Maximum Half width were calculated assuming an expected rate of 50%	

The half width of the 95% CI around the proportions will depend on the number of subjects in each of the study cohorts of interest. However, assuming that the expected rate is 50%, the maximum half width will vary from 5% when the sample size is approximately 390 to less than 1% when the sample size is approximately 10,000 or larger as shown in the table above. Maximum half widths for other smaller sample sizes are provided in the figure below.



8.6 Data Management

8.6.1 Obtaining Data Files

Data files from the CPRD database are available in-house and analysis will be performed in-house.

8.6.2 Linking Data Files

In this analysis, linkage to other external databases (e.g. HES, ONS etc) will not be applied.

8.6.3 Review and Verification of Data Quality

Large validation studies have determined that information on all patient referrals and hospitalizations present in the manual medical records in the general practitioners' offices was recorded on the computer over 90% of the time, and that the overall data quality in the CPRD is high. Validation of the CPRD has shown high positive predictive value of some diagnoses, one of which has included fracture epidemiology *(van Staa 2001, Herrett 2015)*

The CPRD provides two sets of data quality criteria: acceptability for patients and up to standard (UTS) time for practices. These criteria do not ensure data quality, but the CPRD recommends that these measures are used as a first step to selecting research-quality patients and periods of quality data recording. The acceptable patient metric is based on registration status, recording of events in the patient record, and valid age and gender. The UTS date is a practice-based quality metric based on the continuity of

recording and the number of recorded deaths. The UTS date is calculated for each participating practice, corresponding to the latest date at which practices meet these minimum quality criteria. *(Herrett 2015)*

8.7 Data Analysis

8.7.1 Planned Method of Analysis

8.7.1.1 General Considerations

All summaries of the data will be descriptive in nature. Continuous variables will be summarized by the number of non-missing values, mean, standard deviation, median, lower and upper quartiles and minimum, maximum. Categorical variables will be summarized as the number and percentage of patients in each category.

Analyses supporting the primary and secondary objectives will describe persistence and compliance among patients initiating an osteoporosis therapy during 2010-2015. Outcomes will be assessed for the entire study population (all patient cohort) and separately, for the cohorts of interest, treatment naïve and non-naïve treated patients. A patient will be counted only once in the all patient and treatment naive cohort to give an overall estimation of persistence to osteoporosis therapy or medication. For the non-naïve treated cohorts patients may be included multiple times depending on the number of osteoporosis therapies they received. Persistence and compliance with osteoporosis therapies will be assessed over 6, 12, 18, and 24 months of follow-up.

8.7.1.2 Missing or Incomplete Data and Lost to Follow-up

This study will rely on register-based data which are known to have a high degree of Completeness, and as such some data until Dec 31st 2015 may not be included at the time of analysis. Reporting of certain variables used in this study is not voluntary so for health care visits and prescriptions all the necessary information can be expected to be present. If information regarding dates, diagnosis codes or treatment information is absent, these records would be excluded from analysis since imputing these types of variables would be difficult to implement and justify. In the very unlikely event that a patient's health care visit or prescription would not have been captured at all by the registers, this instance of missing data would not be possible to identify. All available data collected during the observation period will therefore be used in the

analysis. Imputation for missing data will be explored and further outlined in the statistical analysis plan.

8.7.1.3 Descriptive Analysis

8.7.1.3.1 Description of Study Enrollment

All subjects enrolled into the study who meet the inclusion criteria will be included in the analyses.

8.7.1.3.2 Description of Patient Characteristics

The following demographic and clinical characteristics during the baseline period will be defined for each patient as of the index date:

- Age in years as of the index date
- Age at the first diagnosis of osteoporosis (where available)
- Age at time of menopause and cause of menopause (where available)
- Diagnosis status: osteoporosis or osteopenia or unknown (where available)
- Time since diagnosis of osteoporosis or osteopenia (where available)
- History of all fractures over age of 50 yrs (except fractures of fingers, toes, face or skull)
- Fracture risk assessment (FRAX) for Major Osteoporotic Fracture (MOF) and hip where available, or calculated from the contributory co-morbidities as required by the FRAX calculation tool (see next two bullet points).
- Other risk factors for osteoporotic fracture - where available. We will describe study subjects according to smoking [current, former, never, unknown], alcohol use [yes/no/unknown], alcohol intake (units/day when recorded), BMI (including height or weight separately when recorded), steroid use (total dose used)
- Co-morbid conditions: We will identify prevalent co-morbid conditions (RA, SLE, inflammatory bowel disease, diabetes, heart disease [MI, angina, congestive heart disease], COPD, hyperthyroidism, chronic liver disease, CKD status by eGFR band (i.e. G1, G2, G3a, G3b, G4 and G5), that are diagnosed prior to the index date. We will also describe history of gastrointestinal (GI) disease (GERD, dyspepsia, peptic ulcer or upper gastrointestinal symptoms) in the year before the index date. Each condition will be coded as yes or no.

