Research Protocol

**Title:** Secular trend in sequence of pharmacologic treatment for postmenopausal osteoporosis

Responsible parties

Study Lead:

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# List of abbreviations

* SERMs: Selective estrogen receptor modulators
* BPs: Bisphosphonates
* rhPTH: recombinant human parathyroid hormone 1-34
* PO: Per os
* IV: Intravenous therapy
* BMD: Bone mineral density

# Abstract

This study will describe the change in osteoporosis drug utilization pattern over the past decade. The study will describe the sequence of treatments, as well as patient persistence of each treatment. We will also compare the incidence of fracture within each treatment pattern.

# Amendments and Updates

# Rationale and background

Osteoporosis, a skeletal disease characterized by weakened bones and a heightened risk of fractures, is particularly prevalent among postmenopausal women.(1, 2) Medications such as selective estrogen receptor modulators (SERMs), bisphosphonates (BPs), denosumab, recombinant human parathyroid hormone 1-34 (rhPTH) and romosozuamb are used to improve bone mineral density (BMD) and reduce fracture risk.(3, 4)

Improving medication persistence among osteoporosis patients is important in fracture prevention since non-persistence is well known to be associated with a significantly increased risk of fracture.(5, 6) Here, persistence is defined as the duration of time from initiation to discontinuation of therapy, as outlined by the International Society for Pharmacoeconomics and Outcomes Research Medication Compliance and Persistence Special Interest Group.(7) Persistence is typically reported as a percentage at pre-defined time points (1 year in this study). Previous studies about non-persistence were mostly limited to oral and parenteral BPs within single population. One study examined drug utilization patterns and medication persistence across seven European health databases, revealing suboptimal persistence to oral medications and rare treatment switching.(8) However, only a relatively small proportion of patients were found to be undergoing treatment with denosumab in this population.

Denosumab, a relatively recent anti-osteoporosis drug, is known to provide better persistence than BPs. Despite its widespread use since its approval (2017) and insurance coverage (2019) in South Korea, changes in real-world clinical practices remains elusive.(9)

# Aims and Objectives

This study is multinational cohort study which aims to:

1. Characterize and describe the treatment patterns of osteoporosis drugs in menopausal women.
2. Compare the fracture incidence within treatment patterns.

## AIM 1. Descriptive

* Describe demographics and clinical characteristics of patients treated with each osteoporosis drugs.
* Describe the sequence of osteoporosis drugs prescribed in various patient populations and clinical settings.
* Describe patient persistence in each treatment patterns.
* Describe changes in treatment pattern over the past decades.

## AIM 2. Comparative effectiveness study

* Determine the incidence rate of osteoporotic fractures in patients exposed to denosumab compared to bisphosphonates.
* Perform subgroup analyses based on factors such as age, sex, race, comorbidities to identify any population-specific risks.

# Research Methods

## Study design

This study will be retrospective and observational, describing and evaluating patterns in osteoporosis treatment over time in postmenopausal women. characterizing the sequential pattern of treatment and comparing the risk of osteoporotic fracture after first line treatment to BPs relative to denosumab. Data sources will be administrative claims or electronic health record (EHR) data across the OHDSI network.

## Study population

#### Study Population for Treatment Pathways

The target group is patients ≥50 years or older women who have osteoporosis.

Index rule defining the index date:

* First occurrence of Osteoporosis in a person with a greater than 50-year-old female between 2012-01-01 and 2021-12-31.

Table 1 Osteoporosis Concept Set Definitions

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Excluded | Descendant | Mapped |
| 80502 | Osteoporosis | Condition | FALSE | TRUE | FALSE |
| 45766159 | Secondary osteoporosis | Condition | TRUE | TRUE | FALSE |
| 40480160 | Osteoporotic fracture | Condition | TRUE | TRUE | FALSE |
| 4002134 | Osteoporosis in endocrine disorders | Condition | TRUE | TRUE | FALSE |
| 42538151 | Osteoporosis co-occurrent and due to multiple myeloma | Condition | TRUE | TRUE | FALSE |

* + - 1. **Subgroups: No Denosumab (2012-2016)**

The sub-group is patients ≥50 years or older women who have osteoporosis.

Index rule defining the index date:

* First occurrence of Osteoporosis in a person with a greater than 50-year-old female between 2012-01-01 and 2016-12-31.
  + - 1. **Subgroups: Approval of Denosumab (2017-2018)**

The sub-group is patients ≥50 years or older women who have osteoporosis.

