Non-interventional study protocol

Strontium ranelate (ATC M05BX03)

Title	European Program of Post-Authorization Safety Studies for Protelos®/Osseor® through EU-ADR Alliance
Protocol version identifier	3.0
Date of last version of protocol	7 January 2015
EU PAS register number	Study not registered yet
Active substance	Strontium ranelate (ATC M05BX03)
Medicinal product	Protelos®/Osseor®
Product reference	EU/1/04/288/001-006 (Protelos®) EU/1/04/287/001-006 (Osseor®)
Procedure number	EMEA/H/C/000560/ANX 034 EMEA/H/C/000561/ANX 034
Marketing authorization holder(s)	Les Laboratoires Servier
Joint PASS	No
Research question and objectives	The aims of this PASS program are: 1. To study the effectiveness of the newly established risk minimization measures by characterizing utilization patterns of SR and estimating the prevalence of contraindications and restrictions of indication amongst incident and prevalent SR users 2. To estimate and compare the incidence rates of cardiac and thromboembolic events in new users of SR and new users of bisphosphonates

Country(-ies) of study	Denmark, Italy, Netherlands, Spain, and United Kingdom.
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2. LIST OF ABBREVIATIONS

ATC	Anatomical Therapeutic Chemical
AUH	Aarhus University Hospital, Department of Clinical Epidemiology regional database
BP	Bisphosphonates
CHMP	The Committee for Medicinal Products for Human Use
CPRD	Clinical Practice Research Datalink
CVD	Cerebrovascular Disease
DHPC	Direct Healthcare Professional Communication
EC	European Commission
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EMA	European Medicines Agency
EU	European Union
GPP	Good Pharmacoepidemiology Practices
HSD	Health Search CSD Longitudinal Patient Database
ICD	The International Classification of Diseases
IHD	Ischemic Heart Disease
IPCI	Integrated Primary Care Information Project
ISPE	International Society for Pharmacoepidemiology
MAH	Marketing Authorization Holder
PAD	Peripheral Arterial Disease
PASS	Post-Authorization Safety Study
PRAC	Pharmacovigilance Risk Assessment Committee
PSUR	Periodic Safety Update Report
REB	Research Ethics Board
RMM	Risk Minimization Measures
RRE	Remote Research Environment
SIDIAP	Sistema de Información para el Desarrollo de la Investigación en Atención Primaria
SPC	Summary of Product Characteristics
SR	Strontium Ranelate
STROBE	Strengthening the Reporting of Observational Studies in Epidemiology
TIA	Transient Ischemic Attack
THIN	The Health Improvement Network
UMLS	Unified Medical Language System
WHO	World Health Organization

3. RESPONSIBLE PARTIES

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This protocol has been developed by the investigators and co-investigators, in close collaboration with the MAH.

This study will be conducted according to the ENCePP Code of Conduct.

Servier, as MAH of Protelos®/Osseor® will be responsible to register the protocol in the EU-PAS Register and will update the Register in case of amendments and will enter progress reports as well as the final study report in the Register.

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4. ABSTRACT

Title	*European Program of Post-Authorization Safety Studies for Protelos®/Osseor® through EU-ADR Alliance* *Study number: CLE-12911-046* *Protocol version 3.0* *Authors: Daniel Prieto-Alhambra, Miriam Sturkenboom* *Date: 07 January 2015*
Rationale and background	Strontium ranelate (Protelos®/ Osseor®) has been authorized since 2004 in the European Union for the treatment of osteoporosis in postmenopausal women to reduce the risk of vertebral and hip fracture. Since June 2012, strontium ranelate is also approved for the treatment of osteoporosis in adult men at increased risk of fracture. In the frame of 13th PSUR assessment, data submitted raised concern regarding cardiovascular safety beyond the already recognized risk for venous thromboembolism. As a result of this assessment, an increased risk for serious cardiac disorders, including myocardial infarction has been identified and risk minimization measures specifically targeting this identified risk were recommended by the CHMP. These risk minimization measures included a restriction of the target population by excluding patients with established, current or past history of ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease and/or uncontrolled hypertension, and restricting the indication to severe osteoporosis in postmenopausal women at high risk for fracture to reduce the risk of vertebral and hip fractures and the treatment of severe osteoporosis in adult men at increased risk of fracture. In addition, strontium ranelate therapy should only be initiated by a physician with experience in the treatment of osteoporosis. These changes were disseminated in the form of a DHPC in May 2013. In view of this newly identified risk of serious cardiac disorders, an overall benefit/risk review under Article 20 of regulation (EC) No 726/2004 started in May 2013 and was finalized on 20 February 2014. This led to a restriction of the indication to patients (postmenopausal women and men) with severe osteoporosis at high risk of fracture for whom treatment with other medicinal products approved for

	the treatment of osteoporosis is not possible due to, for example, contraindications or intolerance. As part of RMM, a new DHPC was disseminated in March 2014. The overarching aims of the proposed study are: 1. To study the effect of the risk minimization measures for Strontium Ranelate 2. To estimate and compare the incidence rates of cardiac and thromboembolic events in new users of SR and new users of bisphosphonates
Research question and objectives	PRIMARY OBJECTIVES: **Effectiveness of risk minimization** 1. To characterize utilization patterns of strontium ranelate in three periods: up to May 2013 (first DHPC), between June 2013 and March/2014 (second DHPC), and from April 2014 onwards. 2. To estimate the prevalence of contraindications in SR users during the same three periods. 3. To calculate the prevalence of SR users who fulfil the new indications (after imposition of new restrictions of use) for SR therapy in the same three periods. **Safety** 1. To estimate the incidence rates of cardiac and thromboembolic events in SR users with and without contra-indications prior and after June 2013. 2. To compare the risk of cardiac and thromboembolic events between new users of SR and new users of oral bisphosphonates without contra-indications, both before and after June 2013.
Study design	Multi-national multi-database approach with: 1. Population-based cohort study 2. Nested case control analysis in a cohort of new users of strontium ranelate or oral bisphosphonates (BP).
Population	**Setting** The study will be conducted using routinely collected health care data from databases that participate in the EU-ADR Alliance. EU-ADR Alliance is a network of research institutes that conduct

	pharmacoepidemiological research. For this study data will be used from 5 EU countries: Denmark, Italy, the Netherlands, Spain, and the United Kingdom. **Study population** The study population will comprise the entire source population for the measurement of risk minimization effectiveness. It comprises a cohort of new SR and oral bisphosphonate users for the comparative safety study. Specific inclusion and exclusion criteria will apply Study period: the study period will start in 2004 (2006 for SIDIAP) and end at latest data supply. This period will be split in three analysis periods for the analysis of effectiveness of RMM: 1. Up to May 2013 (first DHPC and SmPC revision): *reference period* 2. From June 2013 to March 2014 (second DHPC and SmPC revision): *transitional period* 3. And from April 2014 onwards: *assessment period* Similarly, the study period will be split in two analysis periods for the safety studies: 1. Up to May 2013 2. From June 2013 onwards
Variables	**Safety endpoints** 1. Acute myocardial infarction 2. Thromboembolic events (deep venous thrombosis and pulmonary embolism) 3. Cardiovascular death **Contra-indications** Venous thromboembolism, ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease, uncontrolled hypertension **New indications/prescribing conditions** Experienced prescriber; treatment not in first line; severe osteoporosis
Data sources	Data from 5 electronic healthcare databases (all listed in ENCePP registry of data sources except Aarhus) 1. The Integrated Primary Care Information Project (IPCI) from the Netherlands, 2. The Sistema d'Informació per al Desenvolupament

	de la Investigació en Atenció Primària (SIDIAP) from Spain, 3. The Health Improvement Network (THIN) from the UK, 4. Aarhus Database (Denmark), and 5. The HSD-Thales database (Italy)
Study size	All users of strontium ranelate during study period (> 100,000 prevalent and 30,000 incident users expected based on feasibility) & cohort of new oral bisphosphonates users for comparison of safety.
Data analysis	**Utilization of strontium ranelate** *Population level*: Incidence and prevalence of SR use will be described by year, month, age and gender. *Patient level*: patterns of use (switching, stopping and duration) will be described for all incident and prevalent users. Baseline characteristics will be described for all incident and prevalent SR users. Analyses will be stratified by period (as described above), by month, country, age, and gender. **Prevalence of contra-indications and new indications of use/restrictions** We will assess the prevalence (and 95% Confidence Intervals) of contra-indications and new indications/restrictions for incident and prevalent users of SR at a patient level in the three periods defined above (*reference*, *transitional*, and *assessment*), as well as by year, month, country, age and gender. Interrupted time series analyses will be carried out to assess the impact of the RMM on these. Each contributing data source will be analysed using an interrupted times series design (Ramsay, 2003), using repeated measures before (up until May 2013) and after intervention (from April 2014 onwards) to control for secular trends. Trends in the *reference* period (up until May/13) will therefore be compared to those in the *assessment* period (April/14 onwards) using the *transitional* period (June/13 to March/14) as a lag time for the intervention to take effect. Sensitivity analyses excluding participating countries where legal restrictions have been put in place for the prescription of SR in primary care (i.e. Spain) will be carried out and reported accordingly. **Safety**

	Crude, as well as age and sex-specific incidence rates of cardiac, thromboembolic (deep vein thrombosis and pulmonary embolism) events, and cardiovascular death during use of SR will be estimated in strata of persons with 0, 1, 2, or more contra-indications amongst persons initiating SR prior and after June 2013. Estimates will be further stratified by age and gender. The risk of cardiac, thromboembolic events and cardiovascular death will be compared between current use of SR and past use of SR/BP as well as between current use of SR and current use of BP, in persons without contra-indications at start of osteoporosis therapy. Each case will be matched by age, index date, gender, and country/data source to 10 controls. Nested case-control analyses will be done using conditional logistic regression. Sensitivity analyses excluding participating countries where legal restrictions are in place for the prescription of SR in primary care (i.e. Spain) will be reported.

Milestone	**Planned date**
Protocol submission to EMA	by 30 June 2014
Protocol approval by EMA	March 2015 *
Contract signature for study roll-out phase	April 2015*
Registration in the EU PAS register	April 2015*
Start of data collection	April 2015*
Statistical Analysis Plan	May 2015
End of data collection	End of June 2015
PSUR Update 1	October 2015
Start of data collection (second wave)	April 2016
End of data collection (second wave)	End of June 2016
PSUR Update 2	October 2016
Start of data collection (third wave)	April 2017
End of data collection (third wave)	End of June 2017
PSUR Update 3	October 2017
Final report of study results	End of November 2017

**Delay will impact the subsequent dates.*

5. AMENDMENTS AND UPDATES

Not applicable.

6. MILESTONES

Milestone	Planned date
Protocol submission to EMA	by 30 June 2014
Protocol approval by EMA	March 2015 *
Contract signature for study roll-out phase	April 2015*
Registration in the EU PAS register	April 2015*
Start of data collection	April 2015*
Statistical Analysis Plan	May 2015
End of data collection	End of June 2015
PSUR Update 1	October 2015
Start of data collection (second wave)	April 2016
End of data collection (second wave)	End of June 2016
PSUR Update 2	October 2016
Start of data collection (third wave)	April 2017
End of data collection (third wave)	End of June 2017
PSUR Update 3	October 2017
Final report of study results	End of November 2017

**Delay will impact the subsequent dates*

Milestones have been planned to maximise the efficiency and availability of data retrieval from the different data sources. A summary of such information is provided here:

Data source (Country)	Periodicity of updates	Time of the year when updates are released	Data availability for each update
SIDIAP (Spain)	Yearly	April-May	End (December 31st) of previous calendar year
IPCI (NL)	Yearly (twice is possible)	April-May	Variable as GPs provide not all at same time
THIN (UK)	Three times per year	Irregular	Variable as GPs provide not all at same time
HSD (Italy)	Every 6 months	June and December	End of previous calendar year (in June); up to June in December.
AUH (Denmark)	Yearly	May	December 31st the previous year

Both national regulations and prescribing practices have changed throughout the participating databases in recent months. As a consequence, in Italy, where GPs in primary care are not allowed anymore to initiate or renew strontium ranelate treatment since December 2013, the number of incident strontium ranelate users in the assessment period is expected to be null or very low. This point will be assessed for the first PSUR update (October 2015) as part of the analyses of the utilization patterns at population level (see section 9.7.2.1).

7. RATIONALE AND BACKGROUND

7.1. Product

Strontium ranelate (Protelos®/ Osseor®) has been authorized since 2004 in the European Union for the treatment of osteoporosis in postmenopausal women to reduce the risk of vertebral and hip fracture. Since June 2012, strontium ranelate is also approved for the treatment of osteoporosis in adult men at increased risk of fracture. In both indications, the daily dose is 2 g daily (oral). Strontium ranelate is currently authorized in 104 countries and marketed in 91 countries.

7.2. Regulatory action

In the frame of 13th PSUR assessment, data submitted raised concern regarding cardiovascular safety beyond the already recognized risk for venous thromboembolism. Analysis of pooled data from randomized studies in around 7,500 post-menopausal women with osteoporosis showed an increased risk of myocardial infarction with Protelos/Osseor as compared with placebo (1.7% versus 1.1 %), with a relative risk of 1.6 (95% CI, 1.07 to 2.38), and an increased risk of venous thrombotic and embolic events — 1.9% versus 1.3 % with a relative risk of 1.5 (95% CI, 1.04 to 2.19).

As a result of this assessment, an increased risk for serious cardiac disorders, including myocardial infarction has been identified and risk minimization measures specifically targeting this identified risk were recommended by the CHMP. These risk minimization measures included a restriction of the target population by excluding patients with established, current or past history of ischaemic heart disease, peripheral arterial disease and/or cerebrovascular disease and/or uncontrolled hypertension, and restricting the indication to severe osteoporosis in postmenopausal women at high risk for fracture to reduce the risk of vertebral and hip fractures and the treatment of severe osteoporosis in adult men at increased risk of fracture. Patients with significant risk factors for cardiovascular events (e.g. hypertension, hyperlipidaemia, diabetes mellitus and smoking) should only be treated with strontium ranelate after careful consideration. In addition, strontium ranelate therapy should only be initiated by a physician with experience in the treatment of osteoporosis. These changes were disseminated in the form of a DHPC in May 2013.

