Summary Table of Study Protocol

Title	The use, safety, and effectiveness of Prolia in clinical practice among Chinese women with post-menopausal osteoporosis – Taiwan and Hong Kong
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Date of last version of the protocol	02-Jan-2019
EU Post Authorization Study (PAS) Register No	in application
Active Substance	denosumab
Medicinal Product	Prolia
Product Reference	not applicable
Procedure Number	not applicable
Objectives	Among Chinese women being treated in clinical practice for post-menopausal osteoporosis, the objectives are to: 1. Evaluate the effectiveness of denosumab for the reduction of clinical osteoporotic fractures 2. Characterize the safety of denosumab
Regions of Study	Taiwan, Hong Kong
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Marketing Authorization Holder

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Investigator's Agreement

I have read the attached protocol entitled "The use, safety, and effectiveness of Prolia in clinical practice among Chinese women with post-menopausal osteoporosis ─ Taiwan and Hong Kong", dated 02-Jan-2019, and agree to abide by all provisions set forth therein.

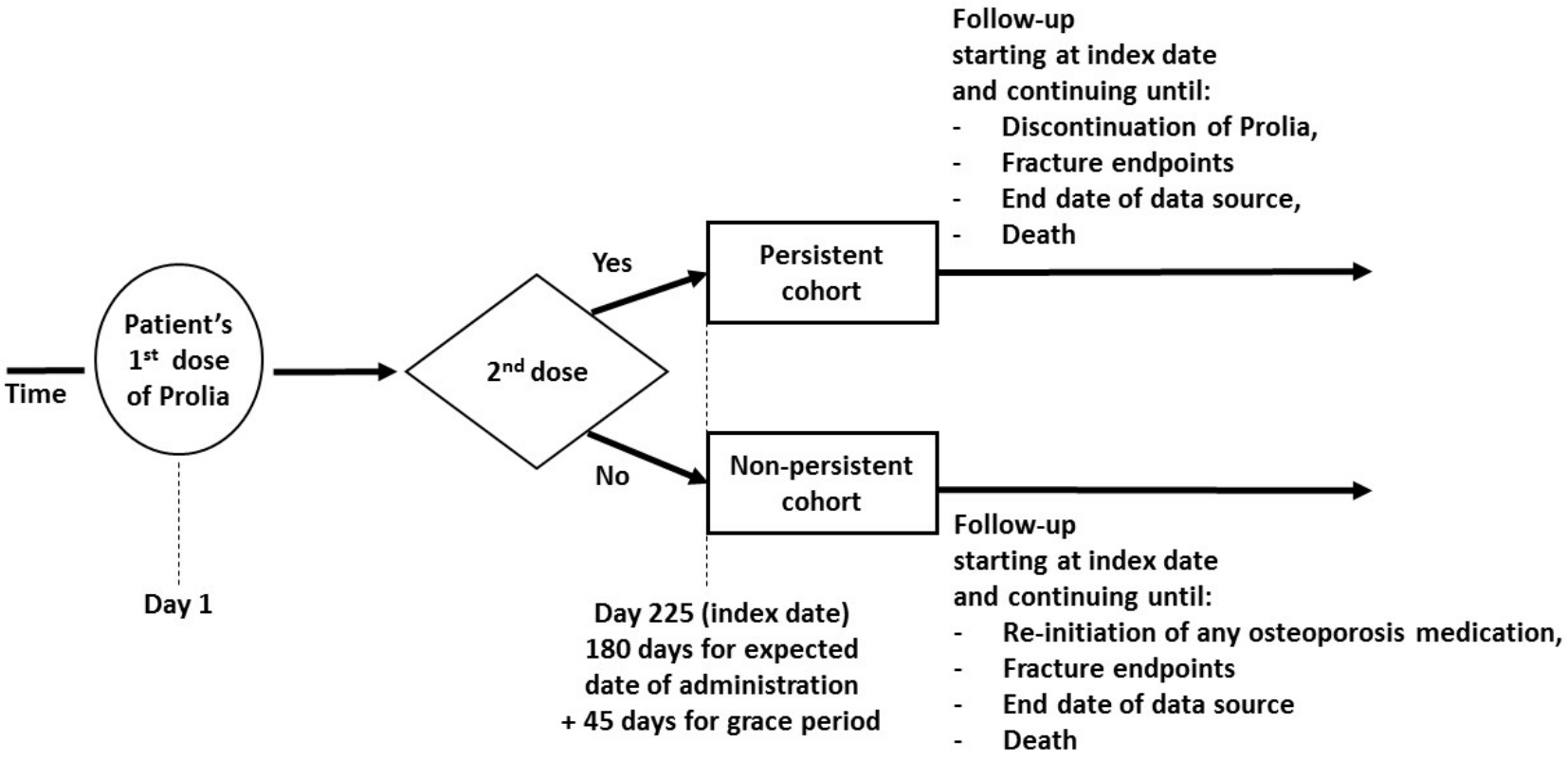
I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

Signature

Name of Investigator Date

Study Design Schema I

Objective to evaluate the effectiveness of denosumab



Primary effectiveness endpoint:

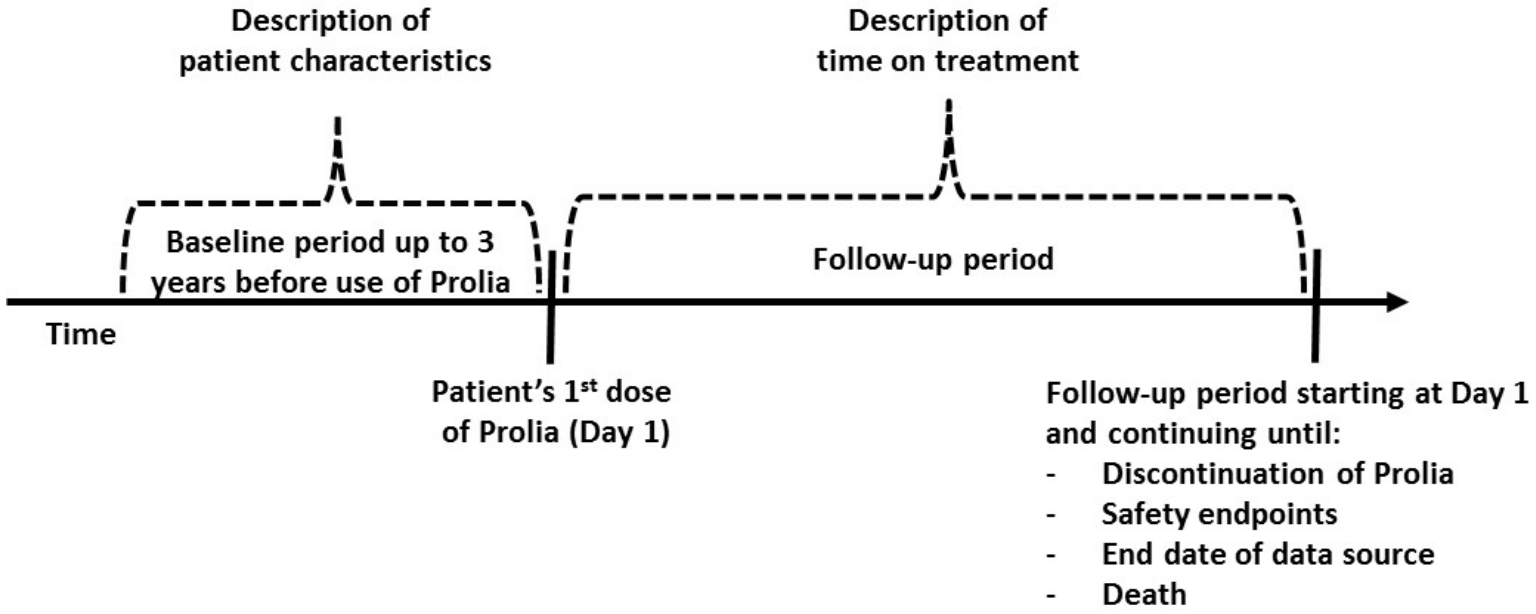
- Hip fracture

Secondary effectiveness endpoints:

- Clinical vertebral fracture
- Non-vertebral fracture (hip, wrist, forearm, humerus)

Study Design Schema II

Objective to characterize safety in all subjects who received at least one dose of Prolia



Three safety endpoints:

- Osteonecrosis of the jaw
- Atypical femur fracture
- Hypocalcemia

1. Table of Contents

List of Appendices

2. List of Abbreviations

AFF	Atypical femur fracture
CDARS	Clinical Data Analysis and Reporting System
HCPCS	Healthcare Common Procedure Coding System
ICD-9-CM	International Classification of Diseases, 9th Revision, Clinical Modification
NHIRD	National Health Insurance Research Database
ONJ	Osteonecrosis of the Jaw
ORSR	Observational Research Study Report
PPV	Positive predictive value
PMO	Post-menopausal osteoporosis
PS	Propensity score
RCT	Randomized controlled trial
RWE	Real-world evidence

3. Responsible Parties

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4. Abstract

Study Title

The use, safety, and effectiveness of Prolia in clinical practice among Chinese women with post-menopausal osteoporosis ─ Taiwan and Hong Kong

Study Background and Rationale

Prolia, first approved by the European Medical Agency and the U.S. Food and Drug Administration in 2010, is approved as a treatment of post-menopausal osteoporosis (PMO) in more than 80 countries and regions. In these locations, more than 9 million patients have used Prolia in clinical practice.

The safety and effectiveness of Prolia in clinical practice is yet to be characterized within a Chinese population. Within the geography of native Chinese, the use of Prolia in clinical practice began in 2011 in Hong Kong and in 2012 in Taiwan. The indication statements for Prolia in Taiwan and Hong Kong include, "Treatment of postmenopausal women with osteoporosis at a high risk for fracture". Based on the number of PMO patients with use of Prolia in Taiwan and Hong Kong; the multiple years of available follow-up; the availability of clinical practice data that is well-established for health research by academic institutions; and the fit-for-purpose nature of this data containing the fracture and safety endpoints of clinical interest ─ There is an opportunity to characterize the use, safety, and effectiveness of Prolia in clinical practice among Chinese women outside of an investigational study setting.

Research Question and Objectives

Among Chinese women being treated in clinical practice for post-menopausal osteoporosis, the objectives are to:

1. Evaluate the effectiveness of denosumab for the reduction of clinical osteoporotic fractures.
2. Characterize the safety of denosumab

Study Design

In this retrospective cohort study, a new user cohort of patients will be followed from their first dose of Prolia use through earliest date of: endpoints, treatment discontinuation, death, or end date of data source.

The study design includes both a comparative analysis for effectiveness and a descriptive analysis for safety. For the effectiveness analysis, subject incidence of fracture endpoints and relative fracture risk will be compared between those persistent

and those non-persistent to Prolia after a run-in period of 6 months of Prolia initial therapy. For the safety analysis, the subject incidence rate of endpoints will be reported among all patients who received at least one dose of Prolia.

Data Source

Two databases provide anonymized, patient-level data on demographics, administration of biological medicines, drug dispensing, diagnosis and procedures received at hospitalization or outpatient consultation, and mortality. One database is the National Health Insurance Research Database (NHIRD) of the Taiwan Bureau of National Health Insurance, which serves a population of 23 million through a single-payer national health insurance program for medical and dental care. Nearly 99% of Taiwan population is enrolled in this program. The second database is from the electronic medical records of the Clinical Data Analysis and Reporting System (CDARS) of the Hong Kong Hospital Authority, which serves a population of 7 million. CDARS includes data on approximately 80% of all hospital admissions in Hong Kong. NHIRD data through December 2016 and CDARS data through August 2018 are included in this study.