Index rule defining the index date:

* First occurrence of Osteoporosis in a person with a greater than 50-year-old female between 2017-01-01 and 2018-12-31
  + - 1. **Subgroups: Insurance coverage of Denosumab (2019-2021)**

The sub-group is patients ≥50 years or older women who have osteoporosis.

Index rule defining the index date:

* First occurrence of Osteoporosis in a person with a greater than 50-year-old female between 2019-01-01 and 2021-12-31

### Treatment of Interest

Treatments of Interest are anti-osteoporosis drug that can be prescribed or dispensed for the treatment of osteoporosis. We define osteoporosis treatment as a prescription of anti-osteoporosis drug for at least a month.

#### Treatment of Interest: Bisphosphonate PO

Index rule defining the index date (earliest event per person):

* Exposure to bisphosphonate PO (Dosing Internal 1 day) with Days’ Supply greater or equal to 28
* Exposure to bisphosphonate PO (Dosing Internal 1 week) with Days’ Supply greater or equal to 4
* Exposure to bisphosphonate PO (Dosing Internal 1 month) with Days’ Supply greater or equal to 1

Inclusion rules based on the index date:

* At least 1 occurrence of osteoporosis in a female over 50 between all days before and 0 days before index date

Exit rules defining the cohort end date:

* Allowance for 180-day gaps between consecutive prescriptions of Bisphosphonate PO

Table 2 Bisphosphonate PO (Dosing Interval 1 day) Concept Set Definitions

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Excluded | Descendant | Mapped |
| 40174497 | risedronate sodium 5 MG | Drug | FALSE | TRUE | FALSE |
| 40173601 | alendronic acid 5 MG | Drug | FALSE | TRUE | FALSE |
| 40173589 | alendronic acid 10 MG | Drug | FALSE | TRUE | FALSE |

Table 3 Bisphosphonate PO (Dosing Interval 1 week) Concept Set Definitions

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Excluded | Descendant | Mapped |
| 40174493 | risedronate sodium 35 MG | Drug | FALSE | TRUE | FALSE |
| 40173605 | alendronic acid 70 MG | Drug | FALSE | TRUE | FALSE |
| 19123238 | risedronate 35 MG | Drug | FALSE | TRUE | FALSE |
| 21104349 | Alendronate 0.7 MG/ML | Drug | FALSE | TRUE | FALSE |

Table 4 Bisphosphonate PO (Dosing Interval 1 month) Concept Set Definitions

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Excluded | Descendant | Mapped |
| 40174485 | risedronate sodium 150 MG | Drug | FALSE | TRUE | FALSE |
| 40174363 | ibandronic acid 150 MG | Drug | FALSE | TRUE | FALSE |

#### Treatment of Interest: Bisphosphonate IV

Index rule defining the index date (earliest event per person):

* Exposure to bisphosphonate IV (Dosing Internal over 6 month) with Days’ Supply greater or equal to 1

Inclusion rules based on the index date:

* At least 1 occurrence of osteoporosis in a female over 50 between all days before and 0 days before index date

Exit rules defining the cohort end date:

* Allowance for 180-day gaps between consecutive prescriptions of Bisphosphonate IV

Table 5 Bisphosphonate IV Concept Set Definitions

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Excluded | Descendant | Mapped |
| 19126449 | zoledronic acid 0.05 MG/ML | Drug | FALSE | TRUE | FALSE |
| 40174359 | ibandronic acid 1 MG/ML | Drug | FALSE | TRUE | FALSE |

#### Treatment of Interest: SERM

Index rule defining the index date (earliest event per person):

* Exposure to SERM (Dosing Internal 1 day) with Days Supply greater or equal to 28

Inclusion rules based on the index date:

* At least 1 occurrence of osteoporosis in a female over 50 between all days before and 0 days before index date

Exit rules defining the cohort end date:

* Allowance for 180-day gaps between consecutive prescriptions of SERM

Table 6 SERM (Dosing Interval 1 day) Concept Set Definitions

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Excluded | Descendant | Mapped |
| 44814411 | raloxifene hydrochloride 60 MG | Drug | FALSE | TRUE | FALSE |
| 42949553 | Raloxifene / vitamin D3 Oral Capsule | Drug | FALSE | TRUE | FALSE |
| 44506575 | bazedoxifene 20 MG | Drug | FALSE | TRUE | FALSE |
| 2060008 | bazedoxifene / cholecalciferol Oral Tablet | Drug | FALSE | TRUE | FALSE |