In view of this newly identified risk of serious cardiac disorders, an overall benefit/risk review under Article 20 of regulation (EC) No 726/2004 started in May 2013 and was finalized on 20 February 2014 (EMA/112925/2014, 2014). This led to a restriction of the indication to patients (postmenopausal women and men) with severe osteoporosis at high risk of fracture for whom treatment with other medicinal products approved for the treatment of osteoporosis is not possible due to, for example, contraindications or intolerance. As part of RMM, a new DHPC was disseminated in March 2014.

Following the outcome of this referral, the MAH has to conduct a non-interventional safety study to evaluate the effectiveness of the applied risk minimization measures.

7.3. Observational studies on strontium ranelate use and cardiovascular risk

In the subsequent months, 3 observational studies based on electronic health care databases were published studying the association between strontium ranelate use and cardiovascular risk.
In a nation-wide Danish study by Abrahamsen *et al* (2014), all incident users of SR in the period 2005-2007 in Denmark were identified. In these patients the prevalence of IHD/PAD/CVD (new contraindications) combined was 19.2% in women and 29.5% in men. The risk of myocardial infarction or that of stroke did not differ significantly from other anti-osteoporosis medications, but a 20% increase in all-cause mortality was observed in the group using SR.

A second population-based nested case-control study (Cooper, 2014) used data on women treated with anti-osteoporosis medications in the UK CPRD database between 2002 and April/2012. Amongst 112,445 eligible cohort members, current or past use of SR (compared to no use of SR whatsoever) was not associated with an increased risk of myocardial infarction or cardiovascular death (adjusted OR 1.05, 95% CI [0.68-1.61] and OR 0.96, 95% CI [0.76-1.21] respectively).

Finally, a third study using Danish registers and recently published in the Annals of Rheumatic Diseases (Svanstrom, 2014) has studied the association in women between use of SR and risk of acute coronary syndrome and all-cause mortality using a cohort design. In this case, incident users of SR in 2005-2011 were compared to users of the most commonly used anti-osteoporosis medications (alendronate and risedronate) with similar disease severity. As in the two previous studies, the risk of acute coronary syndrome and death was similar for SR compared to alendronate/risedronate users, with adjusted HR 0.89, 95% CI [0.52-1.55] and HR 0.96, 95% CI [0.76-1.21].

8. RESEARCH QUESTION AND OBJECTIVES

This regulatory requested post-authorization safety study will address the following main research questions:

1. What is the effectiveness of the risk minimization measures in different EU member states?
2. Is strontium ranelate associated with an increased risk of cardiac and thromboembolic events?

Therefore, our objectives are:

PRIMARY OBJECTIVES:

Effectiveness of risk minimization

1. To characterise utilization patterns of strontium ranelate in three periods: up to May 2013 (*reference* period), from June 2013 to March 2014 (*transitional* period), and from April 2014 onwards (*assessment* period).
2. To estimate the prevalence of contraindications in SR users during the same three periods: up to May 2013 (*reference* period), from June 2013 to March 2014 (*transitional* period), and from April 2014 onwards (*assessment* period).

3. To calculate the prevalence of SR users who fulfil the new indications (after imposition of new restrictions of use) for SR therapy in these three periods: up to May 2013 (*reference* period), from June 2013 to March 2014 (*transitional* period), and from April 2014 onwards (*assessment* period).

Safety

1. To estimate the incidence rates of cardiac and thromboembolic events in SR users with and without contra-indications prior and from June 2013.
2. To compare the risk of cardiac and thromboembolic events between new users of SR and new users of oral bisphosphonates without contra-indications, both before and from June 2013.

All of these research objectives will be addressed for the overall eligible population but also after stratification by country, gender, period (three analysis periods (reference, transitional, and assessment) for the assessment of RMM effectiveness, and two periods (before and from June 2013) for the safety studies), month and age, and presence/absence of contra-indications, when applicable/relevant.
In addition, sensitivity analyses excluding participating countries where legal restrictions are in place for the prescription of SR in primary care (i.e. Spain) will be carried out for both the RMM effectiveness and safety studies, and reported accordingly.

9. RESEARCH METHODS

9.1. Study design

A multinational, multi-database non-interventional population-based cohort design has been chosen as primary design for the assessment of the effectiveness of risk minimization measures.

For the safety study a multinational, multi-database non-interventional nested case control study will be conducted in a cohort of new strontium ranelate or new oral bisphosphonate users.

9.2. Setting

This study will be conducted by the EU-ADR Alliance, an academic Alliance of pharmacoepidemiological research institutes in the EU that have decided to collaborate in a distributed fashion to conduct active drug surveillance studies. These institutes have been working together in several EC funded drug safety projects in a similar distributed fashion. Data from the following five European electronic health care databases will be obtained for this study: the Integrated Primary Care Information Project (IPCI) from the Netherlands, the Health Search Database (HSD) from Italy, The Health Improvement Network (THIN) from the UK, the Sistema d'Informació per al Desenvolupament de la Investigació en Atenció Primària (SIDIAP) from Spain, and the Aarhus University Prescription Database from Denmark.

9.2.1. Source population

The source population consists of all subjects that are registered for at least one year with one of the participating databases during the study period.

9.2.2. Study Period

The study period will start on January 1st 2004 (year of licensing) for all databases except January 1st 2006 for SIDIAP (as data is only available from 2005, and a 1-year washout is required) and will end at the most recent version of data that is available with each of the database custodians.
The study period will be divided into three analysis periods for the assessment of RMM effectiveness: up to May 2013 (*reference* period before first DHPC and revised SmPC), between June 2013 and March 2014 (*transitional* period), and after April 2014 (*assessment* period after second DHPC and new SmPC revision).
As for the safety studies, the study period will be divided in two analysis periods: 1.up to May 2013 (when the first DHPC was published, imposing new contraindications), and 2.from June 2013 (when patients with any of the new contraindications should not be prescribed SR any longer) onwards.

9.2.3. Study population

The study population for this study comprises:
1. The source population for the measurement of RMM effectiveness.
2. New (not using drug in year prior to cohort entry) strontium ranelate users and new oral bisphosphonates users (BP) for the safety study.

9.2.4. Inclusion criteria

Effectiveness of RMM
Patients may enter the study cohort when they meet the following inclusion criteria:
1. Continuous enrolment in the database for at least 1 year prior to the start of follow-up.

Safety
1. Continuous enrolment in the database for at least 1 year prior to the start of follow-up.
2. 50 years or older upon cohort entry (prescription for new SR or oral BP). The chosen cut-off for an age restriction (50 years) is based on a standard age for menopause and related disorders including post-menopausal osteoporosis, which will avoid or minimize the inclusion of users of anti-osteoporosis medications for reasons other than fracture prevention such as Paget's disease of bone.
3. Incident use of strontium ranelate (no use in year prior to cohort entry) or incident use of oral bisphosphonates (alendronic, risedronic, and ibandronic acid) during follow-up.

The list of ATC/BNF codes used for the identification of patients is detailed in Appendix 14.3.1.

9.2.5. Exclusion criteria

9.2.5.1. Effectiveness of RMM

None.

9.2.5.2. Incidence rates of safety endpoints

None.

9.2.5.3. Comparative safety study

Patients with any of the newly defined contra-indications will be excluded:

1. Established, current or past history of ischemic heart disease (IHD),
2. Peripheral arterial disease (PAD),
3. Cerebrovascular disease (CVD),
4. Uncontrolled hypertension, defined by MAH using an operational definition as follows: a patient will be defined as 'uncontrolled hypertension' if the 3 following conditions apply:
   a. There is a previous diagnosis of hypertension coded in electronic medical records.
   b. There is documented use of any anti-hypertensive therapy (either at that time or in the previous year before SR/BP initiation).
   c. There are at least two readings of Systolic Blood Pressure≥150 or Diastolic Blood Pressure≥95 mmHg recorded in the 3 months prior to SR/BP initiation.

Also, eligible patients with a diagnosis of Paget's disease of bones will be excluded. And for the outcome VTE we will exclude patients with a previous VTE.

9.2.6. Follow-up

9.2.6.1. Effectiveness of risk minimization

Patients will be followed from the latest of the following dates:

- Start of study period.
- One year of valid data in database.

Until the earliest date of:

- The end of enrolment in the database (due to moving out or death).
- Date of last data capturing in the database.

These analyses will be performed in three periods *(reference, transitional, and assessment periods as defined above)* based on the date of cohort entry.

9.2.6.2. Safety study

Patients will be followed from the date of incident prescription of strontium ranelate or oral bisphosphonate (after one year of non-use) which follows the latest of the following dates:

- Start of study period.
- One year of valid data in database.

Until the earliest date of:

- The end of enrolment in the database (due to moving out or death).
- Date of last data capturing in the database.

The safety study will be performed in two periods (up till May 2013 and from June 2013 onwards) based on the date of cohort entry.

9.3. Variables

9.3.1. Safety endpoints

Ascertainment of cases: cases will be all persons with a first occurrence after cohort entry of:

- Acute myocardial infarction.
- Thromboembolic events (deep venous thrombosis and pulmonary embolism).
- Cardiovascular death.

Cases will be identified from the medical records (see codes in Appendix 14.3).

Acute myocardial infarction has been recently validated in all of the participating data sources (Coloma, 2013; Ramos, 2012) and will therefore not need further linkage or validation studies.

Thromboembolic events have been validated in the UK CPRD/THIN (Lawrenson, 2000) and Aarhus (Severinsen, 2010), and these previously validated algorithms will be used to identify cases. A random sample of cases of thromboembolic events in each data source will be validated using either free text manual review (IPCI, HSD, and Aarhus) or linkage to hospital admissions data (THIN and SIDIAP). If the estimated positive predictive value in these samples is >75%, no further validation will be performed for thromboembolic events. Otherwise, all the events observed in the safety study (i.e. cases) will be individually validated, and only those found to be valid (either by manual review or related hospital admission from hospital records databases, as proposed above) will be defined as cases.

As for cardiovascular death, HSD, IPCI and SIDIAP will combine ICPC and ICD9/ICD10 codes (for hospital admission/primary care records) respectively with mortality using a time specific window to define cardiovascular death. In THIN, data will be linked to the official mortality registry (office for national statistics) for cause of death. In Aarhus, safety endpoints will be identified in the patient registry (hospital discharge and death registry) and no manual validation in the medical records will be done.

Control selection: In the nested case control study, each case will be matched by age (same year of birth), index date, gender, and country/data source to 10 controls selected from the cohort using incidence density sampling.

9.3.2. Contra-indications and new indications

CONTRA-INDICATIONS

- History of Ischemic heart disease (IHD): myocardial infarction, angina pectoris, coronary artery bypass surgery (diagnoses or nitrate use) in year prior to SR therapy initiation.
- History of Peripheral arterial disease (PAD) in year prior to SR therapy initiation.
- History of transient ischemic attack (TIA) or stroke (ischemic or haemorrhagic) in year prior to SR therapy initiation.
- Uncontrolled hypertension, defined by MAH as the combination of the following: 1.previous diagnosis of hypertension coded in electronic medical records; 2.documented use of any anti-hypertensive therapy (either at that time or in the previous year before SR therapy initiation); and 3. at least two readings of Systolic Blood Pressure≥150 or Diastolic Blood Pressure ≥95 mmHg recorded in the 3 months prior to SR therapy initiation.
- History of thromboembolic events (pulmonary embolism and deep venous thrombosis) in year prior to SR therapy initiation.

NEW INDICATIONS OF USE

Regarding the new restrictions, some of these criteria are not directly captured in the databases. Thus, operational definitions are proposed using some proxies which could lead to some misclassification or underestimation of the new restrictions. Therefore, some validation or refinement steps based on data availability and quality are required and will be further discussed with each of the academic partners before data extraction; for instance through feasibility assessed on a random sample.

- *A physician with experience in the treatment of osteoporosis*. The operational definition for this in our data sources will be:
  - Therapy initiation in secondary care settings (where available: Aarhus Database)

  OR
  - Therapy initiation in primary care by a physician with a “high number” of patients diagnosed with osteoporosis or on anti-osteoporosis treatment under his/her care. As both national regulations and prescribing practices have changed throughout the participating databases in recent months (e.g. general practitioners are not allowed to either initiate or prescribe repeat prescriptions of SR in Italy, different to Spain, where GPs cannot initiate but can issue repeat prescriptions of the drug), the definition of “high number” of patients with a diagnosis or treatment for osteoporosis will be based on national figures: a GP will be classified as “experienced” (with a high number of osteoporotic patients) if the number of patients with a diagnosis or treatment for osteoporosis registered with him/her is above a discriminant threshold; for instance, in the top quartile (percentile 75 or above) in the same country/data source.

- *Initiation of SR therapy not in first line*, will be operationalized as:
  - Previous use of other anti-osteoporosis drugs at any time before SR therapy

  OR
  - History of any formal contra-indications or precautions for the use of oral bisphosphonates (according to SmPC for alendronic, risedronic and ibandronic acid) not recognised as contra-indications or precautions for the use of SR [Appendix 14.3] at any time before SR therapy.

- *Use of SR for the treatment of severe osteoporosis*, will be operationalized as:
  - History of a previous osteoporotic fracture [Appendix 14.3.2] (at any time before SR therapy initiation).

  OR
  - High absolute fracture risk, defined as ≥10% 5-year fracture risk according to the Garvan prediction tool (Nguyen, 2008) (where data on age and either bone mineral density or weight are available for the estimation of risk).

9.3.3. Exposure

Study drugs

The main drug of interest in both the effectiveness of RMM as well as safety study is Strontium ranelate (ATC M05BX03).

The safety will be compared with users of oral bisphosphonates (active comparator) (ATC M05BA04 – alendronate, M05BA06 - ibandronate, or M05BA07 - risedronate)

While a number of the databases contain information on drug dispensing, for ease of description we refer to data as relating to ”prescriptions” throughout the protocol.

Duration of treatment

In order to create episodes of drug use the duration of treatment will be calculated using the following definitions:

- *Legend duration*: Total units /prescribed daily dose.
- *Normal duration*: Total number of defined daily doses (DDDs) prescribed: Total Units*Strength)/DDD value.

In order to define periods of continuous use of study drugs, any two prescriptions of the same drug will be concatenated if the gap between the end of the first of the two prescriptions and the start of the second of the two prescriptions was less than 30 days apart, a carry-over period of 30 days will be added after last prescription to account for lack of compliance and carry-over effects.