Patient Eligibility Criteria

The study population includes women aged 55 years or older (i.e., postmenopausal) who received at least one dose of Prolia. To ensure that included women are receiving Prolia for the indication of PMO, all are excluded with a history of Paget's disease or malignancy. To be representative of all patients being treated with Prolia in clinical practice, there are no other exclusion criteria.

Variables

The primary endpoint is hip fracture. The second endpoints are clinical vertebral and non-vertebral (hip, humerus, wrist, and distal forearm) fractures. Safety endpoints include three important identified risks in the Global Risk Management Plan for Prolia: osteonecrosis of the jaw (ONJ), atypical femur fracture (AFF), and hypocalcemia. Endpoints will be identified by published algorithms, which have been validated against the gold standard of medical record review, for the diagnoses and procedures received by the patient at clinical care. Covariates include: demographics, medical histories, medication use, and measures of health seeking behavior.

Study Size

The study size is dependent on the number of patients treated with Prolia in clinical practice. Simple counts in the data source to support protocol development suggest the study will include about 40,000 patients in Taiwan and 3000 patients in Hong Kong; and

the mean follow-up during therapy use will be about 1.5 years. Additional counts suggest that, of every 4 patients initiating Prolia, 3 will enter the persistent cohort (i.e., receive a second administration of Prolia) and 1 will enter the non-persistent to Prolia cohort (i.e., discontinue therapy after one administration of Prolia).

For the characterization of safety, a study size of 60,000 person-years of observation in Taiwan (40,000 patients * 1.5 years) will provide > 99% probability of detecting at least 1 subject with an event given the true rate is 1 per 10,000 person-years. For the evaluation of the effectiveness, the study size in Taiwan will provide 94% probability of detecting a fracture risk reduction of 30% between the persistent and non-persistent to Prolia cohorts for a fracture endpoint occurring at an annual incidence rate of at least 2%.

Data Analysis

The two databases will be analyzed independently according to the common protocol and the following endpoints will be reported for each database. The Taiwan database, which provides sufficient statistical power, will be the primary database used to support conclusions.

In the analyses for effectiveness, the primary endpoint of hip fracture risk will be compared between the persistent cohort and non-persistent cohort following risk adjustment of measurable prognostic differences (i.e., covariates) between cohorts. Results for treatment effectiveness will be presented as a propensity score-matching hazard ratio for time to the first event with 95% confidence interval. Secondary fracture endpoints including clinical vertebral fracture and non-vertebral fracture risk will be analyzed using the same approach. To characterize the safety of Prolia, the safety endpoints of subject incidence per 10,000 person-years of follow-up will be reported for ONJ, AFF, and hypocalcemia.

In the sensitivity analysis, the analytical strategy to evaluate the potential for residual confounding and bias will include a series of analyses to evaluate the robustness of results from the primary analysis of effectiveness. These analyses include: subgroups, alternative algorithms to identify fractures, alternative methods of propensity score analyses, and an assessment of the extent of residual confounding that would be required to refute an observed difference in fracture incidence between cohorts.

5. Amendments and Updates

None

6. Milestones

Milestone	Planned date
Start of data collection (i.e., start of data extraction)	Q1 2019
End of data collection (i.e., analytical data set is available completely)	Q1 2019
Final report of study results	Q2 2019

7. Background and Rationale

7.1 Disease

Post-menopausal osteoporosis is a disorder due to bone loss that damages skeletal architecture, weakens the skeleton and predisposes a patient to fracture. Osteoporotic fractures result in increased mortality, disability, and health care costs (Cummings SR et al, 2002; Johnell O et al, 2006). In Mainland China, the prevalence of osteoporosis (approximately 1 in 3 post-menopausal women) is more than double the prevalence of one decade ago (Chen et al, 2016). Accordingly, the rate of hip fractures is rising rapidly and now more than 4 per 1000 women ages 75 to 79 of age in Beijing will have a hip fracture each year (Xia et al, 2012).

7.2 Therapeutic Area

Pharmacological agents approved in China for PMO treatment include bisphosphonates (alendronate, zoledronic acid, risedronate, and ibandronate), calcitonin (salmon calcitonin and elcatonin), hormone replacement therapy (raloxifene), teriparatide, intact parathyroid hormone (PTH 1-84), and strontium ranelate (Lin X et al., 2015). Denosumab, while not available in China, has been included in the recent treatment guidelines for osteoporosis due to its efficacy (Chinese Society of Osteoporosis and Bone Mineral Research, 2017). Denosumab is a fully human monoclonal antibody that binds and neutralizes the activity of RANK ligand. Clinical benefits of denosumab treatment derive from its inhibition of RANK ligand binding to RANK thereby inhibiting the formation, activation, and survival of osteoclasts; decreasing bone resorption; and increasing bone mass, volume, and strength (Kostenuik et al, 2005). In the pivotal 3-year fracture study, Prolia reduced the risk of new radiographic vertebral fracture, non-vertebral fracture, and hip fracture by 68%, 20%, and 40%, respectively, compared with placebo and led to greater gains in bone mineral density and reduced bone remodeling as assessed by biochemical markers of bone turnover (Cummings et al, 2009).

7.3 Rationale

The safety and efficacy of Prolia has been studied extensively in clinical trials. More than 20,000 subjects have been exposed to denosumab in clinical trials, including the pivotal

phase III placebo-controlled fracture study in women with PMO (Cummings et al, 2009) and its long-term open-label extension, which provided up to 10 years of denosumab exposure (Bone et al, 2017), as well as a bridging fracture study in Japan (Nakamura et al, 2014). Prolia, first approved by the European Medical Agency and the U.S. Food and Drug Administration in 2010, is approved as a treatment of PMO in more than 80 countries and regions. In these locations, more than 9 million patients to date have used Prolia in clinical practice.