#### Treatment of Interest: Denosumab

Index rule defining the index date (earliest event per person):

* Exposure to Denosumab (Dosing Internal over 6 month) with Days Supply greater or equal to 1

Inclusion rules based on the index date:

* At least 1 occurrence of osteoporosis in a female over 50 between all days before and 0 days before index date

Exit rules defining the cohort end date:

* Allowance for 180-day gaps between consecutive prescriptions of denosumab

Table 7 Denosumab Concept Set Definition

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Excluded | Descendant | Mapped |
| 40222445 | denosumab 60 MG/ML | Drug | FALSE | TRUE | FALSE |

#### Treatment of Interest: rh PTH

Index rule defining the index date:

* Exposure to rh PTH (Dosing Internal over 6 month) with Days Supply greater or equal to 1

Inclusion rules based on the index date:

* At least 1 occurrence of osteoporosis in a female over 50 between all days before and 0 days before index date

Exit rules defining the cohort end date:

* Allowance for 180-day gaps between consecutive prescriptions of rh PTH

Table 8 rhPTH Concept Set Definitions

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Excluded | Descendant | Mapped |
| 40222445 | denosumab 60 MG/ML | Drug | FALSE | TRUE | FALSE |

### Study Population for Comparative effectiveness study

The target group consists of patients who initiated denosumab treatment and who meet the criteria below. Patients who initiate bisphosphonate and meet the criteria below are included in the comparator group.

Index rule defining the index date:

* Exposure to one of the treatments of interest longer than 30 days

Inclusion rules based on the index date:

* At least 1 occurrence of osteoporosis in a female over 50 between all days before and 0 days before index date
* None of exposure to anti osteoporosis treatments other than the drug of interest between all days before 0 days before index date

Exit rules defining the cohort end date:

* Allowance for 210-day gaps between consecutive prescriptions of the drug of interest

Table 9 Anti-Osteoporosis (without Denosumab) Concept Set Definition

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Excluded | Descendant | Mapped |
| 1524674 | zoledronic acid | Drug | FALSE | TRUE | FALSE |
| 1578445 | tiludronate | Drug | FALSE | TRUE | FALSE |
| 1521987 | teriparatide | Drug | FALSE | TRUE | FALSE |
| 1436678 | tamoxifen | Drug | FALSE | TRUE | FALSE |
| 1511251 | romosozumab | Drug | FALSE | TRUE | FALSE |
| 1516800 | risedronate | Drug | FALSE | TRUE | FALSE |
| 1513103 | raloxifene | Drug | FALSE | TRUE | FALSE |
| 1511646 | pamidronate | Drug | FALSE | TRUE | FALSE |
| 36850663 | LASOFOXIFENE | Drug | FALSE | TRUE | FALSE |
| 1512480 | ibandronate | Drug | FALSE | TRUE | FALSE |
| 1552929 | etidronate | Drug | FALSE | TRUE | FALSE |
| 44506794 | bazedoxifene | Drug | FALSE | TRUE | FALSE |
| 1557272 | alendronate | Drug | FALSE | TRUE | FALSE |
| 1594148 | abaloparatide | Drug | FALSE | TRUE | FALSE |

Table 10 Anti-Osteoporosis (without Bisphosphonate) Concept Set Definition

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Excluded | Descendant | Mapped |
| 1521987 | teriparatide | Drug | FALSE | TRUE | FALSE |
| 1436678 | tamoxifen | Drug | FALSE | TRUE | FALSE |
| 1511251 | romosozumab | Drug | FALSE | TRUE | FALSE |
| 1513103 | raloxifene | Drug | FALSE | TRUE | FALSE |
| 36850663 | LASOFOXIFENE | Drug | FALSE | TRUE | FALSE |
| 40222444 | denosumab | Drug | FALSE | TRUE | FALSE |
| 44506794 | bazedoxifene | Drug | FALSE | TRUE | FALSE |
| 1594148 | abaloparatide | Drug | FALSE | TRUE | FALSE |

### Outcomes

#### Primary outcome: Osteoporotic Fracture

Index rule defining the index date:

* Occurrence of Osteoporotic Fracture

Exit rules defining the cohort end date:

* Allowance for 365-day offsets from index date

Table 11 Osteoporotic Fracture Concept Set Definition

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Excluded | Descendant | Mapped |
| 40480160 | Osteoporotic fracture | Condition | FALSE | TRUE | FALSE |
| 40441585 | Stress fracture | Condition | FALSE | TRUE | FALSE |
| 4279139 | Fracture of bones of trunk | Condition | FALSE | TRUE | FALSE |
| 4278672 | Fracture of forearm | Condition | FALSE | TRUE | FALSE |
| 4222001 | Collapse of vertebra | Condition | FALSE | TRUE | FALSE |
| 4187096 | Fracture of lower limb | Condition | FALSE | TRUE | FALSE |
| 4185758 | Fracture of lower leg | Condition | FALSE | TRUE | FALSE |
| 4174520 | Fracture of vertebral column | Condition | FALSE | TRUE | FALSE |
| 4129393 | Fracture of cervical spine | Condition | FALSE | TRUE | FALSE |
| 4069306 | Idiopathic osteoporosis with pathological fracture | Condition | FALSE | TRUE | FALSE |
| 4050747 | Fracture of upper limb | Condition | FALSE | TRUE | FALSE |
| 4013613 | Fracture of lumbar spine and/or pelvis | Condition | FALSE | TRUE | FALSE |
| 4001458 | Fatigue fracture of vertebra | Condition | FALSE | TRUE | FALSE |
| 442560 | Fracture of femur | Condition | FALSE | TRUE | FALSE |
| 73571 | Pathological fracture | Condition | FALSE | TRUE | FALSE |
| 4307254 | Closed fracture | Condition | TRUE | TRUE | FALSE |
| 4302223 | Fracture of bone of head | Condition | TRUE | TRUE | FALSE |
| 4154098 | Dupuytren's fracture dislocation ankle | Condition | TRUE | TRUE | FALSE |
| 4115182 | Fracture malunion - ankle and/or foot | Condition | TRUE | TRUE | FALSE |
| 4115176 | Pathological fracture - ankle and/or foot | Condition | TRUE | TRUE | FALSE |
| 4071876 | Fracture of hand | Condition | TRUE | TRUE | FALSE |
| 4067766 | Pathologic fracture of bone at site of neoplasm | Condition | TRUE | TRUE | FALSE |
| 4059173 | Fracture of ankle | Condition | TRUE | TRUE | FALSE |
| 4048393 | Fracture of foot | Condition | TRUE | TRUE | FALSE |
| 4015350 | Fracture at wrist and/or hand level | Condition | TRUE | TRUE | FALSE |
| 441406 | Disorder of fetus or newborn | Condition | TRUE | TRUE | FALSE |

#### Secondary outcome: Osteoporotic Fracture (Vertebral w/o Neck)

Index rule defining the index date:

* Occurrence of osteoporotic vertebral fracture (excluded Neck)

Exit rules defining the cohort end date:

* Allowance for 365-day offsets from index date

Table 12 Osteoporotic Vertebral Fracture Concept Set Definition

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Excluded | Descendant | Mapped |
| 4053828 | Fracture of thoracic spine | Condition | FALSE | TRUE | FALSE |
| 4129394 | Fracture of lumbar spine | Condition | FALSE | TRUE | FALSE |

#### Secondary outcome: Osteoporotic Fracture (Hip)

Index rule defining the index date:

* Occurrence of osteoporotic hip fracture (Proximal femur)

Exit rules defining the cohort end date:

* Allowance for 365-day offsets from index date

Table 13 Osteoporotic Hip Fracture Concept Set Definition

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Excluded | Descendant | Mapped |
| 45767037 | Pathological fracture of femur due to osteoporosis | Condition | FALSE | TRUE | FALSE |
| 4138412 | Fracture of proximal end of femur | Condition | FALSE | TRUE | FALSE |
| 4230399 | Closed fracture of hip | Condition | FALSE | TRUE | FALSE |

#### Secondary outcome: Osteoporotic Fracture (Non-Vertebral & Non-Hip)

Index rule defining the index date:

* Occurrence of osteoporotic pelvis fracture
* Occurrence of osteoporotic Clavicle+Scapula+Sternum fracture
* Occurrence of osteoporotic upper leg (distal femur) fracture
* Occurrence of osteoporotic lower leg fracture
* Occurrence of osteoporotic upper arm fracture
* Occurrence of osteoporotic lower arm fracture
* Occurrence of osteoporotic shoulder fracture
* Occurrence of osteoporotic wrist fracture
* Occurrence of osteoporotic ankle fracture
* Occurrence of osteoporotic knee fracture