Exposure categorization for safety studies

For the incidence rate calculations the period of drug use will be divided in mutual exclusive periods of a month to be able to investigate the rate of cardiac events during current, recent or past use. The period 0-180 days after cessation of study drugs use will be classified as recent use and the period 181 days or more will be classified as past use. If patients switch from SR to BP or vice versa, they will contribute to the respective exposure category.

For the case control study we follow the same categorization. A patient will be classified as current user if the last prescription is ongoing or stopped less than 30 days ago before the index date. Patients will be classified as recent users if last prescription stopped between 30 and 180 days before the index date. Patients are past users if the last prescription for a study drug stopped more than 180 days before index date.

9.3.4. Co-variables (potential confounders)

All potential confounders listed here will be identified both at cohort entry (for characteristics of new SR users and BP users -See Section 9.7.3.1) and at index date for cases & controls within the safety study (See Section 9.7.3.3).

General potential confounders

- Age (matching factor).
- Gender (matching factor).
- Calendar time (matching factor).
- Alcohol abuse (if available).
- Health seeking behaviour: number of visits to general practitioner or hospital contacts in the year before cohort entry/index date.
- Use of any drugs: number of different compounds used in the year previous to cohort entry/index date.

Cardiovascular risk factors

- Hyperlipidemia according to coded diagnoses or the presence of a raised level of total cholesterol or LDL cholesterol in medical records at cohort entry/index date (also precautionary condition).
- Use of lipid lowering agents (ATC C10) at cohort entry/index date.
- Smoking status (if available) at cohort entry/index date (precautionary condition).
- Type 2 diabetes mellitus: based on recorded diagnosis or use of oral anti-diabetic agents (ATC A10B) (precautionary condition) at cohort entry/index date.
- History of diagnosed obesity (if body mass index is unavailable) at cohort entry/index date.
- Diagnosis of chronic kidney disease (as recorded in medical records) at cohort entry/index date.
- Diagnosis of hypertension on or before cohort entry/index date.
- Use of antihypertensive drugs in the year prior to cohort entry/index date: alpha blockers (ATC C02CA), B-blockers (ATC C07), ACE inhibitors (ATC C09A/C09B), Angiotensin II inhibitors (ATC C09C/C09D), calcium channel blockers (ATC C08C)).
- Use of low-dose aspirin (ATC B01AC06) or clopidogrel (ATC B01AC04) in the year prior to cohort entry/index date.
- Previous use of anticoagulants in the year prior to cohort entry/index date: vitamin K antagonists (ATC B01AA), heparins (ATC B01AB), direct thrombin inhibitors (ATC B01AE), direct factor Xa inhibitors (ATC B01AF).

Osteoporosis/Fracture risk factors

- History of osteoporotic fracture as a proxy for osteoporosis severity (all but skull/face, fingers, and toes) prior to cohort entry/index date (Appendix 14.3.1).
- Previous use of anti-osteoporosis medications (ATC M05B) in the year prior to index date/cohort entry.
- Previous use of prescribed vitamin D supplements (ATC A11CC01, A11CC03, A11CC04, A11CC05, A11CC06, and A11CC20) in the year prior to index date/cohort entry.
- Previous use of prescribed calcium supplements (ATC A12AA01, A12AA02, A12AA03, A12AA04, A12AA05, A12AA06, A12AA07, A12AA08, A12AA09, A12AA10,

A12AA11, A12AA12, A12AA13, A12AA20, and A12AA30) in the year prior to index date/cohort entry.

- Previous use of prescribed calcium and vitamin D (concomitant) supplements (ATC A12AX) in the year prior to index date/cohort entry.
- Previous use of systemic glucocorticoids (ATC H02AB) in the year prior to index date/cohort entry.

9.4. Data sources

This study will be conducted using routinely collected data from different data sources that participate in the EU-ADR Alliance. These databases provide representative clinical information as collected in actual practice conditions in different European healthcare settings. The proposed databases have been selected based on their geographic location, the availability of longitudinal population-based data on drug utilization, and their experience in previous multi-database studies on both drug utilization and safety. Five countries from different European areas (two from Southern Europe, two from Central Europe, and one Scandinavian nation) and with very different rates of use of SR (from lowest in Netherlands, to highest in Spain) are included in order to provide heterogeneous and representative data for the evaluation of the effectiveness of the RMM, as well as to guarantee sufficient statistical power for the comparative study. All of the participating databases are part of the EU-ADR alliance, a stable collaboration framework for running drug utilization and safety studies in a federated manner.

Table (9.4) 1 - Overview of contributing databases

Country	**Netherlands**	**United Kingdom**	**Denmark**	**Italy**	**Spain**
Name of the database	IPCI	THIN	Aarhus	HSD- Thales	SIDIAP
Type of database	MR	MR	ADM	MR	MR
# patients, millions	1.2	3.5	1.8	1.5	5.1
Age categories	All	All	All	>15 years	>15 years
Date in	Yes	Yes	Yes	Yes	Yes
Date out	Yes	Yes	Yes	Yes	Yes
Date death	Yes	Yes	Yes	Yes	Yes
Prescriptions					
Outpatient Rx	Yes (specialist incomplete)	Yes (specialist incomplete)	Yes	Yes (specialist incomplete)	Yes (specialist incomplete)
Coding of drugs	ATC	BNF/Multilex	ATC	ATC	ATC
Dosing regimen	Yes	Yes	No	Yes (incomplete)	Yes
Outcomes					
Hospitalizations	Yes	Yes	Yes	Yes	Yes
Outpatient diagnoses	Yes	Yes	Yes	Yes	Yes
Coding of disease	ICPC	READ	ICD-10	ICD-9 CM	ICD-10
Cause of death	Yes (from text)	If linked to death registry	Yes	No	No

ADM = administrative; ATC = Anatomical Therapeutic Chemical; BNF = British National Formulary; ICPC = International Classification of Primary Care; MR = Medical Records

All of the chosen databases comply with European Union (EU) guidelines on the use of medical data for medical research and have been validated for pharmaco-epidemiological research (Cazzola, 2011; Vlug, 1999).

The databases will be THIN (UK), HSD (Italy), IPCI (NL), the Aarhus University Database (DK) and SIDIAP (Spain). Table (9.4) 1 provides an overview of key elements of these databases. The total number of persons in the source population will be around 12 million as of 2012.
HSD (Italy), IPCI (Netherlands), SIDIAP (Spain) and THIN (UK) are listed under the ENCePP resources database: (www.encepp.eu/encepp/resourcesDatabase.jsp).

9.4.1. IPCI Database

In 1992 the Integrated Primary Care Information Project (IPCI) was started by the Department of Medical Informatics of the Erasmus University Medical Centre. IPCI is a longitudinal observational database that contains data from computer-based patient records of a selected group of general practitioners (GPs) throughout The Netherlands, who voluntarily chose to supply data to the database. Collaborating practices are located throughout The Netherlands and the collaborating GPs are comparable to other GPs in the country according to age and gender. In the Netherlands, all citizens are registered with a GP practice, which forms the point of care and acts as a gatekeeper in a two-way exchange of information with secondary care. The medical records of each patient can therefore be assumed to contain all relevant medical information including medical findings and diagnosis from secondary care.
The IPCI database is representative for the Dutch population regarding age and gender (Voordouw, 2004).
The database contains information on about 1.5 million patients. This is the cumulative amount of patients who have ever been part of the dynamic cohort of patients who have been registered. The International Classification of Primary Care (ICPC) is the coding system for patient complaints and diagnoses, but diagnoses and complaints can also be entered as free text. Prescription data such as product name, quantity prescribed, dosage regimens, strength and indication are entered into the computer (Vlug, 1999). The National Database of Drugs, maintained by the Royal Dutch Association for the Advancement of Pharmacy, enables the coding of prescriptions, according to the ATC classification scheme recommended by the World Health Organization (WHO, 2008). Approval needs to be obtained for each study from the governance board.

9.4.2. HSD – CSD Longitudinal Patient Database

The Italian partner for the study will use the Health Search CSD Longitudinal Patient Database (HSD), a longitudinal observational database that is representative of the Italian general population. HSD was established in 1998 by the Italian College of General Practitioners (Filippi, 2005). The HSD contains data from computer-based patient records from a selected group of GPs covering a total of 1.5 million patients) located throughout Italy. These GPs voluntarily agreed to collect data for the database and attend specified training courses. The database includes information on the age, gender, and identification of the patient, and GP registration information, which is linked to prescription information, clinical events and diagnoses, hospital admission, and causes of death. All diagnoses are coded according to ICD-9-CM. Drug names are coded according to the ATC classification system (WHO, 2008). To be included in the study, GPs must have provided data for at least 1 year

and meet standard quality criteria pertaining to: levels of coding, prevalence of well-known diseases, and mortality rates (Cricelli, 2003). The HSD has been used as data source for a number of peer-reviewed publications on the prevalence of disease conditions, drug safety and prescription patterns in Italian primary care (Cazzola, 2011). Approval for use of data is obtained from the Italian College of General Practitioners for each study.

9.4.3. THIN Database

The Health Improvement Network (THIN) is a database of primary care medical records from the UK. General practitioners are trained to complete their medical records using the Vision general practice computer system (InPractice Systems, London, UK). This electronic record serves as the primary medical records for the practice.
Data recorded in THIN include demographics, details from GPs' visits such as medical diagnoses and prescriptions written by the GPs, diagnoses from specialist referrals and hospital admissions, some results of laboratory tests, some lifestyle characteristics and other measurements as taken in the practice. Within the database, diagnoses are recorded using READ codes. Prospective data collection for THIN began in September 2002, with electronic medical records that date back to 1985. In addition, practices may retrospectively enter significant medical events into the electronic medical record. Currently, the database has 2.7 million active patients registered. Recently a validation study was conducted by Lewis *et al* (2007) which concluded that "THIN data that are collected outside of the Clinical Practice Research Datalink (CPRD) appear as valid as the data collected as part of the CPRD".
As the primary aim of the collection of data in the THIN database is patient management, data will reflect only those events that are deemed to be relevant to patient's care. In addition; use of THIN data is not appropriate in studies where individual ethnicity, occupation, employment, and/or socio-economic status are important variables. As for all prescription databases, over-the-counter (OTC) drug use and non-compliance to medication prescriptions might be an issue. As the average follow-up within the THIN database is 5.5 years, the THIN database is not suitable to conduct long-term follow-up studies. Approval needs to be obtained for each study from the THIN governance board.

9.4.4. Aarhus Database

The Aarhus University Prescription database comprises clinical and prescription data on the population of former North-Jutland, Aarhus, Rinkjebing and Viborg counties, which since 2007 are called the Central Denmark Region and the North Denmark Region. This population covers a total of 1.8 million inhabitants and is representative of the population of Denmark (Ehrenstein, 2010). Data available on these subjects comprise their eligibility, dispensing data, hospitalizations and procedures and the population can also be linked to other National Danish registries. Dispensing data comprise the filled prescriptions for all ambulatory patients and contains information on name of the drug, ATC code, package identifier (strength and route of administration), and the date of refill. These data can be linked to the national registry of patients that comprises information on admissions to Danish somatic hospitals, emergency rooms and outpatient clinics, diagnosis codes and procedures are registered. These databases have been used in numerous studies and are proven valid for pharmaco-epidemiological research (Ehrenstein, 2010). The study must be announced at the governance committee.

9.4.5. SIDIAP Database

GPs play an essential role in the public health care system of Spain, as they are responsible for primary health care, long-term prescriptions and specialist and hospital referrals. The Spanish public health care system covers more than 98% of the population. SIDIAP Database comprises of electronic medical records of a representative sample of patients attended by GPs in Catalonia (North-East Spain), covering a population of more than 5.1 million patients (about 80% of the total of 7.5 million population of Catalonia) from 274 primary care practices with 3,414 participating GPs. The SIDIAP data comprises the clinical and referral events registered by primary care health professionals (GPs and nurses) and administrative staff in electronic medical records, comprehensive demographic information, prescription and corresponding pharmacy invoicing data, specialist referrals, primary care laboratory test results, and hospital admissions and their major outcomes.

Health professionals gather this information using ICD-10 codes, and structured forms designed for the collection of variables relevant for primary care clinical management, such as country of origin, sex, age, height, weight, body mass index, tobacco and alcohol use, blood pressure measurements, blood, and urine test results. Only GPs who meet quality control standards can participate in the SIDIAP database. Encoding personal and clinic identifiers ensures the confidentiality of the information in the SIDIAP Database. Recent reports have shown the SIDIAP data to be useful for epidemiological research (Garcia-Gil Mdel, 2011).
Studies performed using SIDIAP data require previous approval by both the Scientific and the Ethics Committee.

9.5. Study size

As this study will be carried out using routinely collected data, all eligible participants will be included. Based on feasibility counts from all data providers, the number of prevalent (already users in 2011) and incident (non-users in 2011) users of strontium ranelate in the proposed sources of data in the year 2012 are provided in Table (9.5) 1. After study start the exact numbers of included and excluded persons will be known over the entire period. We expect to have more than 100,000 prevalent and over 30,000 incident SR users over the study period.