While randomized clinical trials (RCTs) provide the best evidence of therapy efficacy in a research setting; real-world evidence (RWE) provides additional knowledge of a therapy's effectiveness and safety in the clinical setting reflecting how medicine is actually practiced, among the types of patients not included in trials (e.g., patients with multiple co-morbidities), and in terms of the clinical outcomes most relevant to patients and to health care providers (Sherman et al, 2016). RWE is being used to provide empirical evidence to complement RCTs for developing medical products, guiding healthcare practice and policy-making (Sun X et al, 2018), and increasingly for informing regulatory decision-making (Corrigan-Curay J et al, 2018; Duke-Margolis 2017).

The safety and effectiveness of Prolia in clinical practice is yet to be characterized within a Chinese population. Within the geography of native Chinese, the use of Prolia in clinical practice began in 2011 in Hong Kong and in 2012 in Taiwan. The indication statements for Prolia in Taiwan and Hong Kong include, "Treatment of postmenopausal women with osteoporosis at a high risk for fracture". Based on the number of PMO patients with use of Prolia in Taiwan and Hong Kong; the multiple years of available follow-up; the availability of clinical practice data that is well-established for health research by academic institutions; and the fit-for-purpose nature of this data containing the fracture and safety endpoints of clinical interest ─ There is an opportunity to characterize the use, safety, and effectiveness of Prolia in clinical practice among Chinese women outside of an investigational study setting.

7.4 Study Hypothesis and Estimates

Hypothesis: The hypothesis is that Prolia treatment for PMO in a real-world, clinical setting among Chinese women is effective in reducing the incidence of clinical fractures. The subject incidence of fracture endpoints and relative risk will be compared between those persistent and those non-persistent to Prolia. The fracture endpoints are:

Primary

- Hip fracture

Secondary

- Clinical vertebral fractures
- Non-vertebral fractures (hip, humerus, wrist and distal forearms)

Expectations for the magnitude of fracture reduction can range based on the yet to be determined underlying fracture risk of patients treated in the study population, the yet to be determined duration of therapy in this study relative to the 3-year duration of phase III study (Cummings et al, 2009), and the results of similar RWE studies of Prolia in the U.S. population (Yusuf AA et al, 2018) of alendronate in Taiwan (Lin TC et al, 2011).

Estimates: This study will provide the incidence rates for three important identified risks in the Global Risk Management Plan for Prolia in all subjects who received at least one dose of a Prolia, including ONJ, AFF, and hypocalcemia. The safety endpoints are:

- ONJ
- AFF
- Hypocalcemia

Context for these endpoints is provided by the incidence rates in: (1) the clinical studies FREEDOM (Cummings et al, 2009) and FREEDOM extension conducted in Western countries (Bone et al, 2017), (2) the on-going pharmacovigilance Study 20090522, now including more than 200,000 women on Prolia, conducted within the U.S., Sweden, Denmark, and Norway (Amgen 2017; Xue et al, 2013), and (3) prior study including Chinese PMO patients.

For ONJ, incidence rates were:

- 5.2 cases per 10,000 participant-years in the clinical studies,
- 1.2 to 4.4 cases per 10,000 person-years (age-adjusted to the U.S. 2010 census population) in Study 20090522,
- 6.9 to 8.2 cases per 10,000 person-years in a PMO population in Taiwan treated with alendronate, raloxifene, or calcitonin (Lin et al, 2014)

For AFF, incidence rates were:

- 18.1 to 35.3 cases per 10,000 person-years (age-adjusted) in Study 20090522 (as defined by fracture of the subtrochanteric or diaphyseal femur)
- 5 cases per 10,000 patient-years in bisphosphate treated population in Sweden (with radiographic confirmation) (Schilcher J et al, 2011)

For hypocalcemia, incidence rates were:

- 0.6 to 2.8 cases per 10,000 person-years (age-adjusted) in Study 20090522

8. Research Question and Objectives

Among Chinese women being treated in clinical practice for PMO, the objectives are to:

1. Evaluate the effectiveness of denosumab for the reduction of clinical osteoporotic fractures
2. Characterize the safety of denosumab

9. Research Methods

9.1 Study Design

In this retrospective cohort study, a new user cohort of patients will be followed from their first dose of Prolia use through earliest date of: endpoints, treatment discontinuation, death, or end date of data source.

The study design includes both a comparative analysis for effectiveness and a descriptive analysis for safety. For the effectiveness analysis, subject incidence of fracture endpoints and relative fracture risk will be compared between those persistent and those non-persistent to Prolia after a run-in period of 6 months of Prolia initial therapy. For the safety analysis, the subject incidence of endpoints will be reported among all patients who received at least one dose of Prolia.

9.2 Setting and Study Population

The setting includes all public medical care delivered by the health care systems in Taiwan and Hong Kong. Taiwan has 23.5 million people, of which 3.6 million are women ages 55 and over (Census, 2018). Hong Kong has 7.2 million people, of which 1.3 million are women ages 55 and over (Census, 2018).