- Concomitant meds: We will indicate all women who are currently exposed to each medication at the index date (HRT, other hormonal therapy, calcium, and vitamin D, systemic glucocorticoid therapy, TNFi, anakinra, disease modifying anti-rheumatic drugs (DMARDs), proton pump inhibitors (PPIs) and H_2 blockers) (yes/no). Current use will be defined as having filled a prescription within the 30 days prior to the index date.
- Dementia (including: Alzheimer's disease, vascular dementia, mixed dementia, Lewy-body dementia, fronto-temporal dementia and Parkinson's dementia

Current anti-osteoporosis therapy (treatment status at index date)

- Date of initiation of index medication
- Type of medication being used (e.g. alendronate, risedronate, strontium)
- Mode of administration (e.g. oral, intravenous)
- Frequency of administration (e.g. daily, weekly, monthly, 6-monthly, yearly)
- Date of stopping (defined as drop-out, death, loss to follow-up)

Date of discontinuation of index medication or date of end of follow-up (defined as drop-out, death, loss to follow-up)

History of anti-osteoporosis therapy

- Number of previous anti-osteoporosis therapies
- Type of last medication being used (e.g. alendronate, risedronate, strontium)
- Mode of administration (e.g. oral, intravenous)
- Frequency of administration (e.g. daily, weekly, monthly)

Patient demographics and clinical characteristics will be summarized by level of persistence and compliance for each of the cohorts. Levels of persistence will be defined as non-persistent (< 12 months) and persistence (≥ 12 months). Levels of compliance will be defined as non-compliant (MCR/MPR<0.8) and compliant (MCR/MPR≥0.8).

8.7.1.4 Analysis of the Primary, Secondary and Exploratory Endpoint(s)

Persistence: Persistence measures the accumulation of time from treatment initiation to discontinuation of therapy. In this study, persistence will be quantified using the

Estimated Level of Persistence with Therapy (ELPT) method which determines the percentage of individuals remaining on therapy (persistent) at a given time *(Dezii 2001).*

It will be calculated as the number of days from initiating osteoporosis therapy to their end of therapy (i.e. end date of exposure – index date) and will be estimated as the proportion of patients refilling each subsequent prescription within the grace period every 6 months. Patients not within the permissible grace period will be considered as non-peristent. The percentage of patients persisting at 6, 12, 18 and 24 months, 3 and 5 years will be estimated.

Kaplan-Meier methods will be used to estimate non-persistence. The number of days a subject is persisting on therapy will be estimated with discontinuation considered as a failure event. Patients without an event will be censored at the date of last follow-up. From the Kaplan-Meier curve, the median time on therapy in days will be calculated.

All analyses will performed for each cohort: all paitents, treatment naïve and non-naïve treated cohorts and will be done using the base case grace period assumption of 30 days.

Compliance: Compliance is quantified using the Medication Possession Ratio (MPR) for oral therapies and medication coverage ratio (MCR) for parenteral therapies. The MPR will be calculated as: sum of the days' supply of medication divided by the number of days between the first prescription and the exhaustion of the last prescription during the predetermined time windows. Since the MPR definition itself involves at least two fill dates MPR calculations in this analysis will exclude women with only one filled prescription during the predetermined time windows. The MCR measures the percentage of days that the patient was covered by an long acting agent (e.g. zoledronate) agent over a given time interval after receiving the injection.

The MPR and MCR will be calculated for the share of the cohort that remained compliant at 6, 12, 18, 24 months, 3 and 5 years. Compliance will be defined as MCR/MPR ≥0.8. The percentage of patients compliance along with 95% confidence intervals will be estimated for each cohort and follow up. The base case grace gap period assumption of 30 days will also be considered.

An overall estimate of persistence and compliance will be derived for the all patient cohort whereas treatment naïve and non-naïve cohorts will be summarized by osteoporosis medication.

8.7.1.5 Sensitivity Analysis

Sensitivity analysis re-estimating compliance and persistence will be performed by allowing alternative medication gaps (or grace periods) of 60, 90 and 120 days. Additional sensitivity analysis will be conducted to test different definitions of the grace period. Instead of applying the grace period based on a fixed number of days post completion of the previous day's supply, grace periods will be defined on a per patient basis based on the day's supply of the previous medication. For example, a patient with refills consisting of a 90 day supply will receive a grace period of 90 days after completion of the previous day's supply in comparison to a patient with a refill period of 30 days which will receive a 30 day grace period after completion of the previous day's supply. This method will allow for longer grace periods when patients are prescribed longer day's supply.

8.7.1.5.1 Subgroup Analysis

Persistence and compliance will be summarized (point estimates and 95% confidence intervals) for the following subgroups of interest where patient numbers permit (i.e. ≥ 100 patients).