Table (9.5) 1 - Number of SR users in available data sources in 2012

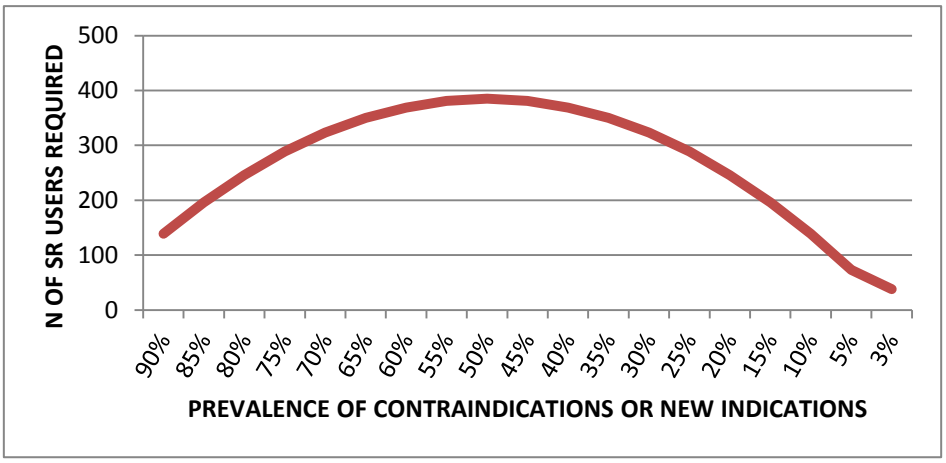
Country	**Data source**	**Denominator**	**Incident users**			**Prevalent users**		
			Total	*Men*	*Women*	*Total*	*Men*	*Women*
Italy	HSD	1.5 million	1209	80	1129	10129	613	9616
Spain	SIDIAP	5.1 million	4008	383	3625	14502	917	13585
UK	THIN	3.5 million	514	65	449	2563	255	2308
DK	Aarhus	1.8 million	46	5	41	464	42	412
NL	IPCI	1.2 million	42	1	41	106	14	92
TOTAL		13.1 million	5819	534	5285	27764	1841	26013

9.5.1. RMM effectiveness study

Based on published studies, the combined prevalence of MI, CVD and PAD before the DHPC published in May 2013 is assumed to be of 19.2% in female and 29.5% in male new users of SR (Abrahamsen, 2014).
A total of **320** male users of SR will suffice to estimate with a 95% confidence and an absolute precision of ± 0.05, an unchanged prevalence of MI/CVD/PAD of 29.5%. Similarly, **239** female SR users would suffice to estimate with a 95% confidence and an absolute precision of ± 0.05, an unchanged prevalence of MI/CVD/PAD of 19.2%.
Regarding the prevalence of new indication/restrictions of use (severe osteoporosis, and second line therapy), recent data suggest that the prevalence of these would range from 13.0% (Svanstrom, 2014) to 53.1% (Abrahamsen, 2014) for previous fragility fracture (severe osteoporosis), and from 40.4% (Svanstrom, 2014) to 47.9% (Abrahamsen, 2014) for the use of SR as a second line anti-osteoporosis treatment. Given this, 383 users of SR would suffice to estimate (with 95% confidence and 5% precision) an unchanged prevalence of 53.1% (most conservative scenario) for both indications. Lower numbers would be needed if this prevalence either increases or decreases (See Figure (9.5.1) 1).

A number of scenarios with different possible prevalence rates of MI/CVD/PAD, previous osteoporotic fracture, and use as a second line anti-osteoporosis therapy amongst SR users in subsequent years in the period before the publication of the DHPC in May 2013 (*reference*) and after the publication of the second DHPC from April 2014 onwards (*assessment* period) are presented in Figure (9.5.1) 1.

Figure (9.5.1) 1 - Number of SR users required to estimate the prevalence of contraindications or new indication/restrictions with a 5% absolute precision



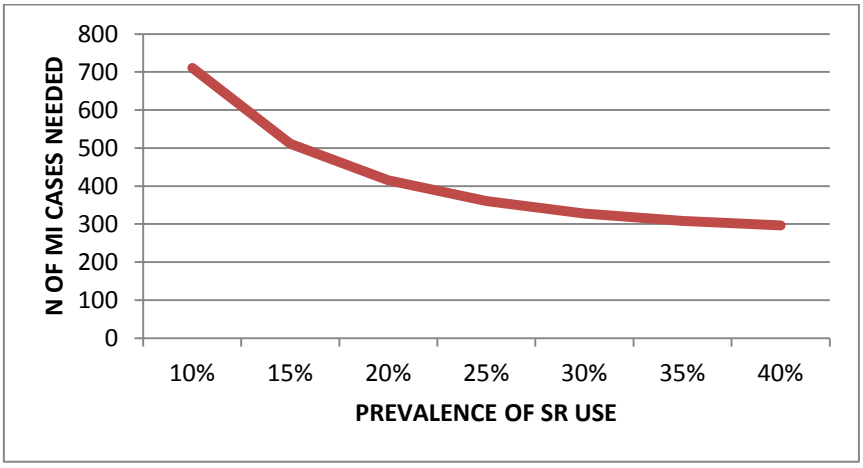
For the interrupted time series analyses (see details below), sample size calculations are related to the estimation of the number of observations or time points at which data will be collected. According to the quality criteria of Ramsey et al, at least 10 pre- and 10 post-intervention data points would be needed to reach at least 80% power to detect a change (if the autocorrelation is >0.4) (Ramsay, 2003). Our outcomes will be estimated at monthly intervals to ensure that >10 data points are available for both the pre-defined *reference* and *assessment* analysis periods.

9.5.2. Safety study

Bearing in mind that the number of incident users identified in 2012 is of 5,819 patients, we expect that at least 30,000 incident SR users will be included for the period 2004-2012, and a lower number of people (500 to 1,000 per annum) will be eligible for the prospective cohort of incident users as identified in 2013-2015 due to the DHPC, making a total of 31,500 to 33,000 SR users. With the combined prevalence of exclusion criteria described above (29.5% for men and 19.2% for women) (Abrahamsen, 2014) and a 90% participants being of female gender (based on feasibility counts for 2012 in Table (9.5) 1), a minimum of 25,128 incident SR users would be included. Considering a prevalence of SR use of 20% in osteoporotic treated population, around 125,640 incident bisphosphonate users are expected, making a total of over 150,000 study participants.

We assume a conservative annual incidence rate of acute myocardial infarction of 0.19/100 person-years in the general population of participants in EU-ADR databases (Coloma, 2013). Based on this and assuming an average follow-up period after cohort entry of 2 years we would expect 570 cases. Accepting an alpha risk of 0.05, with 90% power, and a prevalence of SR use of 20% amongst controls, **415** MI cases and a 1:10 case-control ratio (**4150** controls) would suffice to recognize as statistically significant an odds ratio greater than or equal to 1.5. Different scenarios of SR use ranging from 10% to 40% and the corresponding number of MI cases required for an OR ≥1.5 (at fixed alpha 0.05, power 90%) are shown in Figure (9.5.2) 1.

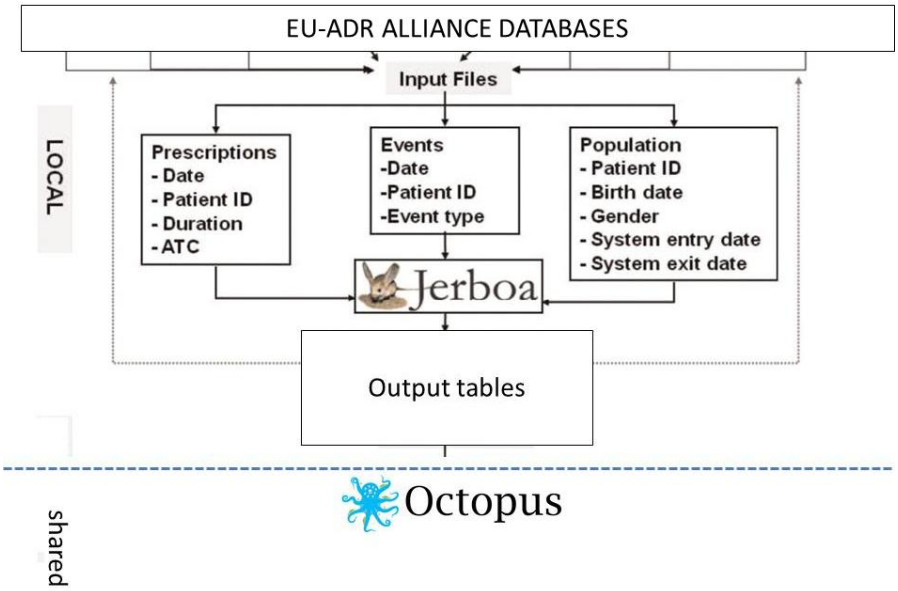
Figure (9.5.2) 1 - Number of MI cases required to ensure 90% power to detect as significant an OR ≥1.5 for the association between SR use and MI.



9.6. Data management

The EU-ADR Alliance works in a federated manner: data extraction and elaboration is done locally and pooling of aggregated data is done on a remote research environment (see Figure (9.6) 1 for overview).

Figure (9.6) 1 - Model for data sharing and elaboration



Due to the different database characteristics and coding schemes it is not possible to use one single data extraction algorithm for all the databases. To reconcile differences across terminologies a shared semantic foundation will be built for the definition of events under study by selecting disease concepts from the Unified Medical Language System (UMLS, V.2008AA), and set up a multi-step and iterative process for the harmonization of event data. The sequential steps of this process are shortly described below:

All events/outcomes and (contra)-indications will be ascertained using a list of agreed ICD (Denmark, Italy, and Spain), ICPC (Netherlands) and READ (UK) codes. The proposed lists of codes (See Appendix 14.3.2) were created following a number of steps:
1. Clinical definition;
2. Preliminary list of concept identifiers using UMLS Metathesaurus Browser;
3. Addition of codes found after literature review of validated lists of codes for each of the study outcomes in each of the databases; and
4. Consensus with academic partners involved in the management and analysis of each of the data sources. As coding might change over time, relevant codes might be updated during the course of the project. Harmonization of these code lists will take place between databases by comparison of population based age and sex specific incidence rates, according to standard quality assurance procedures in the EU-ADR Alliance (see below).

The sets of codes proposed in Appendix 14.3.2 will be further discussed with each of the academic partners during the first months of the study, and before data extraction.

9.6.1. Identification of Unified Medical Language System® (UMLS®) concepts

A UMLS concept is identified by a Concept Unique Identifier (CUI) and describes a single medical notion that can be expressed using different synonyms (terms). For each event, a medical definition will be created and, based on such definition relevant UMLS concepts are identified and projected into the database-specific terminologies. In addition, for those databases where free text is available, the labels of the codes are considered for free text search of the events.

9.6.2. Definition of data extraction algorithm

Based on the relevant diagnostic codes and key words (for free text search), a data extraction algorithm will be constructed for each event based on the consensus of the data providers. This data extraction algorithm will then be implemented by all databases.

9.6.3. Event data extraction

Subsequently, each database extracts data locally and transforms them into a simple common data model, i.e. standardized patient, drug and event files linkable via a patient unique identifier.

9.6.4. Benchmarking of incidence rates of events

For each endpoint and covariate we benchmark database-specific incidence rates (IRs) using Jerboa©, scripts will be generated by Erasmus MC. The observed IRs are compared with IRs estimated from previous database studies and literature. Outliers are identified and further investigated in an iterative manner.
We have used this multi-step process successfully in several other European multi-database projects. It maximizes the involvement of the data providers in the study by utilizing their knowledge on the characteristics and the process underlying the data collection.
After completion of harmonization, output tables for calculation and analysis of study endpoints will be created by the local data processors using the following steps (see Figure (9.6.4) 1).

Figure (9.6.4) 1 - Process to be followed by local data processors

9.6.5. Data elaboration

A standardized Jerboa© script and instructions will be created by Erasmus MC to create the study specific output tables. This will be double coded in Jerboa (JAVA) and SAS (version 9.2).

9.6.6. Missing data

Since the underlying data represent attended medical care we assume that absence of information of clinical events means absence of that condition. Lack of information on smoking, and alcohol use may occur, but this is unlikely differential.

9.6.7. Data sharing

A study-specific folder on the central Octopus remote research environment (RRE) for secure access by members will be used to analyze the output provided by Jerboa©. These output files will contain only anonymized de-identifiable data that will be shared in the RRE where members will have a secure and restricted access and where data will be analyzed. SAS, version 9.2, will be used for post-processing of data.

9.7. Data analysis

Below the main statistics will be described, a detailed statistical analysis plan will be prepared after PRAC approval of protocol.

9.7.1. Statistical elements

Categorical data will be presented in counts (n) and proportions (%) with 95% confidence intervals (95% CIs). 95% CIs will be calculated using the normal or Poisson distribution.

For continuous data, number of observations (n), number of patients with missing information (if applicable), mean, and standard deviation will be reported for normally distributed variables. Median and inter-quartile range will be presented for non-normally distributed continuous variables.

For the comparison of groups Chi-square, independent samples T-tests and Wilcoxon tests will be used to test for differences in categorical, normally distributed and non-normally distributed continuous variables respectively.

Analyses will be performed for the overall eligible population but also after stratification by gender, period, and presence/absence of (contra) indications, when applicable/relevant.

Effectiveness of RMM will be assessed using interrupted time series analyses.

Nested case-control analyses will be done using conditional logistic regression.

9.7.2. Effectiveness of the RMM

9.7.2.1. Utilization of Strontium ranelate

Utilization patterns population level

Incidence of SR use will be calculated by dividing the number of new users in each month of the year by the amount of population person-time in each month. A new user is defined as a person without a prescription for SR in the 365 days prior to the index prescription.

Prevalence of SR use will be calculated by dividing the number of patients who have at least one day of SR use in a specific time unit (month or year) by the amount of population person-

time in that time unit (Note person-time is used rather than the number of persons due to the dynamic character of the underlying population).

Prevalence and incidence of SR use in each of the data sources will be calculated with their 95% CIs calculated assuming a binomial and Poisson distribution respectively. All estimates will be stratified by time (month, period and calendar years) as well as by country (database), age and sex and country.

Utilization patterns patient level
For patient level analyses SR users will be divided into incident and prevalent users. Incident users are all persons who have a first prescription for SR during the study period (one year of absence prior), prevalent users are persons who have at their first prescription during the analysis period evidence of prior prescriptions in the year before the start of the period. For prevalent users we do not know how long they have been using SR.

Persistence of use: persistence is the time since start of SR to the time of stopping or switching. Persistence will be calculated only for incident users.
Stopping: stopping is defined as lack of SR treatment within a gap of 30 days after the end of the last prescription in the treatment episode. Stopping will be calculated only for incident users.

Switching: switching is defined as stopping SR treatment and start of another osteoporosis treatment, during use or within a gap of 30 days after stopping. Switching will be assessed both for incident as well as prevalent users.
The gap period will be varied to 0 and to 90 days to look at the impact of the choice of gap period on these variables. Kaplan Meier models will be used to estimate persistence of use.

9.7.2.2. Prevalence of contra-indications and new restrictions

We will assess the effectiveness of the RMM identified (started in May/2013 and finalized in March/2014) using interrupted time series analyses. In such methods, the coefficient and p-value for a change in secular trends of drug use (regarding both contraindications and restrictions/indications) after both time points/interventions is used to quantify the effectiveness of the proposed RMM. In these analyses, the *transitional* period going from start to finalization of the RMM (June/2013 to March/2014) will be used as a 'lag time' preceding the *assessment* period (April/2014 onwards).

Contra-indications
Prevalence of each of the contraindications will be estimated on a patient level (new and prevalent users of SR) by age, sex, period and country. 95% Confidence Intervals will be estimated using a binomial distribution.