Exit rules defining the cohort end date:

* Allowance for 365-day offsets from index date

Table 14 Osteoporotic Pelvis Fracture Concept Set Definition

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Excluded | Descendant | Mapped |
| 4300192 | Fracture of pelvis | Condition | FALSE | TRUE | FALSE |

Table 15 Osteoporotic Clavicle+Scapula+Sternum Fracture Concept Set Definition

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Excluded | Descendant | Mapped |
| 4302740 | Fracture of sternum | Condition | FALSE | TRUE | FALSE |
| 4319889 | Fracture of scapula | Condition | FALSE | TRUE | FALSE |
| 4237458 | Fracture of clavicle | Condition | FALSE | TRUE | FALSE |

Table 16 Osteoporotic Upper Leg (Distal femur) Fracture Concept Set Definition

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Excluded | Descendant | Mapped |
| 440825 | Fracture of shaft of femur | Condition | FALSE | TRUE | FALSE |
| 4135750 | Fracture of femoral condyle | Condition | FALSE | TRUE | FALSE |
| 4135749 | Fracture of distal end of femur | Condition | FALSE | TRUE | FALSE |

Table 17 Osteoporotic Lower Leg Fracture Concept Set Definition

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Excluded | Descendant | Mapped |
| 4185758 | Fracture of lower leg | Condition | FALSE | TRUE | FALSE |

Table 18 Osteoporotic Upper Arm Fracture Concept Set Definition

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Excluded | Descendant | Mapped |
| 442619 | Fracture of humerus | Condition | FALSE | TRUE | FALSE |

Table 19 Osteoporotic Lower Arm Fracture Concept Set Definition

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Excluded | Descendant | Mapped |
| 4278672 | Fracture of forearm | Condition | FALSE | TRUE | FALSE |

Table 20 Osteoporotic Shoulder Fracture Concept Set Definition

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Excluded | Descendant | Mapped |
| 37311960 | Fracture of head of humerus | Condition | FALSE | TRUE | FALSE |

Table 21 Osteoporotic Wrist Fracture Concept Set Definition

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Excluded | Descendant | Mapped |
| 4218884 | Fracture of carpal bone | Condition | FALSE | TRUE | FALSE |

Table 22 Osteoporotic Ankle Fracture Concept Set Definition

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Excluded | Descendant | Mapped |
| 4136841 | Pilon fracture | Condition | FALSE | TRUE | FALSE |
| 4105127 | Fracture of medial malleolus | Condition | FALSE | TRUE | FALSE |
| 4085552 | Fracture of lateral malleolus | Condition | FALSE | TRUE | FALSE |
| 4059173 | Fracture of ankle | Condition | FALSE | TRUE | FALSE |

Table 23 Osteoporotic Knee Fracture Concept Set Definition

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Excluded | Descendant | Mapped |
| 4177025 | Fracture of patella | Condition | FALSE | TRUE | FALSE |

#### Secondary outcome: Osteoporotic Fracture (unspecified site)

Index rule defining the index date:

* Occurrence of osteoporotic unspecified site fracture

Exit rules defining the cohort end date:

* Allowance for 365-day offsets from index date

Table 24 Osteoporotic Unspecified site Fracture Concept Set Definition

|  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- |
| Concept ID | Concept Name | Domain | Excluded | Descendant | Mapped |
| 4067768 | Postmenopausal osteoporosis with pathological fracture | Condition | FALSE | FALSE | FALSE |
| 4003483 | Osteoporosis of disuse with pathological fracture | Condition | FALSE | FALSE | FALSE |
| 4069306 | Idiopathic osteoporosis with pathological fracture | Condition | FALSE | FALSE | FALSE |

#### Negative controls outcome

A total of 161 concepts were selected as negative controls that were not associated with bisphosphonates and denosumab.