Subgroups of interest:

- Type of anti-osteoporotic therapy (e.g alendronate, risendronate, strontium) (secondary objective)
- Time before and after regulatory events (explortatory objective)
    - Denosumab 2014 (ONJ warnings)
    - Strontium 2014 (Cardiovascular warnings)
    - Bisphosphonates 2014 (atypical femoral fractures)
    - Denosumab 2013 (atypical femoral fractures)
    - Strontium 2012 (akin reactions (Stevens Johnson syndrome and/or toxic epidermal necrolysis)
    - Alendronate 2012 (akin reactions (Stevens Johnson syndrome and/or toxic epidermal necrolysis)
    - Strontium 2012 (venous thromboembolis)
- Class of anti-osteoporotic therapy (e.g bisphosphonates, SERM)
- Dosing regimen
- Age group (5 year groups)

8.7.1.5.2 Sensitivity Analysis for Residual Confounding and Bias

There is currently no plan to perform this sort of analyses. The study is purely descriptive. A lot of work was previously performed on this, and it is believed that this sort of analyses would add very little value to this study.

8.7.2 Analysis of Safety Endpoint(s)/Outcome(s)

As this is a retrospective database study where the information accessed will not contain data on adverse events or physician attribution of adverse events to Amgen products, then AEs/ADRs collection will not be applicable to this study.

8.8 Quality Control

The CPRD is currently administered by the UK Medicines and Healthcare products Regulatory Agency (MHRA). The UK Department of Health (DoH) collects the information from GPs and routinely checks the data for accuracy and validity. Validation of the CPRD has shown high positive predictive value of some diagnoses and, where evaluated, comparisons of incidence with other UK data sources are also broadly similar. (*Herrett 2015)*

Storage of records and archiving of statistical programming and analytical data files will be handled in compliance with Amgen standard procedures.

8.9 Limitations of the Research Methods

Although we will identify all postmenopausal women who are on anti-osteoporotic therapy during the study period, we may miss some younger women with surgical menopause or chemotherapy induced menopause if such treatment or procedures occurred prior to a patient's registration date in the CPRD. Diagnoses and events that occur prior to entry into the database may not be recorded in the computer files in the CPRD though many important medical events and diagnoses are noted as historical entries. We will identify all available osteoporosis therapy in the UK; however, we may have limited information on parenteral treatments such as intravenous zolendronic acid, intravenous ibandronate, and calcitonin since GPs do not always record treatments that do not require a prescription or where the treatment may be provided in secondary care. There will be some patients for whom assessing compliance may be difficult if they receive too many prescriptions with ambiguous dosing instructions. For example, when the instruction is "take as directed" we may not be able to calculate the prescription length. We will look at intervals of repeated prescriptions and other instructions to best evaluate overall prescribing and compliance for each patient.

8.9.1.1 Information Bias

The proposed analyses will use a unit of evaluation based on the episode of therapy use, not person. As a result of the all patient cohort containing patients that may appear more than once due to the unit of evaluation, it is possible that we are not accounting for repeated measurements which could bias our estimates of persistence. Additionally, it is estimated around two-thirds of women don't switch therapies, therefore the amount of correlated data will be low.

8.9.1.2 Selection Bias

The proposed analyses will use a unit of evaluation based on the episode of therapy use, not person. As a result of the all patient cohort containing patients that may appear more than once due to the unit of evaluation, it is possible that we are not accounting for repeated measurements which could bias our estimates of persistence/compliance. However given the analysis of sub cohorts which will have each person appearing only once, we can assess the sensitivity of that assumption. Additionally, it is estimated around two-thirds of women don't switch, therefore the amount of correlated data will be low.

Another potential bias of this design is that we are only capturing GP based prescriptions and if a person is diagnosed/treated initially by a consultant in the hospital setting we might miss one or multiple prescriptions before they are captured in primary care. For example, in some hospitals in the UK, the patient may not be transferred from secondary to primary care after their first denosumab injection

As CPRD is a general practitioner database, the recording of subcutaneous or intravenous medications that are prescribed and administered in a hospital or in an alternative setting are likely to be limited. An evaluation of Prescription Cost Analysis Data in the UK (number of items dispensed in the community in England) over the period of 2010-2015 indicated that the number of parenteral bisphosphonates prescriptions dispensed, in the community setting, to range between 250-550 per year in total.

Therefore, calculating persistence and compliance levels for these medications may be limited.

There may be bias in capturing those subcutaneous or intravenous therapies that are recorded in the CPRD dataset and interpreting the results. The reasons why some records exist and not others cannot be explained by available data in CPRD. Therefore, as a result of small sample sizes based on preliminary estimates, interpretation of

meaningful results may not be appropriate for dissemination, and will be used for exploratory analysis only.