In this setting, the use of Prolia is related to the indication statements, reimbursement policies, and clinical guidelines. In Taiwan, the indication is, "Treatment of postmenopausal women with osteoporosis at a high risk for fracture. In postmenopausal women with osteoporosis, Prolia reduces the incidence of vertebral, non-vertebral, and hip fractures". The Taiwan Bureau of National Health Insurance reimburses for osteoporosis therapies only for patients who have had osteoporosis-related vertebral or hip fracture. Prolia was first reimbursed for clinical practice in Taiwan in March 2012. In Hong Kong, the indication is "Treatment of postmenopausal women with osteoporosis at a high risk for fracture." The Hong Kong Hospital Authority, which manages public medical care, subsidizes osteoporosis drugs for patients who have had a fracture (Kwok and Choy, 2017). According to the Osteoporosis Society of Hong Kong's guideline for

clinical management of osteoporosis (Ip et al, 2013), treatment options include, "For postmenopausal women aged 65 years or older, bisphosphonates or denosumab may be considered the first-line therapy; the choice of agents can be individualized". Prolia was first reimbursed for clinical practice in Hong Kong in 2011.

9.2.1 Study Period

The study period begins before first use of Prolia in each health care system and ends at last available data within data source (i.e., Taiwan 2009 – December 2016; Hong Kong 2010 - August 2018).

9.2.2 Subject Eligibility

The study population includes women aged 55 years or older (i.e., postmenopausal) who received at least one dose of Prolia. To ensure that included women are receiving Prolia for the indication of PMO, all are excluded with a history of Paget's disease or malignancy. To be representative of all patients being treated with Prolia in clinical practice, there are no other exclusion criteria.

9.2.2.1 Inclusion Criteria

- Use of Prolia in clinical practice
- Complete data available on age and sex

9.2.2.2 Exclusion Criteria

- Males
- Less than 55 years old at initial use of Prolia
- History of any malignancy within 1 year before initial use of Prolia
- History of Paget's disease within 1 year before initial use of Prolia

9.2.3 Baseline Period

The baseline period for covariate assessment is inclusive of the 12 months prior to the patient's index date.

9.2.4 Study Follow-up

For the effectiveness analysis, the index date is defined as day 225 (180 days for expected date of administration + 45 days for grace period) after patient's initial use of Prolia, and continue through earliest date of (see schema I):

I. Persistent cohort: discontinuation of Prolia, fracture endpoints, end date of available data in source, or death

II. Non-persistent cohort: re-initiation of osteoporosis medication, fracture endpoints, end date of available data in source or death

The 45-day grace period allows for potential administrative challenges associated with return clinic visits (e.g., scheduling appointments, obtaining prior authorization) and based on the duration of denosumab activity.

Safety analyses included all subjects who received at least one dose of Prolia. Patient follow-up will start at the Day 1 and continue through earliest date of: Prolia discontinuation (6 months [recommended dosage] + 45 days [a grace period]), safety endpoints, 4 years after index date, death, or end of study period (December 2016 in Taiwan; August 2018 in Hong Kong) (see schema II).

9.2.5 Exposure Assessment

The exposure of interest is receipt of Prolia. Prolia is identifiable by the National Codes "K00918209" and "KC00918209" in the Taiwan data and by comparable codes in the Hong Kong data. Patients will be considered as exposed from time of their initial date of Prolia administration through treatment discontinuation (i.e., 6 months + 45 days since previous date of Prolia administration).

The exposure assessment to Prolia is of greater validity than an assessment to other osteoporosis medications for two reasons. One reason is that since denosumab does not embed in bone tissue and its mean half-life is 25.4 days, it is cleared from the body within approximately 6 months. This is unlike bisphosphonates, whose plasma half-life is short, but whose skeletal retention is up to several years. The second reason for valid exposure assessment to Prolia is that denosumab being a medication administered by a health care professional ensures that the patient used the therapy, which is unlike a RWE study of oral medications for which exposure is based on an assumption that a patient actually used all pills prescribed.

9.2.6 Covariate Assessment

The covariate assessment periods are:

I. The 1-year period before patients' initial use of Prolia (day 1) will be used to identify exclusion criteria of malignancy and Paget's disease.

II. The 1-year period before index date (day 225) for the effectiveness analysis will be used to describe the patient and disease characteristics of the study cohorts, and for risk adjustment of prognostic differences for fracture between cohorts. Covariates include demographic characteristics (age at index date, calendar year of index date, urbanization level of residence) and history of co-morbidities, medication use, and of health seeking behavior (see Appendix A).

III. The 3-years period before Prolia initiation (day 1) will be used to identify the

history of osteoporosis related covariates - pervious fractures and osteoporosis medication exposures.

9.2.7 Outcome Assessment

9.2.7.1 Safety

Three safety outcomes in this study are important identified risks in the Global Risk Management Plan for Prolia. Outcomes will be identified by published algorithms.

- Osteonecrosis of the Jaw (ONJ) is generally associated with tooth extraction or local infection with delayed healing. The AAOMS clinical definition for ONJ includes exposed bone or bone that can be probed through a fistula in the maxillofacial region that has persisted for longer than 8 weeks in a patient without prior of radiation to jaws or metastatic disease to the jaws (Ruggiero et al, 2014). For the case definition in this study, the following three-step algorithm was applied (Lin et al, 2014):
    1. Identify patients that could be a case of ONJ by having inpatient or outpatient codes for aseptic necrosis of the jaw, inflammatory conditions of the jaw, periapical abscess with sinus, or alveolitis of jaw (Xue et al, 2013; Solomon et al, 2013; Lin et al, 2014)(see Appendix B);
    2. Among these potential ONJ cases, identify cases with a persistent diagnosis record ≥ 8 weeks and no gaps > 30 days between diagnosis;
    3. Among these potential ONJ cases with a persistent diagnosis, identify cases with concomitant use of broad-spectrum oral antibiotics, including penicillin, cephalosporin, clindamycin, and fluoroquinolone therapies.
- Atypical femur fracture (AFF) is a no trauma or minimal trauma fracture occurring along the femoral diaphysis from just distal to the lesser trochanter to just proximal to the supracondylar flare. For the clinical definition, these fractures have a characteristic appearance on imaging with a simple transverse or oblique fracture with breaking of the cortex and diffuse cortical thickening of the proximal femoral shaft (Shane et al, 2014). The case definition in this study, and consistent with prior study (Xue et al, 2013), is a patient receiving inpatient care with a diagnosis for non-traumatic subtrochanteric or diaphyseal (shaft) fracture of the femur (see Appendix C). Notably, the case definition is inclusive of the site of AFF but does not include the characteristic features apparent upon imaging.
- Hypocalcemia can be caused by the use of denosumab. The case definition is a patient receiving inpatient or emergency room care with a primary diagnosis for

hypocalcemia (see Appendix D). This definition does not include secondary diagnoses of hypocalcemia, which are likely to represent a consequence of underlying diseases such as chronic renal failure, malabsorption, or hypoparathyroidism.