Table 25 Negative controls outcomes

|  |  |
| --- | --- |
| Concept ID | Concept Name |
| 73026 | Abnormal breath sounds |
| 4262562 | Abnormal heart beat |
| 436409 | Abnormal pupil |
| 443702 | Abnormal response to nerve stimulation |
| 137989 | Abnormal results of cardiovascular function studies |
| 443585 | Abrasion and/or friction burn of multiple sites |
| 4088290 | Absence of breast |
| 4088768 | Absent nipple |
| 436015 | Accidental poisoning from foodstuffs and poisonous plants |
| 44783954 | Acid reflux |
| 374957 | Acquired stenosis of external ear canal |
| 435720 | Adverse anesthesia outcome |
| 4173136 | Agnosia |
| 434916 | Amphetamine or psychostimulant dependence, continuous |
| 4103642 | Amputated toe |
| 4061157 | Antenatal ultrasound scan abnormal |
| 439136 | Asphyxia, in liveborn infant |
| 132736 | Bacteremia |
| 436011 | Bends |
| 81878 | Benign paroxysmal positional vertigo |
| 4228429 | Carnitine deficiency |
| 4213540 | Cervical somatic dysfunction |
| 4090271 | Choroidal atrophy |
| 201613 | Chronic nonalcoholic liver disease |
| 4066505 | Clicking hip |
| 196454 | Colostomy and enterostomy malfunction |
| 4201390 | Colostomy present |
| 434675 | Complication of gastrostomy |
| 4022071 | Convalescence |
| 380724 | Corneal ghost vessels |
| 201606 | Crohn's disease |
| 436233 | Delayed milestone |
| 438759 | Descemet's membrane fold |
| 4067861 | Deviation of finger |
| 434482 | Diethylstilbestrol poisoning |
| 4115402 | Difficulty sleeping |
| 4268911 | Disorientated |
| 201091 | Disproportion - major pelvic abnormality |
| 372329 | Dissociated deviation |
| 4155818 | Does climb |
| 433441 | Ectopic production of endocrine substance |
| 433111 | Effects of hunger |
| 435170 | Effects of thirst |
| 4029271 | Essential fatty acid deficiency |
| 193598 | Extravasation of urine |
| 4059015 | Falls |
| 4092896 | Feces contents abnormal |
| 4182437 | Female genital cutting |
| 4262519 | Female sexual arousal disorder |
| 4005743 | Female sterility |
| 4118057 | Fetal or neonatal effect of maternal oligohydramnios |
| 80463 | Fetus with chromosomal abnormality with antenatal problem |
| 4229403 | Flat anterior chamber of eye |
| 4264617 | Foot-drop |
| 374801 | Foreign body in ear |
| 441487 | Frostbite |
| 436957 | Functional disorders of polymorphonuclear neutrophils |
| 439788 | Galactosemia |
| 4101305 | Gaucher's disease |
| 4168318 | Genetic disorder carrier |
| 437744 | Heat exhaustion |
| 4163735 | Hemochromatosis |
| 439871 | Hemospermia |
| 4012570 | High risk sexual behavior |
| 4012934 | Homocystinuria |
| 372897 | Homonymous hemianopia |
| 438941 | Hydantoin derivative poisoning |
| 437390 | Hypoxemia |
| 443447 | Iatrogenic hypotension |
| 432596 | Immune defect |
| 4344500 | Impingement syndrome of shoulder region |
| 193020 | Incomplete emptying of bladder |
| 441417 | Incoordination |
| 434485 | Increase in body fat |
| 4012368 | Increased frequency of urination |
| 440276 | Infection AND/OR inflammatory reaction due to internal prosthetic device, implant AND/OR graft |
| 440053 | Infestation by insect |
| 4168222 | Intra-abdominal and pelvic swelling, mass and lump |
| 440710 | Intraretinal microvascular abnormality |
| 4168681 | Irritability and anger |
| 434063 | Jaw to cranial base anomaly |
| 72404 | Joint stiffness |
| 432593 | Kwashiorkor |
| 197676 | Large liver |
| 133088 | Late amputation stump complication |
| 437176 | Late effect of accidental fall |
| 439743 | Late effects of respiratory tuberculosis |
| 436041 | Leech infestation |
| 377873 | Lid lag |
| 435516 | Lipoprotein deficiency disorder |
| 4051630 | Malingering |
| 436426 | Malleus mobility reduced |
| 258540 | Marfan's syndrome |
| 432798 | Mechanical complication of internal orthopedic device, implant AND/OR graft |
| 439795 | Minimal cognitive impairment |
| 441536 | Mixed acid-base balance disorder |
| 134315 | Myelophthisis |
| 441553 | Myoclonus |
| 4195085 | Nasal congestion |
| 443933 | Nicotiana tabacum poisoning |
| 4209423 | Nicotine dependence |
| 434016 | Nondependent opioid abuse, continuous |
| 375277 | Non-infectious pinna disorders |
| 4035269 | Non-ketotic hyperglycinemia |
| 40480893 | Nonspecific tuberculin test reaction |
| 194439 | Obstetric perineal wound disruption |
| 438130 | Opioid abuse |
| 4091513 | Passing flatus |
| 4022076 | Patient dependence on care provider |
| 437092 | Physiological development failure |
| 253796 | Pneumothorax |
| 439971 | Poisoning by anticoagulant |
| 439234 | Poisoning by cardiotonic glycoside |
| 444043 | Poisoning by intravenous anesthetic |
| 436860 | Poisoning by irritant cathartic |
| 440919 | Poisoning by methadone |
| 436294 | Poisoning by phenothiazine-based tranquilizer |
| 433951 | Poisoning by tranquilizer |
| 440924 | Poisoning by vasodilator |
| 4318502 | Poisoning due to scorpion venom |
| 437369 | Postmature infancy |
| 4202045 | Postviral fatigue syndrome |
| 4094448 | Pregnancy test negative |
| 434319 | Premature ejaculation |
| 46286594 | Problem related to lifestyle |
| 4197184 | Pseudobulbar affect |
| 440068 | Psychosexual dysfunction |
| 435028 | Puerperal pyrexia of unknown origin |
| 254163 | Pulmonary aspiration of gastric contents |
| 436246 | Reduced libido |
| 436828 | Saliva abnormal |
| 4111720 | Sequelae of subarachnoid hemorrhage |
| 4233565 | Severe protein-calorie malnutrition (Gomez: less than 60 percent of standard weight) |
| 137682 | Skin sensation disturbance |
| 4305303 | Sleep deprivation |
| 4125590 | Slurred speech |
| 4019836 | Social exclusion |
| 443172 | Splinter of face, without major open wound |
| 443082 | Starvation |
| 4229897 | Stupor |
| 440457 | Threatened miscarriage |
| 4194160 | Thyroid function tests abnormal |
| 443526 | Toxic effect from eating shellfish |
| 437732 | Toxic effect of chromium |
| 433369 | Toxic effect of food contaminant |
| 443892 | Toxic effect of hydrocyanic acid |
| 441759 | Toxic effect of inorganic lead compound |
| 440612 | Toxic effect of tobacco and nicotine |
| 4201387 | Tracheostomy present |
| 4199550 | Unable to mobilize |
| 4002572 | Uncomplicated sedative, hypnotic AND/OR anxiolytic withdrawal |
| 4092743 | Unsteady when standing |
| 197096 | Urethra and bladder neck atresia and stenosis |
| 195590 | Urethral stricture |
| 442282 | Urinary casts |
| 4088910 | Uterine cervix absent |
| 4088920 | Uterus absent |
| 197036 | Vesicoureteric reflux |
| 314754 | Wheezing |
| 440193 | Wristdrop |