8.9.2 External Validity of Study Design

Large validation studies have determined that information on all patient referrals and hospitalizations present in the manual medical records in the general practitioners' offices was recorded on the computer over 90% of the time, and that the overall data quality in the CPRD is high (see section 9.8). *(Jick H 1991, Jick SS 1992, Jick SS 2003)*

8.9.3 Analysis Limitations

The completion of some of the important variables such as smoking status and alcohol consumption has been noted in the past to be poor in the CPRD. This would affect our ability to describe the frequency of occurrence of these important characteristics in our population and our ability to effectively control for or assess their impact on the risk of occurrence of our events.

8.9.4 Limitations Due to Missing Data and/or Incomplete Data

The data contained within the CPRD, is only as current as the information that has been erntered into it. Therefore, whilst the study endpoint is 31st December 2015, some data may not have been entered into CPRD by some GPs by this time point.

9. Protection of Human Subjects

All data used in the CPRD is taken from anonymised electronic health records and thus no patients will be identifiable.

9.1 Informed Consent

The CPRD Group collects data from practices including the entire medical record; however, strong patient identifiers (e.g. name, address, date of birth, NHS number and post-code) are not collected. Information collected includes demographic information (including age and sex), medical symptoms, signs and diagnoses, therapy, referrals to hospitals or specialists, laboratory tests and pathology results, lifestyle factors (e.g. height, weight, BMI, smoking and alcohol consumption) and patient registration details. The current standard practice for the use of such pseudonymised data is adopted by CPRD and technically does not require consent. However, CPRD works with contributing practices to ensure patients are aware of such use of their data and of their right to dissent from the use of their pseudonymised data if they so wish. All patient records are collected from a contributing practice except where individual patients have exercised their right to opt out of contributing to the CPRD. *(CPRD annual report 2014)*

9.2 Institutional Review Board (IRB)/Independent Ethics Committee (IEC)

The study will be submitted to the Independent Scientific Advisory Committee (ISAC) body of the CPRD. This is a non-statutory expert advisory board established in 2006 to provide advice on research related requests to access data from the CPRD.

9.3 Confidentiality

All data used in the CPRD is taken from anonymised electronic health records and thus no patients will be identifiable.

10. Collection of Safety Information and Product Complaints

As this is a retrospective database study where the information accessed will not contain data on adverse events or physician attribution of adverse events to Amgen products, then AEs/ADRs collection will not be applicable to this study.

Safety Data Collection Language:

Reporting of individual adverse events is not applicable for secondary data collection studies.

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11. Administrative and Legal Obligations

11.1.1 Protocol Amendments and Study Termination

Amgen may amend the protocol at any time. If Amgen amends the protocol, written agreement from the Investigator must be obtained where applicable per local governing law and/or regulations. The IASC must be informed of all major amendments and give approval.

Amgen reserves the right to terminate the study at any time. Both Amgen and the Investigator reserve the right to terminate the Investigator's participation in the study according to the contractual agreement. The Investigator is to notify Amgen in writing of the study's completion or early termination.

12. Plans for Disseminating and Communicating Study Results

[redacted]

12.1 Publication Policy

Authorship of any publications resulting from this study will be determined on the basis of the International Committee of Medical Journal Editors (ICJME) Recommendations for the Conduct, Reporting, Editing and Publication of Scholarly Work in Medical Journals, which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved. Authors should meet conditions 1, 2, and 3 and 4.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for corporate review. The vendor agreement will detail the procedures for, and timing of, Amgen's review of publications.

13. References

1. NIH Consensus Development Panel: Osteoporosis Prevention, Diagnosis, and therapy. *JAMA* 2001; 285: 785-795.

2. Drake MT, Clarke BL, Lewiecki EM. The pathophysiology and treatment of osteoporosis. *Clin Ther*. 2015; 37: 1837-1850.

3. Hernlund E, Svedbom A, Ivergard M, et al. Osteoporosis in the European Union: Medical management, epidemiology and economic burden. *Arch Osteoporos*. 2013; 8: 136.

4. Cramer JA, Roy An, Burrell A, et al. Medication Compliance and Persistence: Terminology and Definitions. *Value Health*. 2008; 11: 44-47.

5. Vermeire E, Hearnshaw P, Van Royen P, et al. Patient adherence to treatment: three decades of research. A comprehensive review. *J Clin Pharm Ther*. 2001; 26: 331-342.

6. Lam W-Y, Fresco P. Medication adherence measures: An overview. *BioMed Res Int*. 2015; 2015: 217047

7. Iglay K, Cartier SE, Rosen VM, et al. Meta-analysis of studies examining medication adherence, persistence, and discontinuation of oral antihyperglycemic agents in type 2 diabetes. *Curr Med Res Opin*. 2015; 31: 1283-1296.