Interrupted time series analyses will be carried out to assess the impact of the RMM on these. Each contributing data source will be analyzed using an interrupted times series design (Kastner, 2011), using repeated measures before (up until May 2013) and after intervention (from April 2014 onwards), using a *transitional* lag time period (from June 2013 to March 2014, both included) to control for secular trends. Using this design, each database acts as its own control.

Using the interrupted times series approach, we estimate the trend in the prevalence rates in monthly intervals during the study period in the three analysis periods, and test for changes pre- and post- intervention, using the *transitional* period as a pre-specified lag time for the intervention to take effect on a) the overall (absolute rate) of outcome, and b) the slope of the trend in rates of outcome.

Segmented linear regression models will be used to estimate the monthly proportions of outcomes. Controlling for baseline level and trend, the models estimate changes in levels and trends of rates after the pre-defined interventions. The regression model includes terms to estimate the pre-existing level for each rate in the first months of the observation period (intercept), trend in the rate before the interventions were introduced, change in level of the rate during the transitional/lag time period, and change in trend after the intervention (Serumaga, 2011).

These analyses will be conducted separately for prevalent and incident SR users.

New restrictions

Prevalence of each of the new restrictions for indication will be estimated on a patient level (new and prevalent users of SR) by age, sex, period and country. 95% Confidence Intervals will be estimated using a binomial distribution.

Interrupted time series analyses with segmented linear regression will be carried out to assess the impact of the RMM on these, as described above. Primary outcomes of interest will be proportion of SR users with: 1. A history of previous osteoporotic fracture/s or a "high estimated fracture risk" (as defined above); 2. Therapy initiation by a physician experienced in the treatment of osteoporosis (as defined above). 3. SR use not in first line (as defined above).

These analyses will be conducted separately for prevalent and incident SR users.

9.7.3. Safety Studies

9.7.3.1. Characteristics of study cohorts

Characteristics of the study cohorts will be described for bisphosphonates new users and strontium ranelate new users. These will be all contra-indications, precautionary conditions and co-variables. Chi-square tests will be conducted to test differences in distributions.

9.7.3.2. Absolute rates of safety endpoints

The crude and age and sex specific incidence rates of each of the safety endpoints events will be estimated separately in new SR and oral bisphosphonate users assuming a Poisson distribution. Incidence rates will be stratified by period (up till May/2013 and from June/2013 onwards) and by number of newly defined (contra) indications at cohort entry. Graphs will be created that show the incidence rates of endpoints during use of study drugs and after use of study drugs.

9.7.3.3. Relative risks

Using a matched case control approach we will use conditional logistic regression to estimate the association with the occurrence of endpoints and between current use of SR and 1) past use of study drugs; 2) current use of bisphosphonates. Control for confounding will be based on the change in estimate method as proposed by Greenland *et al* (1993). All analyses will be stratified by period. We will primarily consider factors measured at baseline, and only for those at index date for which we are sure they cannot be an intermediate between drug exposure and outcome.

9.7.4. Pooling

All estimates will be calculated by databases and pooled according to a meta-analysis approach (random or fixed effects model). In addition, to optimize power, we will conduct a mega-pooled analysis, that will estimate the effects putting all individual level data together (fixed and random effects will be checked).

9.7.5. Sensitivity analyses

Sensitivity analyses will be conducted based on the gap period (persistence assessments) and the risk window for exposure.
In addition, sensitivity analyses excluding participating countries where legal restrictions are in place for the prescription of SR in primary care (i.e. Spain) will be carried out for both the RMM effectiveness and safety studies, and reported accordingly.

9.8. Quality control

This study was designed and shall be implemented and reported in accordance with the Guidelines for Good Pharmacoepidemiology Practices (GPP) of the International Society for Pharmacoepidemiology (ISPE, 2008), the STROBE (Strengthening the Reporting of Observational Studies in Epidemiology) guidelines (von Elm, 2008), and with the ethical principles laid down in the Declaration of Helsinki.

This study is fulfilling the criteria of a 'European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) study' and follows the 'ENCePP Code of Conduct' (2014).

All programs will be programmed according to agreed coding standards and will be validated by double programming or source code review with second programmer involvement.

Only validated software (SAS version 9.2, SAS Institute Inc., Cary, NC) will be used for statistical analysis.

9.9. Limitations of the research methods

This study is non-interventional and as such has several important limitations.

Selection bias
Since the study is based on electronic health care records and does not require active consent of participants, lack of participation that may lead to selection bias is not an issue in this study.

Information bias

Information bias may occur to not measuring correctly exposure, outcomes or co-variates.
Regarding exposure, most databases that participate in the study capture prescriptions rather than dispensings. Misclassification of exposure may occur due to lack of 'picking up' the prescribed medication and non-compliance. This may overestimate utilization of SR/BP and lead to non-differential misclassification of the comparative studies. Misspecification of the risk window may lead to information bias. The effect of a potential misspecification will be addressed in sensitivity analyses
Lack of recording of certain co-variates (e.g. history of fractures rather than BMD) may lead to misclassification and underestimation of the contra-indications and new indications. Similarly, lack of recording of safety events may lead to misclassification of the safety endpoints. However, previous work has shown very high validity of the coding of myocardial infarction, with positive predictive values ranging from 75% to 100% within EU-ADR Alliance partners (Coloma, 2013). DVT and VTE were only validated in some databases before and will therefore need validation in each of the data sources. Cardiovascular death may be misclassified if no autopsy is done. Validation studies will be conducted in databases where this information is not yet available (See Section 9.3.1).

Confounding

Due to the observational design chosen, causality in the observed associations will not be established. Instead, associations between drug use and risks will be assessed. As confounding by indication (with SR patients most likely to suffer more severe osteoporosis) will likely produce differences between SR and bisphosphonate users, especially after the different DHPCs, we will use several methods to deal with between-person confounding:

1. Restriction: comparative studies will be conducted only in persons without contra-indications to restrict the population to those that would be prescribed SR according to the new label.
2. Matching: for the comparative studies we will match cases to controls on age, sex, date, country.
3. Adjustments: we will adjust for all co-variables that are associated with a 10% change in the primary risk estimate.

9.10. Other aspects

No other aspects.

10. PROTECTION OF HUMAN SUBJECTS

For this study, participants from 5 different EU states will process individual data as collected in national electronic health record databases. Due to the sensitive nature of this personal medical data, it is important to be fully aware of ethical and regulatory aspects and to strive to take all reasonable measures to ensure compliance with ethical and regulatory issues on privacy.

All of the databases used in this study are already used for pharmaco-epidemiological research and have a well-developed mechanism to ensure that European and local regulations dealing with ethical use of the data and adequate privacy control are adhered to.

In agreement with these regulations, rather than combining person level data and performing only a central analysis, local analyses will be run, which generate non-identifiable data with less information that will be pooled across databases.

The output files are stored in the central Remote Research Environment (RRE) of the Erasmus MC. These output files do not contain any data that allow identification of subjects included in the study. In fact, each record is completely anonymous and does not contain any identifier key. Starting from this, the RRE implements further security measures in order to ensure a high level of stored data protection, according with the article 34 of legislative decree 196/2003 and article 22 of Regulation (EC) 45/2001.

In addition, a scientific advisory committee consisting of 3 external experts has been constituted to guarantee scientific soundness of the study and also to follow-up on the progress and the appropriate conduct of the study. The members of the scientific advisory committee will be involved in review of the data and preparation of the reports (yearly and final).
Members of the scientific advisory committee are the following: Dr. S Perez-Gutthann, Prof. Dr. Kim Fox and Prof. Dr. Cyrus Cooper.

11. MANAGEMENT AND REPORTING OF ADVERSE EVENTS/ADVERSE REACTIONS

According to the new guidelines for good pharmacovigilance practice (EMA/873138/2011) there is no requirement for expedited reporting of adverse drug reactions from studies with secondary use of data (such as electronic health care databases).

All the identified adverse events/reactions will be summarized in the final study report.

12. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

As the study progresses interim results will be reported in a yearly basis.

Dissemination activities to be undertaken will have mainly, although not exclusively, a scientific nature (articles in scientific journals, presentations at conferences, etc.).
In order to allow national competent authorities to review the results and interpretations to be published in advance, the marketing authorization holder will communicate to the Agency and the competent authorities of the Member States in which the product is authorized, the final manuscript of the article within two weeks after first acceptance for publication.

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14. APPENDIX

14.1. List of stand-alone documents

Not applicable

14.2. ENCePP checklist for study protocols

European Network of Centres for Pharmacoepidemiology

Doc.Ref. EMEA/540136/2009
ENCePP Checklist for Study Protocols (Revision 2, amended)

Adopted by the ENCePP Steering Group on 14/01/2013

The European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) welcomes innovative designs and new methods of research. This Checklist has been developed by ENCePP to stimulate consideration of important principles when designing and writing a pharmacoepidemiological or pharmacovigilance study protocol. The Checklist is intended to promote the quality of such studies, not their uniformity. The user is also referred to the ENCePP Guide on Methodological Standards in Pharmacoepidemiology which reviews and gives direct electronic access to guidance for research in pharmacoepidemiology and pharmacovigilance.

For each question of the Checklist, the investigator should indicate whether or not it has been addressed in the study protocol. If the answer is “Yes”, the page number(s) of the protocol where this issue has been discussed should be specified. It is possible that some questions do not apply to a particular study (for example in the case of an innovative study design). In this case, the answer ‘N/A’ (Not Applicable) can be checked and the “Comments” field included for each section should be used to explain why. The “Comments” field can also be used to elaborate on a “No” answer.

This Checklist should be included as an Annex by marketing authorization holders when submitting the protocol of a non-interventional post-authorization safety study (PASS) to a regulatory authority (see the Guidance on the format and content of the protocol of non-interventional post-authorization safety studies). Note, the Checklist is a supporting document and does not replace the format of the protocol for PASS as recommended in the Guidance and Module VIII of the Good pharmacovigilance practices (GVP).

Study title:
European Program of Post-Authorization Safety Studies for Protelos®/Osseor® through EU-ADR Alliance

Study reference number:
TBC

Section 1: Milestones	Yes	No	N/A	Page Number(s)
1.1 Does the protocol specify timelines for				
1.1.1 Start of data collection[1]	☒	☐	☐	14
1.1.2 End of data collection[2]	☒	☐	☐	14
1.1.3 Study progress report(s)	☒	☐	☐	14
1.1.4 Interim report(s)	☒	☐	☐	14
1.1.5 Registration in the EU PAS register	☒	☐	☐	14
1.1.6 Final report of study results	☒	☐	☐	14

Comments:

Section 2: Research question	Yes	No	N/A	Page Number(s)
2.1 Does the formulation of the research question and objectives clearly explain:				
2.1.1 Why the study is conducted? (e.g. to address an important public health concern, a risk identified in the risk management plan, an emerging safety issue)	☒	☐	☐	15-16
2.1.2 The objectives of the study?	☒	☐	☐	16-17
2.1.3 The target population? (i.e. population or subgroup to whom the study results are intended to be generalised)	☒	☐	☐	18
2.1.4 Which formal hypothesis(-es) is (are) to be tested?	☐	☒	☐	
2.1.5 if applicable, that there is no *a priori* hypothesis?	☐	☐	☒	

Comments:

Section 3: Study design	Yes	No	N/A	Page Number(s)
3.1 Is the study design described? (e.g. cohort, case-control, randomised controlled trial, new or alternative design)	☒	☐	☐	18
3.2 Does the protocol specify the primary and secondary (if applicable) endpoint(s) to be investigated?	☒	☐	☐	21-22
3.3 Does the protocol describe the measure(s) of effect? (e.g. relative risk, odds ratio, deaths per 1000 person-years, absolute risk, excess risk, incidence rate ratio, hazard ratio, number needed to harm (NNH) per year)	☒	☐	☐	33-36

Comments:

1 Date from which information on the first study is first recorded in the study dataset or, in the case of secondary use of data, the date from which data extraction starts.
2 Date from which the analytical dataset is completely available.

Section 4: Source and study populations	Yes	No	N/A	Page Number(s)
4.1 Is the source population described?	☒	☐	☐	18
4.2 Is the planned study population defined in terms of:				
4.2.1 Study time period?	☒	☐	☐	18
4.2.2 Age and sex?	☒	☐	☐	27
4.2.3 Country of origin?	☒	☐	☐	24-27
4.2.4 Disease/indication?	☐	☐	☒	
4.2.5 Co-morbidity?	☒	☐	☐	23-24
4.2.6 Seasonality?	☐	☐	☒	
4.3 Does the protocol define how the study population will be sampled from the source population? (e.g. event or inclusion/exclusion criteria)	☒	☐	☐	18-19

Comments:

Section 5: Exposure definition and measurement	Yes	No	N/A	Page Number(s)
5.1 Does the protocol describe how exposure is defined and measured? (e.g. operational details for defining and categorising exposure)	☒	☐	☐	22
5.2 Does the protocol discuss the validity of exposure measurement? (e.g. precision, accuracy, prospective ascertainment, exposure information recorded before the outcome occurred, use of validation sub-study)	☐	☐	☒	
5.3 Is exposure classified according to time windows? (e.g. current user, former user, non-use)	☒	☐	☐	22
5.4 Is exposure classified based on biological mechanism of action and taking into account the pharmacokinetics and pharmacodynamics of the drug?	☒	☐	☐	
5.5 Does the protocol specify whether a dose-dependent or duration-dependent response is measured?	☒	☐	☐	22

Comments:

Section 6: Endpoint definition and measurement	Yes	No	N/A	Page Number(s)
6.1 Does the protocol describe how the endpoints are defined and measured?	☒	☐	☐	20
6.2 Does the protocol discuss the validity of endpoint measurement? (e.g. precision, accuracy, sensitivity, specificity, positive predictive value, prospective or retrospective ascertainment, use of validation sub-study)	☒	☐	☐	20, 36

Comments:

Section 7: Confounders and effect modifiers	Yes	No	N/A	Page Number(s)
7.1 Does the protocol address known confounders? (e.g. collection of data on known confounders, methods of controlling for known confounders)	☒	☐	☐	23-24

Section 7: Confounders and effect modifiers	Yes	No	N/A	Page Number(s)
7.2 Does the protocol address known effect modifiers? (e.g. collection of data on known effect modifiers, anticipated direction of effect)	☐	☐	☒	

Comments:

Section 8: Data sources	Yes	No	N/A	Page Number(s)
8.1 Does the protocol describe the data source(s) used in the study for the ascertainment of:				
8.1.1 Exposure? (e.g. pharmacy dispensing, general practice prescribing, claims data, self-report, face-to-face interview, etc.)	☒	☐	☐	24-27
8.1.2 Endpoints? (e.g. clinical records, laboratory markers or values, claims data, self-report, patient interview including scales and questionnaires, vital statistics, etc.)	☒	☐	☐	24-27
8.1.3 Covariates?	☒	☐	☐	24-27
8.2 Does the protocol describe the information available from the data source(s) on:				
8.2.1 Exposure? (e.g. date of dispensing, drug quantity, dose, number of days of supply prescription, daily dosage, prescriber)	☒	☐	☐	24-27
8.2.2 Endpoints? (e.g. date of occurrence, multiple event, severity measures related to event)	☒	☐	☐	24-27
8.2.3 Covariates? (e.g. age, sex, clinical and drug use history, co-morbidity, co-medications, life style, etc.)	☒	☐	☐	24-27
8.3 Is a coding system described for:				
8.3.1 Diseases? (e.g. International Classification of Diseases (ICD)-10)	☒	☐	☐	24-27
8.3.2 Endpoints? (e.g. Medical Dictionary for Regulatory Activities(MedDRA) for adverse events)	☒	☐	☐	24-27
8.3.3 Exposure? (e.g. WHO Drug Dictionary, Anatomical Therapeutic Chemical (ATC) Classification System)	☒	☐	☐	24-27
8.4 Is the linkage method between data sources described? (e.g. based on a unique identifier or other)	☐	☐	☒	

Comments:

Section 9: Study size and power	Yes	No	N/A	Page Number(s)
9.1 Is sample size and/or statistical power calculated?	☒	☐	☐	27-29

Comments:

Section 10: Analysis plan	Yes	No	N/A	Page Number(s)
10.1 Does the plan include measurement of excess risks?	☒	☐	☐	35
10.2 Is the choice of statistical techniques described?	☒	☐	☐	32-35
10.3 Are descriptive analyses included?	☒	☐	☐	32
10.4 Are stratified analyses included?	☒	☐	☐	32-35
10.5 Does the plan describe the methods for adjusting for confounding?	☒	☐	☐	32-35

Section 10: Analysis plan	Yes	No	N/A	Page Number(s)
10.6 Does the plan describe methods addressing effect modification?	☐	☒	☐	

Comments:

Section 11: Data management and quality control	Yes	No	N/A	Page Number(s)
11.1 Is information provided on the management of missing data?	☒	☐	☐	32
11.2 Does the protocol provide information on data storage? (e.g. software and IT environment, database maintenance and anti-fraud protection, archiving)	☒	☐	☐	29-32
11.3 Are methods of quality assurance described?	☒	☐	☐	29-32
11.4 Does the protocol describe possible quality issues related to the data source(s)?	☒	☐	☐	36
11.5 Is there a system in place for independent review of study results?	☒	☐	☐	37

Comments:

Section 12: Limitations	Yes	No	N/A	Page Number(s)
12.1 Does the protocol discuss: 12.1.1 Selection biases? 12.1.2 Information biases? (e.g. anticipated direction and magnitude of such biases, validation sub-study, use of validation and external data, analytical methods)	☒ ☒	☐ ☐	☐ ☐	35 36
12.2 Does the protocol discuss study feasibility? (e.g. sample size, anticipated exposure, duration of follow-up in a cohort study, patient recruitment)	☐	☐	☒	
12.3 Does the protocol address other limitations?	☒	☐	☐	36

Comments:

Section 13: Ethical issues	Yes	No	N/A	Page Number(s)
13.1 Have requirements of Ethics Committee/Institutional Review Board approval been described?	☒	☐	☐	25-27
13.2 Has any outcome of an ethical review procedure been addressed?	☐	☒	☐	
13.3 Have data protection requirements been described?	☒	☐	☐	36-37

Comments:

Section 14: Amendments and deviations	Yes	No	N/A	Page Number(s)
14.1 Does the protocol include a section to document future amendments and deviations?	☒	☐	☐	14

Comments:

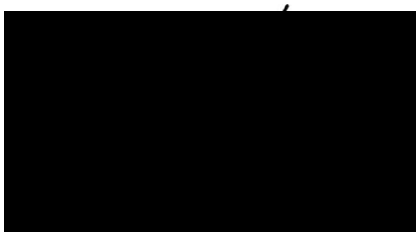
Section 15: Plans for communication of study results	Yes	No	N/A	Page Number(s)
15.1 Are plans described for communicating study results (e.g. to regulatory authorities)?	☒	☐	☐	37
15.2 Are plans described for disseminating study results externally, including publication?	☒	☐	☐	37

Comments:

Name of the main author of the protocol: Daniel Prieto-Alhambra

Date: 07th January 2015

Signature:



14.3. Additional information

14.3.1. List of BNF and ATC codes used for the identification of strontium ranelate and oral bisphosphonate users.

DRUG NAME	ATC (Aarhus, HS, IPCI, SIDIAP)	BNF (THIN UK)
STRONTIUM RANELATE 2g sachets	M05BX03	06.06.02.00
STRONTIUM RANELATE oral susp granules 2g	M05BX03	06.06.02.00
ALENDRONIC ACID (AS SODIUM SALT) oral soln 70mg/100ml	M05BA04	06.06.02.00
ALENDRONIC ACID (AS SODIUM SALT) tabs 10mg	M05BA04	06.06.02.00
ALENDRONIC ACID (AS SODIUM SALT) tabs 10mg	M05BA04	06.06.02.00
ALENDRONIC ACID (AS SODIUM SALT) tabs 10mg	M05BA04	06.06.02.00
ALENDRONIC ACID (AS SODIUM SALT) tabs 5mg	M05BA04	06.06.02.00
ALENDRONIC ACID (AS SODIUM SALT) tabs 70mg	M05BA04	06.06.02.00
ALENDRONIC ACID (AS SODIUM SALT) tabs 70mg	M05BA04	06.06.02.00
ALENDRONIC ACID (AS SODIUM SALT) tabs 70mg	M05BA04	06.06.02.00
ALENDRONIC ACID (AS SODIUM SALT) tabs 70mg	M05BA04	06.06.02.00
ALENDRONIC ACID (AS SODIUM SALT) tabs 70mg	M05BA04	06.06.02.00
ALENDRONIC ACID (AS SODIUM SALT) tabs 70mg	M05BA04	06.06.02.00
ALENDRONIC ACID 10mg tablets	M05BA04	06.06.02.00
ALENDRONIC ACID 5mg tablets	M05BA04	06.06.02.00
ALENDRONIC ACID 70mg tablets	M05BA04	06.06.02.00
IBANDRONIC ACID 50mg tablets	M05BA06	06.06.02.00
IBANDRONIC ACID conc soln inf 2mg/2ml	M05BA06	06.06.02.00
RISEDRONATE SODIUM 30mg tabs	M05BA07	06.06.02.00
RISEDRONATE SODIUM 35mg tabs	M05BA07	06.06.02.00
RISEDRONATE SODIUM 35mg tabs	M05BA07	06.06.02.00
RISEDRONATE SODIUM 5mg tablets	M05BA07	06.06.02.00
RISEDRONATE SODIUM tabs 30mg	M05BA07	06.06.02.00
RISEDRONATE SODIUM tabs 35mg	M05BA07	06.06.02.00
RISEDRONATE SODIUM tabs 5mg	M05BA07	06.06.02.00

14.3.2. List of ICD-10, ICD-9, ICPC and READ codes used for the identification of key health outcomes and covariates.

The sets of codes proposed will be further discussed with each of the academic partners during the first months of the study, and before data extraction.

Myocardial infarction / angina pectoris / aorto-coronary bypass surgery

Terms	ICD10 (SIDIAP, Aarhus hospital outpatients)	ICD9CM (HS, Aarhus hospital admissions)	Read Codes (THIN UK)	ICPC (IPCI)
Cardiac infarction	I22 121			
MI - Myocardial infarction			X200E	
Acute myocardial infarction	I21		G30.. XE0Uh	K75
Acute myocardial infarction, unspecified	I21.9	410.9		
Myocardial infarction (acute) NOS	I21.3	410		
Acute myocardial infarction, unspecified site, episode of care unspecified		410.90		
AMI NOS, unspecified		410.90		
Acute myocardial infarction, subendocardial infarction		410.7	G32..	
Old myocardial infarction*	I25.2	412		
Healed myocardial infarction*			XE2aA G32.11	
Old myocardial infarction*			XE2aA	
Subsequent/recurrent myocardial infarction	I22		G35..	
Subsequent myocardial infarction of unspecified site	I22.9		Gyu36	
Subsequent myocardial infarction of other sites	I22.8		Gyu35 G353.	
Subsequent myocardial infarction of anterior wall	I22.0		G350. GYU3600	
Subsequent myocardial infarction of inferior wall	I22.1		G351.]	
Subsequent acute subendocardial myocardial infarction	I22.2			
Subsequent nontransmural myocardial infarction NOS	I22.2			
Subsequent myocardial infarction (acute) NOS	I22.9			
Reinfarction of myocardium			G35..	
Acute subendocardial myocardial infarction	I21.4		G307.00	
Acute myocardial infarction, subendocardial infarction, episode of care unspecified		410.70		

Terms	ICD10 (SIDIAP, Aarhus hospital outpatients)	ICD9CM (HS, Aarhus hospital admissions)	Read Codes (THIN UK)	ICPC (IPCI)
Nontransmural myocardial infarction	I21.4			
Acute myocardial infarction, of anterolateral wall		410.0	G300.	
Acute anteroseptal myocardial infarction			G3011	
Acute inferior myocardial infarction		410.4	X200K	
Acute myocardial infarction, true posterior wall infarction		410.6		
True posterior myocardial infarction			G306.	
Acute myocardial infarction, of inferoposterior wall		410.3	G303.]	
Other specified anterior myocardial infarction			G301.]	
Acute transmural myocardial infarction of unspecified site	I21.3		Gyu34	
Acute transmural myocardial infarction of anterior wall	I21.0 122.0			
Acute transmural myocardial infarction of inferior wall	I21.1 I21.11 I21.19 122.1			
Acute transmural myocardial infarction of other sites	I21.2 I21.21 I21.29 122.8			
ECG: old myocardial infarction*			3232.	
Anterior myocard.infarct NOS		410.8	G301z	
Other acute myocardial infarct			G30y.	
Other acute myocardial inf.NOS			G30yz	
Inferior myocard. infarct NOS			G308.	
Acute myocardial infarction, of inferolateral wall		410.2	G302.	
Acute lateral myocardial infarction		410.5	X200P	
Lateral myocardial infarct NOS			G305.]	
Acute widespread myocardial infarction			X200S	
Acute posterior myocardial infarction		410.60 410.61 410.62*	X200V	
Posterior myocard.infarct			G304.]	

Terms	ICD10 (SIDIAP, Aarhus hospital outpatients)	ICD9CM (HS, Aarhus hospital admissions)	Read Codes (THIN UK)	ICPC (IPCI)
NOS				
Silent myocardial infarct*			X200a	
ECG: myocardial infarction*			323..	
ECG: myocardial infarct NOS*			323Z.	
Postoperative subendocardial myocardial infarction			XaD2h	
Postoperative myocardial infarction			XaD2b G38..	
Postop MI, unspec			XaD2i	
Acute anterior myocardial infarction		410.1	Xa0YL	
Acute Q wave myocard infarct			XaAC3	
Acute myocardial infarction, subendocardial infarction		410.71 410.72		
Non-Q wave myocardial infarction NOS	I21.4 122.2			
Non-ST elevation (NSTEMI) myocardial infarction	I21.4 122.2			
Unstable angina	I20.0		X2009 G311.13	
Crescendo angina	I20.0		XE0Ui G311.11	
Intermediate coronary syndrome	I20.0	411.1		
Angina at rest			X2007 G311.14 G311.200	
Impending infarction			XE0Ui G311.12	
Worsening angina			XE0Ui	
Other acute forms of ischemic heart disease	I24	411.8		
Preinfarction syndrome			G311.11	
Crescendo angina			G311.12	
Impending infarction			G311.13 G311100	
Unstable angina			G311.14 G311200	
Angina at rest			G311000	
Myocardial infarction aborted			G311011	
Acute coronary syndrome			G311Z00	
Angina decubitus			G330.00	
Nocturnal angina			G330000	
New onset angina			G33Z600	
Old MI / Healed MI *			G32..00 G32.11	

Terms	ICD10 (SIDIAP, Aarhus hospital outpatients)	ICD9CM (HS, Aarhus hospital admissions)	Read Codes (THIN UK)	ICPC (IPCI)
Subsequent MI			G35..	
Other chronic ischaemic heart disease*			G34..	
Presence of aortocoronary bypass surgery*	Z95.1			
Aortocoronary bypass*		36.1		
Coronary artery bypass graft operations*			792..	
PTAC*			793G.	
Other acute and subacute forms of ischemic heart disease (HS data only)**		411		

** Not to be used for the identification of new (incident) events but just for the characterization of baseline patient characteristics (history of).*

*** According to partners from HS, all 411* codes would identify acute myocardial infarction in HS*

Cerebro-vascular disease (stroke/TIA)

Terms	ICD10	ICD9CM	Read Codes	ICPC
Stroke, not specified as haemorrhage or infarction	I64			
Stroke NOS	I63.9			K90
Cerebrovascular accident			X00D1	
Stroke and cerebrovascular accident unspecified			XE2aB	
Stroke NOS			XaEGq	
Cerebrovascular Disease		430-432 (Except 432.1 "Subdural hemorrhage") 433-435* 436, 437*, 438		
Sequelae of stroke, not specified as haemorrhage or infarction *	I69.4			
Sequelae of stroke, not specified as haemorrhage or infarction *			Gyu6C	
CVA - Extension of cerebrovascular accident			Xa1hE	
Lacunar stroke			X00DA	
Brain stem stroke syndrome	G46.3		G663.	
Cerebellar stroke syndrome	G46.4		G664.	
Personal history of stroke *			ZV125	
Sequelae of stroke NOS *	I69.3			
Stroke of uncertain pathology			X00DR	
TACI - Total anterior cerebral circulation infarction			X00D6	
PACI - Partial anterior cerebral circulation			X00D7	
Anterior circulation stroke of uncertain pathology			X00DS	
Posterior circulation stroke of uncertain pathology			X00DT	
Transient cerebral ischaemic attack, unspecified	G45.9			
TIA - Transient ischaemic attack			XE0VK XaEGK	
Other transient cerebral ischaemic attacks and related syndromes	G45.8		Fyu55	
Vertebro-basilar artery syndrome	G45.0			
Carotid artery syndrome	G45.1			
Multiple and bilateral precerebral artery syndromes	G45.2			
Transient ischemic attack (TIA), and cerebral infarction without residual deficits (personal history)*		V12.54		
Subarachnoid haemorrhage			G60..00	
Ruptured berry aneurysm			G600.00	