# Data Analysis Plan

## Treatment Pathways

The treatment pathway analysis will be conducted using an R package that contains the same SQL as ATLAS' Cohort Pathway Analysis. Cohort Pathways analyses describe treatment sequences during the post-index period, providing valuable insight into treatment utilization. In this study, we summarize anti-osteoporosis treatments received by individuals within the osteoporosis cohort from the first treatment. Additionally, we want to describe the most prevalent first-line osteoporosis medication, the proportion of discontinuers, and the proportion of switchers.

#### Output

|  |  |
| --- | --- |
| Output | Description |
| Sunburst plot | The sunburst plot will show the proportion of anti-osteoporosis prescriptions. The inner circle shows the first medication prescribed by the patient, the second circle shows the second medication, and so on. |
| Sankey plot | The Sankey plot will show the proportion of anti-osteoporosis prescriptions. The first line shows the first medication prescribed by the patient, the second line shows the second medication, and so on. |
| Population characteristics table | The table will be created some select population characteristics by medication-line. |
| Prescriptions by year Plot | The line plot for prescription of anti-osteoporosis by year. |

## Population Level Estimation

#### Covariates for Propensity scores

The types of baseline covariates used to fit the propensity score model will be:

* demographics
  + Age
  + Age group (5-year bands)
  + Race
  + Ethnicity
  + Index Year
* Condition Aggregation
  + In prior 30d
  + In prior 365d
* Drug Aggregation
  + In prior 30d
  + In prior 365d
* Procedure
  + In prior 30d
  + In prior 365d
* Device
  + In prior 30d
  + In prior 365d
* Measurement
  + In prior 30d
  + In prior 365d
  + Range Group in prior 365d
* Observation
  + In prior 30d
  + In prior 365d
* Charlson Index
* Dcsi

The concepts which composed of cohorts definition of target or comparator excluded from the propensity score model.