8. Karlsson L, Lundkvist J, Psachoulia E, et al. Persistence with denosumab and persistence with oral bisphosphonates for the treatment of postmenopausal osteoporosis: a retrospective, observational study, and a meta-analysis. *Osteoporos Int*. 2015; 26: 2401-2411.

9. Li L, Roddam A, Gitlin M, et al. Persistence with osteoporosis medications among postmenopausal women in the UK General Practice Research Database. *Menopause*. 2012; 19: 33-40.

10. Compston JE, Seeman E. Compliance with osteoporosis therapy is the weakest link. *Lancet*. 2006; 368: 973-4.

11. Cramer JA, Gold DT, Silverman SL, Lewiecki EM. A systematic review of persistence and compliance with bisphosphonates for osteoporosis. *Osteoporos Int*. 2007; 18: 1023-1031.

12. Huybrechts KF, Ishak KJ, Caro JJ. Assessment of compliance with osteoporosis treatment and its consequences in a managed care population. *Bone*. 2006; 38(6): 922-8.

13. Siris ES, Selby PL, Saag KG, et al. Impact of osteoporosis treatment adherence on fracture rates in North America and Europe. *Am J Med*. 2009; 122: S3-S13.

14. Imaz I, Zegarra P, Gonzalez-Enriquez J, et al. Poor bisphosphonate adherence for treatment of osteoporosis increases fracture risk: systematic review and meta-analysis. *Osteoporos Int*. 2010; 21: 1943-1951.

15. Choddick G, Sharman Moser S, Goldshtein I. Non-adherence with bisphosphonates among patients with osteoporosis: impact on fracture risk and healthcare costs. Expert Rev Pharmacoecon Outcomes Res. 2016; doi.org/10.1586/14737167.2016.1171145 [ahead of print]

16. Ferguson S, Feudjo-Tepie M, Taylor A, et al. The impact of persistence with bisphosphonates on health resource utilisation and fracture risk in the UK: A study of patients records from the UK Clinical Practice Research Datalink. *J Eval Clin Pract*. 2015; doi: 10.1111/jep.12422 [ahead of print].

17. Silverman S, Gold DT. Compliance and persistence with osteoporosis medications: A critical review of the literature. *Rev Endocr Metab Disord*. 2010; 11: 275-280.

18. Lindsay BR, Olufade T, Bauer J, et al. Patient-reported barriers to osteoporosis therapy. *Arch Osteoporos Int*. 2016; 11: 19.

19. Feudjo-Tepie M, Ferguson S, Roddam A, et al. Comorbidities, bone-sparing agent prescription history and their determinants among postmenopausal women in UK primary care settings: a retrospective database study. *Arch Osteoporos*. 2015; 10: 41

20. Dezii CM. Persistence with drug therapy: a practical approach using administrative claims data. *Manag Care*. 2001; 10: 42-5.

21. Peterson AM, Nau DP, Cramer JA, et al. A checklist for medication compliance and persistence studies using retrospective databases. *Value Health*. 2007; 10: 3-12.

22. Shi L, Ascher-Svanum H, Zhu Bet al. Characteristics and use patterns of patients taking first-generation depot antipsychotics or oral antipsychotics for schizophrenia. *Psychiatr Serv*. 2007; 58: 482-488.

23. Hadji P, Papaioannou N, Geilen E, et al. Persistence, adherence, and medication-taking behaviour in women with postmenopausal osteoporosis receiving denosumab in routine practice in Germany, Austria, Greece, and Belgium: 12-month results from a European non-interventional study. *Osteoporos Int*. 2015; 26: 2479-2489.

24. Seeman E, Compston J, Adachi J, et al. Non-compliance: the Achilles' heel of anti-fracture efficacy. *Osteoporos Int* 2007; 18: 711-719.

25. Cramer JA, Amonkar MM, Hebborn A, et al. Compliance and persistence with bisphosphonate dosing regimens among women with postmenopausal osteoporosis. *Curr Med Res Opin*. 2005; 21(9): 1453-60.

26. Iglay K, Cao X, Mavros P, et al. Systematic literature review and meta-analysis of medications adherence with once-weekly versus once-daily therapy. *Clin Ther*. 2015; 37: 1813-1821.

27. Kothawala, P., E. Badamgarav, S. Ryu, R.M. Miller, and R.J. Halbert. Systematic review and meta-analysis of real-world adherence to drug therapy for osteoporosis. *Mayo Clin Proc*. 2007; **82**(12): 1493-501.

28. Brankin E, Walker M, Lynch N, Aspray T, Lis Y, Cowell W. The impact of dosing frequency on compliance and persistence with bisphosphonates among postmenopausal women in the UK: evidence from the three databases. *CMRO*. 2006; 22(7): 1249-1256.

29. Gallagher AM, Rietbrock S, Olson M, van Staa TP. Fracture outcomes related to persistence and compliance with oral bisphosphonates. *J Bone Miner Res*. 2008; 23(10):1569-1575.