9.2.7.2 Fractures

The primary endpoint is hip fracture. Secondary endpoints include clinical vertebral and non-vertebral fractures (hip, humerus, wrist, and distal forearm). All fractures will be identified from inpatient claims only. The diagnosis codes to identify fractures in two regions are distinct to reflect local clinical practice (see Appendices E, F, G, H). Fractures due to a motor vehicle accident (see Appendix I) on the same date were not included as endpoints.

9.2.8 Validity of Outcome Assessment

9.2.8.1 Validity of Safety Endpoints

The PPV for ONJ diagnosis is low and has been reported to range from approximately 20% (Wright NC et al, 2015) to 30% (Amgen study report). In order to improve the specificity of these possible cases, we further adopted the AAOMS definition: cases with persistent ONJ symptoms for more than 8 weeks and no history of radiation, and recorded broad-spectrum oral antibiotics, including penicillin, cephalosporin, clindamycin, and fluoroquinolone therapies, were regarded as ONJ cases.

The PPV for subtrochanteric and diaphyseal fractures, the site of AFF fractures, is high; however, the PPV for AFF is low and has been reported in range from approximately 10% (Narongroeknawin et al, 2012) to 20% (Amgen study report).

The PPV for hypocalcemia related to use of Prolia has been reported to be 40%, and was higher for emergency department records than inpatient claims (82% vs. 24%) (Wang et al, 2018).

9.2.8.2 Validity of Fracture Endpoints

Medical record retrieval and clinical adjudication of reported fractures comprise the gold standard for fracture identification in clinical trials and cohort studies. The algorithms to identify fracture endpoints intentionally favor specificity over sensitivity in order to not bias results of comparative analysis towards the null. The algorithm will miss true fractures seen only in the outpatient setting that are non-operatively managed.

High coding accuracy for clinical fractures has been demonstrated in the data source of CDARS. In this prior study, original clinical records of patients, including radiology

reports, results from computed tomography or magnetic resonance imaging scans, surgery records, and documentation in medical charts were reviewed by 2 independent physicians to confirm the fracture events. A high coding accuracy was found in the diagnosis for fractures at the hip (PPV = 100%; 104 cases confirmed / 104 cases in CDARS), vertebrae (PPV = 86%; 87 / 101 cases), wrist and forearm (PPV = 100%; 94 / 94 cases), and humerus (PPV = 100%; 83 / 83 cases) (Sing et al, 2017). Similar studies in the U.S., Canada, and Europe has also reported PPVs above 90% for all fracture sites (Hudson et al, 2013; Curtis et al, 2009; Berry SD et al, 2017; Jean S et al, 2012).

9.3 Data Source

Two databases provide patient-level data on demographics, administration of biological medicines, drug dispensing, diagnosis and procedures received at hospitalization or outpatient consultation, and mortality. Both databases are population-based (i.e., nearly all persons in a region are included, hence representative of region) and exemplify data sources for healthcare research, generating real-world evidence to support clinical decision-making and healthcare policy-making. Patient privacy is protected by anonymizing patient records and allowing researchers to see only aggregate data without any information that could identify individuals.

One database is the National Health Insurance Research Database (NHIRD) of the Taiwan Bureau of National Health Insurance, which serves a population of 23 million through a single-payer national health insurance program for medical and dental care. Nearly 99% of Taiwan population is enrolled in this program. For this study, the end date of available data in NHIRD is December 2016. NHIRD has been the data source for more than two thousand studies in peer-reviewed journals.

The second database is from the electronic medical records of the Clinical Data Analysis and Reporting System (CDARS) of the Hong Kong Hospital Authority, which serves a population of more than 7 million through 41 hospitals and more than 100 outpatient clinics. CDARS includes data on approximately 80% of all hospital admissions and their ambulatory clinics in Hong Kong. For this study, the end date of available data in CDARS is August 2018. The CDARS had been extensively used for conducting high-quality large population-based studies (Lau et al, 2017; Man et al, 2017).

9.4 Study Size

The study size is dependent on the number of patients treated with Prolia in clinical practice. Simple counts in the data source to support protocol development suggest the study will include about 40,000 patients in Taiwan and 3000 patients in Hong Kong; and the mean follow-up during therapy use will be about 1.5 years. Additional counts suggest that, of every 4 patients initiating Prolia, 3 will enter the persistent cohort (i.e., receive a second administration of Prolia) and 1 will enter the non-persistent to Prolia cohort (i.e., discontinue therapy after one administration of Prolia).

For the characterization of safety, a study size of 60,000 person-years of observation in Taiwan (40,000 patients * 1.5 years) will provide > 99% probability of detecting at least 1 subject with an event given the true rate is 1 per 10,000 person-years. The study size of 4500 person-years of observation in Hong Kong (3000 patients * 1.5 years) will provide a probability of 33% for detecting at least 1 subject with an event given the true rate is 1 per 10,000 person-years.