Terms	ICD10	ICD9CM	Read Codes	ICPC
Subarachnoid haemorrhage from carotid siphon and bifurcation			G601.00	
Subarachnoid haemorrhage from middle cerbral artery			G602.00	
Subarachnoid haemorrhage from anterior communicating artery			G603.00	
Subarachnoid haemorrhage from posterior communicating artery			G604.00	
Subarachnoid haemorrhage from basilar artery			G605.00	
Subarachnoid haemorrhage from vertebral artery			G606.00	
Subarachnoid haemorrh from intracranial artery, unspecif			G60X.00	
Subarachnoid haemorrhage NOS			G60z.00	
Intracerebral haemorrhage			G61..00	
CVA - cerebrovascular accid due to intracerebral haemorrhage			G61..11	
Stroke due to intracerebral haemorrhage			G61..12	
Cortical haemorrhage			G610.00	
Internal capsule haemorrhage			G611.00	
Basal nucleus haemorrhage			G612.00	
Cerebellar haemorrhage			G613.00	
Pontine haemorrhage			G614.00	
Bulbar haemorrhage			G615.00	
External capsule haemorrhage			G616.00	
Intracerebral haemorrhage, intraventricular			G617.00	
Intracerebral haemorrhage, multiple localized			G618.00	
Intracerebral haemorrhage in hemisphere, unspecified			G61X.00	
Left sided intracerebral haemorrhage, unspecified			G61X000	
Right sided intracerebral haemorrhage, unspecified			G61X100	
Intracerebral haemorrhage NOS			G61z.00	
Other and unspecified intracranial haemorrhage			G62..00	
Intracranial haemorrhage NOS			G62z.00	
[X]Other subarachnoid haemorrhage			Gyu6100	
[X]Other intracerebral haemorrhage			Gyu6200	
[X]Subarachnoid haemorrh from intracranial artery, unspecif			Gyu6E00	
[X]Intracerbral haemorrhge in hemisphere, unspecified			Gyu6F00	
Perinatal subarachnoid haemorrhage			Q412.00	
Evacuation of haematoma from temporal lobe of brain *			7004100	
Evacuation of haematoma from cerebellum *			7004200	
Evacuation of intracerebral			7004300	

Terms	ICD10	ICD9CM	Read Codes	ICPC
haematoma NEC *				
Aspiration of haematoma of brain tissue *			7008200	
[X]Subarachnoid haemorrhage from other intracranial arteries			Gyu6000	
[X]Sequelae of other nontraumatic intracranial haemorrhage *			Gyu6B00	
Sequelae of subarachnoid haemorrhage *			G680.00	
Sequelae of intracerebral haemorrhage *			G681.00	
Sequelae of other nontraumatic intracranial haemorrhage *			G682.00	
H/O sub-arachnoid haemorrhage *			14AF.00	
Subarachnoid haemorrhage			G60..00	
Infarction - precerebral			G63..11	
Cerebral infarct due to thrombosis of precerebral arteries			G63y000	
Cerebral infarction due to embolism of precerebral arteries			G63y100	
Infarction - cerebral			G64..12	
Stroke due to cerebral arterial occlusion			G64..13	
Cerebral infarction due to thrombosis of cerebral arteries			G640000	
Cerebral infarction due to embolism of cerebral arteries			G641000	
Cerebral infarction NOS			G64z.00	
Brainstem infarction NOS			G64z.11	
Cerebellar infarction			G64z.12	
Brainstem infarction			G64z000	
Left sided cerebral infarction			G64z200	
Right sided cerebral infarction			G64z300	
Infarction of basal ganglia			G64z400	
Pure motor lacunar syndrome			G665.00	
Pure sensory lacunar syndrome			G666.00	
Cereb infarct due cerebral venous thrombosis, nonpyogenic			G676000	
Cereb infarct due unsp occlus/stenos precerebr arteries			G6W..00	
[X]Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs			Gyu6300	
[X]Other cerebral infarction			Gyu6400	
[X]Cereb infarct due unsp occlus/stenos precerebr arteries			Gyu6G00	
Lateral medullary syndrome			G64z111	
Cerebrl infarctn due/unspcf occlusn or sten/cerebrl artrs			G6X..00	
Sequelae of cerebral infarction *			G683.00	
Sequelae of stroke,not specfd as h'morrhage or infarction *			G68X.00	
Cereb infarct due unsp occlus/stenos precerebr arteries			G6W..00	
H/O: CVA/stroke *			14A7.00	
H/O: CVA *			14A7.11	
H/O: stroke *			14A7.12	

Terms	ICD10	ICD9CM	Read Codes	ICPC
H/O: Stroke in last year *			14AK.00	
Stroke and cerebrovascular accident unspecified			G66..00	
CVA unspecified			G66..11	
Stroke unspecified			G66..12	
CVA - Cerebrovascular accident unspecified			G66..13	
Brain stem stroke syndrome			G663.00	
Cerebellar stroke syndrome			G664.00	
Left sided CVA			G667.00	
Right sided CVA			G668.00	
CVA - cerebrovascular accident in the puerperium			L440.11	
[X]Other transnt cerebral ischaemic attacks+related syndroms			Fyu5500	
Transient cerebral ischaemia			G65..00	
Transient ischaemic attack			G65..12	
Vertebrobasilar insufficiency			G656.00	
Other transient cerebral ischaemia			G65y.00	
Transient cerebral ischaemia NOS			G65z.00	
Impending cerebral ischaemia			G65z000	
Intermittent cerebral ischaemia			G65z100	
Transient cerebral ischaemia NOS			G65zz00	
Acute cerebrovascular insufficiency NOS			G671000	
Basilar artery syndrome			G650.00	
Insufficiency - basilar artery			G650.11	
Vertebral artery syndrome			G651.00	
Vertebro-basilar artery syndrome			G651000	
Carotid artery syndrome hemispheric			G653.00	
Multiple and bilateral precerebral artery syndromes			G654.00	
Drop attack			G65..11	
Cerebral infarction	I63			
Sequelae of cerebral infarction*	I69.3			
Sequelae of intracerebral haemorrhage*	I69.1			
Transient cerebral ischaemic attacks and related syndrome	G45			
Intracerebral haemorrhage	I61			
Vascular syndromes of brain in cerebrovascular diseases	G46			
Vertebro-basilar insufficiency			G65..13	
Wallenberg syndrome			G64Z100	
Personal history of stroke / cerebrovascular accident*			ZV12511 ZV12512	

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Peripheral vascular disease

Term/Description	ICD10	ICD9CM	Read codes	ICPC
Peripheral Vascular Disease	I73.9	443.9, 443.81	G73y., G73z., Xa0IV, XE0VP, X203Q, Gyu74	K92
Atherosclerosis of arteries of the extremities	I70.2	440.20-440.24 440.29		
Embolism and thrombosis of arteries of the upper extremities	I74.2	444.21		
Embolism and thrombosis of arteries of the lower extremities	I74.3	444.22	XaDtl	
Embolism and thrombosis of arteries of extremities, unspecified	I74.4	444.2		
Embolism and thrombosis of iliac artery	I74.5			
Peripheral angiopathy in diseases classified elsewhere	I79.2			
Insulin-dependent diabetes mellitus with peripheral circulatory complications *	E10.5	250.7		
Non-insulin-dependent diabetes mellitus with peripheral circulatory complications *	E11.5			
Bypass graft of the extremities *		440.3	XC0gN	
Chronic total occlusion of artery of the extremities *		440.4		
Diabetic ulcer lower extremities*		707.1		
Amputation due to diabetes*		785.4		
Embolism and thrombosis of an arm or leg artery			G742.00	
Peripheral arterial embolism and thrombosis NOS			G742z00	
H/O: Peripheral vascular disease procedure *			14NB.00	
Claudication distance			16I..00	
Percutaneous transluminal placement peripheral stent artery *			7A56600	
Diabetes mellitus with gangrene			C107.11	
Diabetes with gangrene			C107.12	
Diabetes mellitus, adult with gangrene			C107200	

Insulin dependent diabetes mellitus with gangrene			C108600	
Insulin dependent diab mell with peripheral angiopathy			C108G00	
Non-insulin dependent diabetes mellitus with gangrene			C109500	
Type II diabetes mellitus with gangrene			C109511	
Type 2 diabetes mellitus with gangrene			C109512	
Non-insulin-dependent d m with peripheral angiopathy			C109F00	
Type II diabetes mellitus with peripheral angiopathy			C109F11	
Type 2 diabetes mellitus with peripheral angiopathy			C109F12	
Type 1 diabetes mellitus with gangrene			C10E600	
Type 2 diabetes mellitus with gangrene			C10F500	
Type II diabetes mellitus with gangrene			C10F511	
Type 2 diabetes mellitus with peripheral angiopathy			C10FF00	
Type 2 diabetes mellitus with peripheral angiopathy			C10FF00	
Other peripheral vascular disease			G73..00	
Peripheral ischaemic vascular disease			G73..11	
Ischaemia of legs			G73..12	
Peripheral ischaemia			G73..13	
Peripheral gangrene			G732.00	
Gangrene of toe			G732000	
Gangrene of foot			G732100	
Gangrene of finger			G732200	
Gangrene of thumb			G732300	

Gangrene of hand			G732400	
Ischaemic foot			G733.00	
Other specified peripheral vascular disease			G73y.00	
Diabetic peripheral angiopathy			G73y000	
Peripheral angiopathic disease EC NOS			G73y100	
Other specified peripheral vascular disease NOS			G73yz00	
Peripheral vascular disease NOS			G73z.00	
Intermittent claudication			G73z000	
Claudication			G73z011	
Vascular claudication			G73z012	
Peripheral vascular disease NOS			G73zz00	
Ischaemic leg ulcer			M271.12	
Ischaemic ulcer diabetic foot			M271000	
Neuropathic diabetic ulcer - foot			M271100	
Mixed diabetic ulcer - foot			M271200	
Arterial leg ulcer			M271300	
Mixed venous and arterial leg ulcer			M271400	
[D]Gangrene of toe in diabetic			R054200	
[D]Widespread diabetic foot gangrene			R054300	

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Pulmonary / deep vein thrombosis

Term/Description	ICD10	ICD9CM	Read codes	ICPC
Phlebitis and thrombophlebitis of femoral vein	I80.1			
Phlebitis and thrombophlebitis of other deep vessels of lower extremities	I80.2			K94.01 K94.15
Pulmonary embolism	I26			K93
Phlebitis and thrombophlebitis of deep vessels of lower extremities		451.1, 451.2**		
Acute venous embolism and thrombosis of deep vessels of lower extremity		453.4		
Pulmonary embolism and infarction		415.1		
Pulmonary embolism Pulmonary embolus Post operative pulmonary embolus Recurrent pulmonary embolism * Deep vein phlebitis and thrombophlebitis of the leg Deep vein thrombosis Deep vein thrombosis, leg DVT - Deep vein thrombosis Thrombophlebitis of the femoral vein Thrombophlebitis of the popliteal vein Thrombophlebitis of the anterior tibial vein Thrombophlebitis of the posterior tibial vein Deep vein thrombophlebitis of the leg unspecified Deep vein thrombosis of leg related to air travel Deep vein thrombosis of lower limb Deep vein thrombosis of leg related to intravenous drug use Deep vein thrombosis of peroneal vein Deep vein phlebitis and thrombophlebitis of the leg NOS Thrombosis of vein of leg Post operative deep vein thrombosis [V] Personal history deep vein thrombosis * [V] Personal history DVT- deep vein thrombosis * [V] Personal history of pulmonary embolism * Thromboembolic pulmonary hypertension *			G401.00 G401.12 G401000 G401100 G801.00 G801.11 G801.12 G801.13 G801600 G801700 G801800 G801A00 G801B00 G801C00 G801D00 G801E00 G801F00 G801z00 G802000 SP12200 ZV12800	

			ZV12811 ZV12900 G41y100	
Personal history of pulmonary embolism		V12.55		
Personal history of venous thrombosis and embolism		V12.51		
Iliac vein thrombosis/embolism			G08Y	

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*** Code to be used for HSD data only following suggestion from co-investigators.*

Osteoporotic fracture

Fracture site	ICD10	ICD9CM	READ	ICPC
			XA0FK, XaB0o, XE1pj, S3zz., TC7..	L76
Unspecific	M80		N3303, N3315, N3316, N331B, NyuB0, NyuB8	
Clavicle	S42.0	810	S20.., S20z.	
Scapula	S42.1	811	S21.., S21z.	
Humerus	S42.2, S42.3, S42.4	812	S22.., S22z., XA0GS, XA0GT, XA0GQ	
Radius/Ulna	S52	813	S230., S2317, S2318, S2319, S2323, S234C, S234D, S234E, S2333, S2356, S235C, S235D, S235E, S23x., S23y., S23z., XE1ks, XA0GX, XA0Ga, XA0Gb, XA0Gl, XA0GV, XA0GW, XA85j, XM16p, XE1ee, XE1kw, XE1kv, XE1ky, XE1kz, 7K1LL	L72
Carpal bone/s	S62.0, S62.1	814	S24.., S4C0y, S4C1y, S4C2y, S4C3y, XA0E4, XA0ES	
Metacarpal bone/s	S62.2, S62.3, S62.4	815	S25.., Xa3he, XA0Gq, XA0Gr	
Arm/upper limb (unspecific)		818		
Hand (unspecific)				L74
Spine	S12, S22.0, S22.1, S32.0, S32.7, S32.8, T08	805	S10z., XE1kW, XE1pT, S10B., XA0G8, Syu34, XA0GB, XA0GM, XA0GN, XE0ln, 7J42z, 7J41., 7J43y, 7J43z, XE0lo, XA0Ds, XA0Dt, XA0Dv, XA0Dw, S10x., S10y., XE1kX, S10A2, XM1JV, XE1kf, Xa1u3, S114., S115., 7J420, 7J42y, 7J421, 7J423, 7J424, 7J425, XE1kn, S11z., XM1JU, N3318, N3319, N331A	
Rib/s/Sternum	S22.2, S22.3, S22.4, S22.5	807.0 to 807.4	XA0Gv, XA0Gw, XA0Gy, XA0Gz, S120., S121., S122., S123., S4J00, S4J10, S4J20, S4J30	
Pelvis	S32.1 to S32.5, S32.8	808	XA0H0, Xa3hd, S10B., S13.., Syu34, S4J01, S4J11, S4J21, S4J31, S108., S109.	