30. Rietbrock S, Olson M, van staa TP. The potential effects on fracture outcomes of improvements in persistence and compliance with bisphosphonates. *QJ Med*. 2009; 102: 35-42

31. Lacey DL, Boyle WJ, Simonet WS, et al. Bench to bedside: elucidation of the OPG-RANK-RANKL: pathway and the development of denosumab. *Nat Rev Drug Discov*. 2012; 11: 401-419.

32. Freemantle N, Satram-Hoang S, Tang E-T, et al. Final results of the DAPS (Denosumab adherence Preference Satisfaction) study: a 24-month, randomized, crossover comparison with alendronate in postmenopausal women. *Osteoporos Int.* 2012; 23: 317-326.

33. Silverman SL, Siris E, Kendler DL, et al. Persistence at 12 months with denosumab in postmenopausal women with osteoporosis: interim results from a prospective observational study. *Osteoporos Int.* 2015; 26: 361-372.

34. Hadji P, Kyvernitakis I, Kann PH, et al. GRAND-4: The German retrospective analysis of long-term persistence in women with osteoporosis treated with bisphosphonates or denosumab. *Osteoporos Int*. 2016; 27: 2967-2978.

35. Papaioannou A, Khan A, Belanger A, et al. Persistence with denosumab therapy among osteoporotic women in the Canadian patient-support program. *Curr Med Res Opin.* 2015; 31: 1391-1401.

36. Fuksa L, Vytrisalova M. Adherence to denosumab in the treatment of osteoporosis and its ultilisation in the Czech Republic. *Curr Med Res Opin*. 2015; 31: 1645-1653.

37. Karlsson L, Lundkvist J, Psachoulia E, et al. Persistence with denosumab and persistence with oral bisphosphonates for the treatment of postmenopausal osteoporosis: A retrospective, observational study, and a meta-analysis. *Osteoporos Int.* 2015; 26: 2401-2411.

38. Lakatos P, Takacs I, Marton I, et al. A retrospective longitudinal database study of persistence and compliance with treatment of osteoporosis in Hungary. *Calcif Tissue Int*. 2016; 98: 215-225.

39. Royal College of Physicians. Falls and Fragility Fracture Audit Programme (FFFAP). Fracture liaison service Database (FLS-DB) facility audit. May 2016. https://www.rcplondon.ac.uk/projects/outputs/fls-db-facilities-audit-fls-breakpoint-opportunities-improving-patient-care [Accessed July 2016]

40. Hiligsmann M, Evers SM, Sedrine WB, et al. A systematic review of cost-effectiveness analyses of drugs for postmenopausal osteoporosis. *PharmacoEconomics*. 2015; 33: 205-224.

41. Hiligsmann M, Boonen A, Rabdenda V, et al. The importance of integrating medication adherence into pharmacoeconomic analyses: the example of osteoporosis. *Exp Rev Pharmacoecn Outcome Res*. 2012; 12: 159-166.

42. Herrett E, Gallagher AM, Bhaskaran K, et al. Data Resource Profile: Clinical Practice Research Datalink (CPRD). *Int J Epidemiol*. 2015; 44: 827-836.

43. Quality Outcomes and Framework Achievement, prevalence and exceptions data, 2012-2013. Technical annex. http://content.digital.nhs.uk/catalogue/PUB12262/qual-outc-fram-tech-anne-2012-13-anx.pdf [Accessed January 2017].

44. Herrett E, Thomas SL, Schoonen WM, et al. Validation and validity of diagnoses in the General Practice Research Database: a systematic review. *Br J Clin Pharmacol*. 2010; 69: 4-14.

45. Jick H, Jick SS, Derby LE. Validation of information recorded on general practitioner based computerised data resource in the United Kingdom. *BMJ* 1991; 302(6779): 766-768.

46. Jick H, Terris BZ, Derby LE, Jick SS. Further validation of information recorded on a general practitioner based computerized data resource in the United Kingdom. *Pharmacoepidemiol Drug Saf.* 1992;1:347-349.

47. Jick SS, Kaye JA, Vasilakis-Scaramozza C et al. Validity of the general practice research database. *Pharmacotherapy.* 2003; 23(5): 686-689.

48. Van Staa TP, Dennison EM, Leufkens HGM, et al. Epidemiology of fractures in England and Wales. *Bone.* 2001; 29: 517-522.

49. Tremblay E, Perreault S, Dorais M. Persistence with denosumab and zoledronic acid among older women: a populations-based cohort study. *Arch Osteoporos*. 2016; 11: 30.

50. Independent Scientific Advisory Committee (IASC) for Medicines and Health Regulatory products Regulatory Agency (MHRA) database Research Annual Report Jan 2014 – Dec 2014.