Expectations for the number of fractures observed in this study are informed by the Taiwan reimbursement criteria that require a prior fracture to be eligible to receive Prolia (i.e., patients are at high fracture risk) and by the cumulative Kaplan-Meier incidence observed in the 3-year FREEDOM clinical trial of clinical vertebral fractures (2.6% placebo arm), non-vertebral fracture (8.0% placebo arm), and hip fracture (1.2% placebo arm) (Cummings et al, 2009). With the sample size of 40,000 in the Taiwan database, assuming the mean follow-up of therapy use of 1.5 years and an enrollment period of 51 months and an exponential distribution for rate of dropout, the power (with a 2-sided type I error of 5%) for detecting a hazard ratio ranging from 0.5 to 0.8 and assumed annual rates of 1%, 2% and 3% for fracture endpoints in the not-persistent cohort is presented in Table 1.

Table 1. Statistical power calculation over a range of annual rates for fracture endpoints for Taiwan cohort (n=40000; ratio= 1:3)

Hazard ratio	Annual rate of fracture endpoints in non-persistent cohort		
	1%	2%	3%
0.8	40%	68%	84%
0.7	75%	96%	>99%
0.6	95%	>99%	>99%
0.5	>99%	>99%	>99%

9.5 Data Management

The data source, including data from electronic medical records and administrative claims, is created for the delivery of health care. In order to use the data source for research, analytical files must be built that define the study cohort and algorithms are used to identify exposures, covariates, and outcomes. Best practices will be used for the reporting of the detailed information behind these operational and design decisions to allow other researchers to reproduce the conduct of study.

9.6 Data Analysis

9.6.1 Planned Analyses

The planned analyses include:

1. Evaluating the effectiveness of denosumab for the reduction of clinical osteoporotic fractures
2. Characterizing the safety of denosumab

9.6.2 Planned Method of Analysis

9.6.2.1 Incomplete Data and Lost to Follow-up

Descriptive analyses (number and percentage) will be used to describe the reasons (discontinuation, end of study, death) for lost to follow-up

9.6.2.2 Descriptive Analysis

9.6.2.2.1 Description of Study Enrollment

Flow charts, starting with the number of all Prolia patients in each data source and ending with the number of Prolia patients included in study, will be used to describe the application of inclusion and exclusion criteria.

9.6.2.2.2 Description of Subject Characteristics

Patient demographics and clinical history during the baseline period will be summarized. Categorical variables will be presented as number and percentage; continuous variables will be presented as number, mean with standard deviation, and median with interquartile range.

9.6.2.2.3 Description of Treatment Use

The total number of Prolia injections per patient during follow-up will be summarized. The distribution of days between Prolia injections will also be summarized.

9.6.2.3 Primary Analysis of the Endpoints

The safety endpoints are:

- subject incidence of ONJ
- subject incidence of AFF
- subject incidence of hypocalcemia

Incidence rates for the safety endpoints will be calculated as the number of patients with an event per 10,000 person-years:

$$\frac{Total\ number\ of\ patients\ with \geq 1\ event}{Sum\ of\ followed\ person-year\ to\ the\ first\ event} \text{ X } 10{,}000$$

The effectiveness endpoints are:

- subject incidence of hip fractures
- subject incidence of clinical vertebral fractures
- subject incidence of non-vertebral fractures

Incidence rates for the effectiveness endpoints will be calculated as the number of patients with a fracture per 100 person-years in the persistent cohort and non-persistent cohort:

$$\frac{Total\ number\ of\ patients\ with \geq 1\ event\ in\ the\ cohort}{Sum\ of\ followed\ person-year\ to\ the\ first\ event\ in\ the\ cohort} \text{ X } 100$$

In the analyses for effectiveness, the primary endpoint of hip fracture risk will be compared between the persistent cohort and non-persistent cohort following risk adjustment of measurable prognostic differences (i.e., covariates) between cohorts. Results for treatment effectiveness will be presented as a propensity score-matching hazard ratio for time to the first event with 95% confidence interval. Secondary fracture endpoints including clinical vertebral fracture and non-vertebral fracture risk will be analyzed using the same approach.

We will use the standardized mean difference to test the differences in baseline covariates between cohorts. Differences >0.1 standardized mean difference (10%) represent a clinically significant difference. Kaplan-Meier method will be used to plot unadjusted survival curves and relative risk reduction. To control confounding for measurable variables we plan to use propensity score (PS) matching. We will calculate PS the for each patient in the study cohort using multivariate logistic regression analysis, conditional on all baseline covariates in section 9.3.2. PS allows one to design and analyze an observational (nonrandomized) study so that it mimics some of the particular characteristics of a randomized controlled trial. In particular, the PS is a balancing score: conditional on the PS, the distribution of observed baseline covariates will be similar

between treated and untreated subjects. The distribution of propensity score for both cohorts will be first described and the balancing of included covariate between two cohorts before and after PS matching will be illustrated. Results for treatment effectiveness will be presented as PS-adjusted hazard ratio with 95% confidence interval, using non-persistent to Prolia cohort as the reference in the matched cohort. The PS-adjusted survival probability will be generated from the Cox model and presented as a survival curve.

9.6.2.4 Sensitivity Analysis

The analytical strategy to evaluate the potential for residual confounding and bias to be present in the analysis will include a series of sensitivity analyses to evaluate the robustness of results from the primary analysis for Prolia effectiveness. The sensitivity analyses include: subgroups, alternative algorithms to identify fractures, an alternative method of PS analysis, a high-dimensional propensity score adjusted analysis to further adjust potential unmeasured confounding and an assessment of the extent of residual confounding that would be required to refute an observed difference in fracture incidence between cohorts.