#### Data Analysis Plan

##### **Calculation of time at risk**

Two time-at-risk period will be used:

* Intent-to-treat (2Y): Starting 1 days after treatment initiation and stopping at the 730 days.
* Intent-to-treat (5Y): Starting 1 days after treatment initiation and stopping at the 1095 days.
* On-treatment: Starting 1 days after treatment initiation and stopping 0 days after treatment end.

Incidence rates will be computed for outcome in time at risk group.

##### **Model specification**

we compare the target cohort with the comparator cohort for the hazards of outcome during the time-at-risk by applying a Cox proportional hazards model. Incidence rates will be computed for each outcome in each exposure group.

###### Statistical model

Propensity score Adjustment will be:

* 1:1 PS matching: One-to-one matching will be performed. A caliper of 0.2 times the standard deviation of the propensity score distribution
* Variable ratio PS matching: The two cohorts were matched with a maximum ratio of 3. A caliper of 0.2 times the standard deviation of the PS distribution
* PS stratification: The target cohort and comparator cohorts will be stratified into ten quantiles of the PS distribution.

Outcome Model Settings will be:

* Cox proportional hazards model will be used to estimate the risk of outcome between target and comparator cohorts.

##### **Analysis to Perform**

The following comparative analysis will be performed:

* 3 comparisons:
  + new users of Denosumab as first-line anti-osteoporosis therapy (Target) vs new users of Bisphosphonate (PO+IV) as first line anti-osteoporosis therapy (Comparator)
  + new users of Denosumab as first-line anti-osteoporosis therapy (Target) vs new users of Bisphosphonate PO as first line anti-osteoporosis therapy (Comparator)
  + new users of Denosumab as first-line anti-osteoporosis therapy (Target) vs new users of Bisphosphonate IV as first line anti-osteoporosis therapy (Comparator)
* 5 outcomes:
  + Osteoporotic fracture
  + Osteoporotic fracture (Vertebral)
  + Osteoporotic fracture (Hip)
  + Osteoporotic fracture (NVNH)
  + Osteoporotic fracture (unspecified)
* 3 time-at-risk:
  + Intent-to-treatment (2Y)
  + Intent-to-treatment (5Y)
  + On treatment
* One model: Cox-regression after 1:1 PS matching

#### Output

|  |  |
| --- | --- |
| Output | Description |
| Propensity score distribution Plot | The propensity score distribution for both cohorts after matching will be provided. |
| Propensity model | The propensity model will show the table that reports the covariates selected from propensity score models, with associated coefficients. |
| Covariate Balance Scatter Plot | Covariate Balance Scatter Plot will show the absolute standardized difference of mean before and after propensity score matching. |
| Attrition diagram | Attrition diagram will show the counts to meet the various inclusion and exclusion criteria, and loss due to matching. |
| Kaplan-Meier plot | Kaplan-Meier plot will display the survival over time in both cohorts. |
| Population characteristics table | A table which lists some select population characteristics before and after matching will be created. |
| Outcome models | The summarized report will be provided from outcome models. It will report the hazards ration, associated 95% confidence interval, the number of persons, amount of time-at-risk, and number outcome in both cohorts. |

# Strengths and Limitations of the Research Methods

## Strength

* Cohort study allow direct estimation of incidence rates following exposure of interest, and the new-user design can capture early events following treatment exposures while avoiding confounding from previous treatment effects. New use allows for a clear exposure index date.
* PS matching and outcome model allow balancing on many baselines potential confounders.

## Limitations

* Even though many potential confounders will be included in this study, there may be residual bias due to unmeasured or mis-specified confounders.

# Protection of Human Subjects

In this study, we will use only de-identified data from CDM. The results of study will be aggregated and will not identify individual subjects.

# Plans for Disseminating and Communicating Study Results

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