Appendices

Appendix A. CPRD READ coding

Read Codes relating to menopause (section 8.2.2)

V2	CTV3	Term	Comment
Bilateral oophorectomy with hysterectomy			
7E045	nil	Abdominal hysterectomy and bilateral salpingoophorectomy	
7E049	XE06a	Total abdominal hysterectomy and bilateral salpingoophorectomy	
7E04B	XaJy8	Laparoscopic total abdominal hysterectomy and bilateral salpingo-oophorectomy	
7E04H	XabO5	Subtotal abdominal hysterectomy and bilateral salpingo-oophorectomy	
7E04P	XabOC	Radical hysterectomy with bilateral salpingo-oophorectomy	
7E056	XaPmp	Laparoscopic-assisted vaginal hysterectomy with bilateral salpingo-oophorectomy	
Bilateral oophorectomy without hysterectomy			
7E102	Xa8PW	Bilateral oophorectomy NEC	
159B.	XaITj	H/O: bilateral oophorectomy	Note date of recording of code unlikely to be date of procedure
7E100	7E100	Bilateral salpingoophorectomy	
7E115	XaB2V	Oophorectomy of remaining solitary ovary NEC	
Chemotherapy induced menopause			
Nil	X40NE	Post-chemotherapy ovarian failure	In CTV3 this appears in the C162. % hierarchy
Radiotherapy induced menopause			
C162. %	C162. %	Postablative ovarian failure	'%' indicates child codes will be included
C1620	C1620	Postsurgical ovarian failure	
C1621	C1621	Postirradiation ovarian failure	
Nil	X40NF	Iatrogenic ovarian failure	
C1622	C1622	Other iatrogenic postablative ovarian failure	
C162y	C162y	Other specified postablative ovarian failure	
C162z	C162z	Postablative ovarian failure NOS	
nil	Xa0bf	Post-radiation menopause	

Primary ovarian insufficiency			
C1634	nil	Early menopause	
nil	X408w	Premature menopause	
C1631	X40NJ	Premature menopause NOS	
PJ62.	PJ62.	Ovarian dysgenesis	
See also C163. % below			
Others?			
nil	Xa0be	Post-hysterectomy menopause	
nil	X408b	Normal menopause	
nil	Xa4eB	Menopause present	
nil	X408c	Delayed menopause	
nil	X76QX	Menopausal problem	
nil	XSJGr	Postmenopausal state	
nil	X408x	Menopause ovarian failure	
nil	XSESu	Ovarian failure	
nil	X40NH	Premature ovarian failure	
nil	X40NK	Autoimmune primary ovarian failure	
nil	X40NG	Resistant ovary syndrome	
C163. %	XE10j	Other ovarian failure	
C1630	C1630	Primary ovarian failure	
C1631	XE10k	Secondary ovarian failure	
C1632	C1632	Hypergonadotrophic ovarian failure	
C1633	C1633	Ovarian hypogonadism	
C1634	C1634	Early menopause	also appears above
C163y	C163y	Other specified other ovarian failure	
C163z	C163z	Other ovarian failure NOS	
nil	X408v	Incipient ovarian failure	
nil	Xa4eB	Menopause present	
1512.	nil	Menopause	
K5A4.	K5A4.	Artificial menopause	
67I1.	XaEFj	Advice about the menopause	but doesn't necessarily imply it has occurred)
The following may also indicate menopause has occurred			
nil	XM0t2	Menopausal symptoms	
nil	Xa06h	Menopause observation	
nil	X74Wi	Menopause monitoring status	
66U..%	XE1TE	Menopause monitoring	
66U1.	66U1.	Menopause initial assessment	
66U2.	66U2.	Menopause follow-up assessment	
66U3.	66U3.	Menopause symptoms present	
66U4.	66U4.	Menopause: LH, FSH checked	
66U5.	66U5.	Menopause: bone density check	
66U6.	66U6.	HRT contraindicated	
66U7.	66U7.	HRT started	
66U8.	66U8.	HRT side-effects	

66U9.	66U9.	HRT changed	
66UA.	66UA.	HRT stopped	
66UB.	66UB.	HRT: unopposed oestrogen	
66UC.	66UC.	HRT: combined oestrog/progest	
66UD.	66UD.	Menopause: dietary advice	
66UE.	66UE.	Menopause: sexual advice	
66UF.	nil	Menopause: gen counselling	
Nil	XaEFj	Advice about the menopause	
66UG.	XaEnl	Patient refuses HRT	
66UH.	XaISA	Hormone replacement therapy bleed pattern – normal	
66UI.	XaISB	Hormone replacement therapy bleed pattern – abnormal	
66UJ.	XaISC	Hormone replacement therapy bleed pattern - not relevant	
66UK.	XaISD	Hormone replacement therapy bleed pattern - no bleeding	
8B64.	XE0hs	Hormone replacement therapy	
8B640	8B640	Hormone Replacement Therapy ongoing treatment	
K5A1.	K5A1.	Bleeding after menopause	
K59B.	XaKJm	Postmenopausal postcoital bleeding	
1583.	nil	H/O: post-menopausal bleeding	
66UL.	XaISE	Years on hormone replacement therapy	
66UZ.	66UZ.	Menopause monitoring NOS	
6A3..	XaIKG	Hormone replacement therapy review	
nil	XaIks	Hormone replacement therapy requested	
nil	XaImh	Health education - hormone replacement therapy	
nil	XaYGE	Advice about risk of hormone replacement therapy	
7G2A4	7G2A4	Insertion of oestrogen implant	
8BPb.	nil	Anti-oestrogen therapy	