Hip/Proximal femur	S72.0, S72.1	820	XaBDT, XaBDU, XaEJD, XA0HE, XA0HF,XA0HG, XA0HH, XA0HI, XA0HK, XA0HL, XE1l4, XE1l5, XE1l6, XE1l7, XE1l8, XE1l9, XM1Ne, XM1Nf, XM1Ng, XM1Nh, XM1Ni, XM1Nj, 7K1L4, X601l, X601L, X601M, X601N, X601P, X601S, X601T, X601U, XaEJD, S30w., S30x., S30z., S300., S301., S302., S303., S3003, S3004, S3014, S304.	L75
Femur (others/unspecific)	S72.2 to S72.9	821	XA0HC, XA0HD, XA0HJ, XA0HN, XA0HO, XA0HP, XA0HQ, XA0HR, XE1lA, XE2ru, XE2rv, S31.., S31z., S3101, S3111, S312x, S312z, S3120, S3122, S3132, S313z, S3130, 7K1L5	L75
Patella	S82.0	822	S32z., S32.., XaCln	
Tibia/Fibula	S82.1 to S82.4	823	S33z., S33.., Xa0m8, Xa85k, XA0HT, XA0HU, XE1lB, XE1lC, XE1lD, XM00Y, XM16s, 7K1L7	L73
Ankle	S82.5, S82.6, S82.8	824	S34.., S4G1., 7K1L8, 7K1E4, XA0Ee, XA0EG, XA0Hh, S4G.., Xa1n1, Xa1mv, Xa1mz	
Tarsal/metatarsal bone/s	S92.0 to S92.3	825	Syu94, XA0Hi, XE1lH, S353., XE1lF, S35z., S3520, S3530, S352z, S353z	
Foot (unspecific)				L74

Not considered as osteoporotic fractures: skull, face, jaw, coccyx, phalanx (fingers and toes), ankle and cervical spine

All-cause death

Terms	ICD10	ICD9CM	Read Codes	ICPC
Dead Died Death Has died			XM01Y XE1hB	A96
Dead NOS			22JZ.	
Instantaneous death	R96.0	798.1	R211. XM1AY Ua1q3	
Unattended death	R98	798.9	R213.	
Unattended death NOS			R213z	
Sudden cardiac death, so described	I46.1		G5751	
Other sudden death, cause unknown	R96	798	RyuC1 R21.. R21z. XM1Ac	
Death occurring less than 24 hours from onset of symptoms, not otherwise explained	R96.1	798.2	R212. R212z	

In the IPCI database, cause of death based on ICD/ICPC/READ codes if recorded, or in free text.

Hypertension only if uncontrolled

Terms	ICD10	ICD9CM	Read Codes	ICPC
Hypertension	I10 I11 I12 I13 I15	401* 402* 403* 404* 405* 362.11 437.2	6627.00 6628.00 6629.00 14A2.00 38DE.00 662b.00 662c.00 662d.00 662F.00 662G.00 662H.00 662O.00 662P000 662q.00 662r.00 67H8.00 7Q01.00 7Q01y00 8B26.00 8BL0.00 8CR4.00 8I3N.00 F421300 G2...00 G2...11 G20..00 G200.00 G201.00 G202.00	K86 K87

Terms	ICD10	ICD9CM	Read Codes	ICPC
			G203.00 G20z.00 G20z.11 G21..00 G210.00 G210000 G210100 G211.00 G211000 G211100 G21z.00 G21z000 G21z011 G21z100 G21zz00 G22..00 G220.00 G221.00 G222.00 G22z.00 G22z.11 G23..00 G230.00 G231.00 G232.00 G233.00 G23z.00 G24..00 G240.00 G240000 G240z00 G241.00 G241000 G241z00 G244.00 G24z.00 G24z000 G24zz00 G2y..00 G2z..00 G672.00 Gyu2.00 Gyu2000 Gyu2100 L122.00 L122000 L122100 L122300 L122z00 L127z00 L128.00 L128200 Lyu1.00	

Precautionary conditions

Terms	ICD10	ICD9CM	Read Codes	ICPC
Type 2 diabetes mellitus	E11	250 (except 250.*1 and 250.*2) 271.4 357.2 366.41	C10.. C101. F4640 G73y0 X00Ag X305t X30kk X40J5 Xa0lK XE11P XE15k XE2Ne	T88 T90
Hyperlipidaemia			44P3.00 44P4.00 C320.00 C320.11 C320.12 C320.13 C320000 C320100 C320200 C320300 C320400 C320500 C320y00 C320z00 C321000 C321.00 C321.11 C321.12 C322.00 C322.11 C322.12 C322.13 C322000 C323.00 C323.11 C323.12 C324.00 C328.00 Cyu8D00 44Q3.00	
Smoking		305.1x V15.82	137J. XE0oq Xa1dC	P17

Covariates

Terms	ICD10	ICD9CM	Read Codes	ICPC
Alcohol abuse **	F10 G31.2 G62.1 G72.1 I42.6 K29.2 K70 K85.2 K86.0 Z50.2 Z71.4	291* 303* 305.0 357.5 425.5 535.3 571.0 571.1 571.2 571.3 790.3 V11.3	**136..** **136Z.** **E01..** **E010.** **G555.** **X306r** **X3071** **Xa2lt**	P15 P16
Obesity **	E66	278.00 278.01	C380. X40Lm X40YM X40YN X40YO X40YQ X40YT	T82
Chronic kidney disease	N18 I12.0	403.01, 403.11, 403.91, 404.02, 404.12, 404.13, 404.92, 404.93, 582-587, V45.1, V56.x 250.4x 403.00 403.10 403.90 404.00 404.01 404.03 404.10 404.11 404.90 404.91 581.x 588.x 792.5 996.68 996.73	1Z1..00 1Z10.00 1Z11.00 1Z12.00 1Z13.00 1Z14.00 1Z15.00 1Z16.00 1Z17.00 1Z17.11 1Z18.00 1Z19.00 1Z19.11 1Z1A.00 1Z1A.11 1Z1B.00 1Z1B.11 1Z1C.00 1Z1C.11 1Z1D.00 1Z1D.11 1Z1E.00 1Z1E.11 1Z1F.00 1Z1F.11 1Z1G.00 1Z1G.11 1Z1H.00 1Z1H.11 1Z1J.00 1Z1J.11 1Z1K.00 1Z1K.11 1Z1L.00 1Z1L.11 7L1A000 A160000 C104.00	U99

Terms	ICD10	ICD9CM	Read Codes	ICPC
			C104.11 C104000 C104100 C104y00 C104z00 C108000 C108011 C108012 C108D00 C108D11 C109000 C109011 C109012 C109C00 C109C11 C109C12 C10E000 C10ED00 C10ED12 C10F000 C10F011 C10FC00 C10FC11 C314.11 C341.00 C341z00 C354711 C373600 Cyu2300 D310000 D310100 G22..00 G22..11 G222.00 G22z.00 G22z.11 G701.00 G703.00 K0...00 K00..00 K00..11 K00..12 K000.00 K001.00 K00y.00 K00y000 K00y100 K00y200	

Terms	ICD10	ICD9CM	Read Codes	ICPC
			K00y300 K00yz00 K00z.00 K01..00 K010.00 K011.00 K012.00 K013.12 K015.00 K016.00 K017.00 K018.00 K019.00 K01A.00 K01B.00 K01w.00 K01w000 K01x000 K01x100 K01x111 K01x200 K01x300 K01x400 K01x411 K01y.00 K01z.00 K02..00 K02..11 K02..12 K020.00 K021.00 K022.00 K023.00 K02y.00 K02y000 K02y200 K02y300 K02yz00 K02z.00 K03..00 K03..11 K03..12 K030.00 K031.00 K032.00 K032000 K032100 K032300 K032400 K032500 K032600 K032y00 K032y11 K032y13 K032y14 K032y15 K032z00 K033.00	

Terms	ICD10	ICD9CM	Read Codes	ICPC
			K034.00 K035.00 K03T.00 K03U.00 K03V.00 K03W.00 K03X.00 K03y.00 K03y000 K03y200 K03yz00 K03z.00 K042.00 K042.11 K05..00 K05..11 K05..12 K050.00 K06..00 K06..11 K060.00 K060.11 K07..00 K070.00 K071.00 K072.00 K07z.00 K08..00 K080.00 K080000 K080100 K080200 K080300 K080z00 K081.00 K08y.00 K08y000 K08y100 K08y300 K08yz00 K08z.00 K09..00 K090.00 K090000 K091.00 K09z.00 K0A..00 K0A2.00 K0A2000 K0A2100 K0A2200 K0A2300 K0A2500 K0A2600 K0A2700 K0A2800 K0A3.00 K0A3000	

Terms	ICD10	ICD9CM	Read Codes	ICPC
			K0A3100 K0A3200 K0A3300 K0A3500 K0A3600 K0A3700 K0A4.00 K0A4100 K0A4200 K0A4300 K0A4500 K0A4W00 K0A4X00 K0A5.00 K0A5000 K0A5100 K0A5200 K0A5300 K0A5600 K0A5X00 K0A7.00 K0B..00 K0B1.00 K0B2.00 K0B4.00 K0B4000 K0B5.00 K0B6.00 K0C..00 K0C0.00 K0C1.00 K0C2.00 K0C4.00 K0D..00 K0E..00 K0y..00 K0y0.00 K0z..00 K100.00 K100000 K100100 K100200 K100300 K100400 K100500 K100z00 K10y.00 K138.00 K138.11 K138000 K138011 K138100 K138200 K138300 K138z00 K138z11	

Terms	ICD10	ICD9CM	Read Codes	ICPC
			K13yz11 K13z.00 K13z000 Kyu0300 Kyu0900 Kyu1.00 Kyu1000 Kyu1400 Kyu1C00 Kyu2.00 Kyu2100 Kyu4000 Kyu5G00 L093.00 P769000 PD03.00 PD03000 PD03011 PD03100 PD04.00 PD04000 PD04011 PD04100 PD04111 PD04z00 PD0z.00 PD1..00 PD1..11 PD1..12 PD1..13 PD1..14 PD10.00 PD11.00 PD11000 PD11100 PD11z00 PD11z11 PD12.00 PD12000 PD12011 PD12100 PD12111 PD12y00 PD12z00 PD13.00 PD13.11 PD1y.00 PD1y000 PD1y011 PD1yz00 PD1z.00 PDz0.00 Q20yz12 Q20yz13 Q48y000 TB00100	

Terms	ICD10	ICD9CM	Read Codes	ICPC
			TB11.00	

*** In some databases alcohol consumption, smoking, and body mass index are available as 'lifestyle factors', not only as recorded diagnoses*

Contraindications / precautions of use of oral bisphosphonates (and not mentioned in the SR SmPC)

Term/Description	ICD10	ICD9CM	Read codes	ICPC
Achalasia	K22.0	530.0	J100.	No code
Balloon dilatation of achalasia			X20Ud	No code
Oesophageal obstruction/stricture/stenosis	K22.2 K31.1 K31.2	530.3	XaB59 J103z XE0aM XaB8i J103z	D84.05 (oesophageal stenosis)
Barrett's esophagus	K22.7	530.85	Xa9Bz X3007	No code
Oesophagitis/Esophagitis	K20	530.1	J101. J101z Xa1q7 X3009	D84.03 (oesophageal reflux with oesophagitis)
Gastro-esophageal reflux disease	K21	530.81	XE0aL XE0aO X3003	D84.00 (oesophageal reflux without oesophagitis)
Esophagic ulcer/perforation/hemorrhage	K22.1 K22.3	530.2 530.4 530.82	J102. J102z	No code
Gastric/duodenal/jejunal/peptic ulcer	K25 K26 K27 K28	531 532 533 534	XE0aP XE0aQ J11y. J11yz	D85.00 D86.00 D86.01
Gastro-intestinal hemorrhage/bleeding	K92.0 K92.1 K92.2 I85.0 I98.21	530.7 530.82 578 456.0 456.1 456.20	J68.. XE0bJ J68zz G850. G8520 XM1RR* XaB3K	D14.00 (haematemesis) D15.00 (melaena) D16.00 (rectal bleeding)
Dysphagia	R13	787.2		D21.00
Diverticulum of oesophagus	K22.5 Q39.6	530.6	PA42. PA45. J106. J106z	D84.01
Gastritis/Duodenitis	K29	535	X301N J155. J15.. J15z. J156. J153. Jyu13 XE2bH J4000 X302J	D87.01

Esophageal surgery	0D11 0D12 0D13 0D15 0D51 0D52 0D53 0D54 0D55 0D71 0D72 0D73 0D74 0D75 0D84 0D87 0DB1 0DB2 0DB3 0DB4 0DB5 0DB7 0DF5 0DH5 0DL1 0DL2 0DL3 0DL4 0DL5 0DM5 0DP5	42	7608. Xa7yZ X20Tp Xa3lm 760.. XaB2P	No code
Hypocalcemia	E83.5	275.41	X40QW	No code

** "History of". Not to be used for incident diagnoses.*
NOTE: No codes are available in any of these coding languages for atypical femoral fracture, which is recognized as a precaution of use in the oral bisphosphonates SmPC.

14.4. Signatures

Protocol Signature page

Study title: European Program of Post-Authorization Safety Studies for Protelos®/Osseor® through EU-ADR Alliance

IRIS Protocol ID Number: CLE-12911-046

Protocol version identifier: 3.0
Version date: 7th January 2015

Protocol Author/s:

Name: Dr. Daniel Prieto-Alhambra, MD MSc PhD

Organization: IDIAP Jordi Gol

Signature:

Protocol Signature page

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Protocol Author/s:

Name: Miriam Sturkenboom, PharmD, PhD

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European Program of Post-Authorization Safety Studies for Protelos®/Osseor® through EU-ADR Alliance

IRIS Protocol ID Number: CLE-12911-046

Protocol version identifier: 3.0
Version date: 7th January 2015

Protocol Approvals:

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