Read codes for medications from CPRD

READ codes from CPRD for bone loss therapy by Category

1. Alendronate sodium I (BCDSP codes: B05919)
   5838009 alendronate sodium 10mg tabs oral daily
   8808001 alendronate sodium 10mg tabs oral daily
   8808002 alendronate sodium 5mg tabs oral daily
   8809001 alendronate sodium 10mg tabs oral daily
   8809002 alendronate sodium 5mg tabs oral daily

2. Alendronate sodium II (BCDSP codes: B05919 & B51031)
   5723009 alendronate sodium 70mg tabs oral weekly
   8809003 alendronate sodium 70mg tabs oral weekly
   10481001 alendronate sodium 70mg tabs oral weekly
   13400001 alendronate sodium+colecalciferol 70mg+70mg tabs oral weekly
   13401001 alendronate sodium+colecalciferol 70mg+70mg tabs oral weekly

3. Etidronate disodium (BCDSP codes: B05907)
   241001 etidronate disodium 200mg tabs oral daily
   2601007 etidronate disodium 200mg tabs oral daily
   3235001 etidronate disodium 200mg tabs oral daily
   4426001 etidronate disodium +calcium carbonate 400mg +1.25g tabs oral daily
   4427001 etidronate disodium +calcium carbonate 400mg +1.25g tabs oral daily
   5082007 DIDRONEL 100mg tabs oral

4. Risedronate sodium I (BCDSP codes: B05921)
   8235001 risedronate sodium 5mg tabs oral daily
   8236001 risedronate sodium (Actonel) 5mg tabs oral daily

5. Risedronate sodium II (BCDSP codes: B05921 & B51024)
   8235002 risedronate sodium 30mg tabs oral weekly
   8236002 risedronate sodium (Actonel) 30mg tabs oral weekly
   9448001 risedronate sodium (Actonel) 35mg tabs oral weekly
   10978001 risedronate sodium 35mg tabs oral weekly
   15787001 risedronate sodium+calcium carbonate+colecalciferol 35mg+2.5g+22mg
   15788001 risedronate sodium+calcium carbonate+colecalciferol 35mg+2.5g+22mg

6. Strontium (BCDSP codes: B07548)
   12844001 strontium 2g susp granules oral daily 12845001 strontium 2g susp granules oral daily

7. Raloxifene (BCDSP codes: B07768)
   8621001 raloxifene 60mg tabs
   11457001 raloxifene 60mg tabs

8. Ibandronic acid, sodium salt I (BCDSP codes: B05924)
   8466001 ibandronic acid, sodium salt, monohydrate 2mg/2ml conc soln inf
   13920001 ibandronic acid, sodium salt, monohydrate 3mg/3ml inj soln inj three mo 13923001 ibandronic acid, sodium salt, monohydrate 3mg/3ml inj soln inj

9. Ibandronic acid, sodium salt II (BCDSP codes: B05924)
    12354001 ibandronic acid, sodium salt, monohydrate 50mg tabs oral daily
    12355001 ibandronic acid, sodium salt, monohydrate (B00000) 50mg tabs oral daily

11. Ibandronic acid, sodium salt III (BCDSP codes: B05924)
    13437001 ibandronic acid, sodium salt, monohydrate 150mg tabs oral monthly
    13438001 ibandronic acid, sodium salt, monohydrate 150mg tabs oral monthly

12. Zoledronate
    12393001 Zoledronic acid 4mg/5ml conc soln inf inf anonymised
    14064001 Zoledronic acid (Aclasta B00000) 5mg/100ml soln inf

13. Teriparatide (BCDSP codes: B08215)
    12066001 Teriparatide 750mg inj inj monthly 12067001
    Teriparatide 750mg inj inj only for one person daily

14. Fluoride (BCDSP codes: B10002 restrict to multilex codes below)
    1906007 Sodium Fluoride 20mg cap oral daily
    1909007 Sodium Fluoride 10mg cap oral daily
    3232007 Sodium Fluoride 20mg tab oral daily

15. Tiludronate disodium 200mg tabs oral daily (BCDSP codes: B13330)
    Tiludronate disodium 200mg tabs oral daily ate disodium

16. Denosumab 60mg subcuntaeous injection 6-monthly