9.6.2.4.1 Subgroup Analysis

The results of primary analysis for effectiveness will be examined by key subgroups, including: 1) age groups (55 - 64 years, 65 - 74 years, 75 years or older); 2) previous exposure to osteoporosis medication in the past 3 years (yes or no); 3) previous fracture histories in the past 3 years (hip, vertebral and others)

9.6.2.4.2 Alternative Definitions

In the primary analysis for effectiveness, the algorithms to identify fracture endpoints intentionally favor specificity over sensitivity. We plan to analyze additional algorithm for vertebral fracture having greater sensitivity and lesser specificity. Any position in inpatient claims for will be used to identify vertebral fracture.

9.6.2.4.3 Alternative Method of Analysis

To examine the robustness of confounding controls for measurable variables in the effectiveness analysis, an alternative method of PS analysis will include inverse probability of treatment weights (IPTW) to estimate the IPTW adjusted hazard ratio in the Cox model.

9.6.2.4.4 Potential Impact of Residual Confounding and Bias

Two additional analysis will be conducted to address the potential impact of residual (or unmeasured) confounding. As extension of PS in the primary analysis, we plan to calculate high-dimensional propensity score (hd-PS) in the additional analysis. The hdPS algorithm is an automated technique that empirically identifies potential confounders or proxies for confounders in longitudinal data sets; the algorithm assesses thousands of diagnosis, procedure, and drug-dispensing codes recorded in administrative databases and then selects the several hundred of those codes, as transformed into binary covariates, that appear most like confounders (Schneeweiss et al, 2009). In claims data, common data dimensions include pharmacy claims, outpatient diagnoses, outpatient services, inpatient diagnoses and inpatient services. From each dimension, the top n most prevalent codes are transformed into binary covariates and then individually considered for selection into a propensity score. With 5 dimensions and the default n = 200 and considering 3 levels of within-patient frequency of occurrence of each code (code occurred once, sporadically, or frequently), there are a possible 3,000 indicator variables that could be added to a propensity score. The hd-PS algorithm then prioritizes each of these variables by its potential to bias the exposure-outcome relation under study, using the formula by Bross (Bross et al, 1966). By default, the algorithm will then include the top k = 500 of these covariates in a propensity score. The hdPS will be used to examine the robustness of confounding controls by hdPS matching.

Second, we plan to assess the extent of residual confounding that would be required to refute an observed difference in fracture incidence between cohorts (i.e., rule-out method). The rule-out method has been described previously (Schneeweiss S, 2006), is publicly available (www.drugepi.org), and is being applied extensively in the literature (Weintraub WS et al, 2012). In brief, in this analysis, we will examine the relationship between the possible unmeasured confounder and fracture risk over a range of possible relative risks ranging from 1 to 10 and for a range in differences from 10% to 50% in the prevalence of unmeasured confounders between cohorts. The results of this illustration will describe and quantitate the scenarios to refute an observed difference in fracture incidence between cohorts.

9.6.3 Analysis of Safety Endpoints

Safety outcomes include three important identified risks in the Global Risk Management Plan for Prolia. The subject incidence rates for the three safety outcomes (ONJ, AFF, and hypocalcemia) will be calculated (see 9.6.2.3 for details).

9.7 Quality Control

Statistical analyses on the final analytical datasets will be conducted by two persons and crosschecked for quality assurance.

9.8 Limitations of the Research Methods

9.8.1 Internal Validity

9.8.1.1 Data quality

Not all relevant data is available within the data source. Of the risk factors for fracture that are commonly considered in clinical practice (Kanis JA et al, 2001), the data source has data on five covariates (age, sex, systemic glucocorticoid use, rheumatoid arthritis diagnosis, and prior fracture), but not data on five covariates (bone mineral density, body mass index, alcohol use, smoking status, parental history of fracture). However, the effects of 5 unmeasured confounders is likely minimal on the interpretation of study results:

1. Most of included Prolia patients experienced osteoporotic fractures per Taiwan National Health Insurance utilization management criteria. Therefore, the BMD distribution should be homogenous (ie, mostly below a threshold) and less likely to be a confounder.
2. A subgroup analysis will be planned in patients free of diseases that strongly correlated to body mass index (eg, diabetes, dyslipidemia).
3. Smoking prevalence is estimated to be low (<4%) in Taiwanese women older than 50 years (Health Promotion Administration, Ministry of Health, Taiwan report 2013). Separate discussion for each unmeasured covariate will be provided in the study report.

The algorithms to identify outcomes reflect an active decision in the trade-off between sensitivity and specificity, see section 9.3.4.1 for Validity of Safety Endpoints.

9.8.1.2 Confounding

Confounding by indication (i.e., pre-treatment variables that influence the treatment decision and are also independent predictors of the outcome) is often the primary challenge for interpretation of a non-randomized study. The design is this study removes consideration for the initial treatment decision, which is one of the potential confounding variables. This study design, coupled with high-quality data sources and a thorough analytic strategy to evaluate other sources of confounding, was selected to provided risk reduction estimates for effectiveness that are valid and clinically meaningful.

9.8.1.3 Study conduct

The study will follow good practices for real-world studies (Berger et al, 2017), including:

- engaging key stakeholders in designing the study
- posting of protocol and analysis plan on the public study registration site for observational studies at the European Network of Centers for Pharmacoepidemiology and Pharmacovigilance (ENCePP®), which is a network coordinated by the European Medicines Agency
- performing the study in two different data sources and at two research institutions to facilitate an assessment for reproducibility in results

9.8.2 External Validity

Because the data source is population-based and the use of limited exclusion criteria, this study is representative of women with PMO being treated with Prolia in Taiwan and Hong Kong. In order to evaluate the external validity for the broader population of Chinese women in different health care systems, the similarities and differences will be reviewed for: 1) the epidemiology of osteoporosis in Taiwan (Wang CY et al, 2017) and in Shanghai (实用预防医学 2018 年2 月 第 25 卷 第 2 期; Li SS et al, 2016); 2) the clinical histories and fracture outcomes among treated PMO patients in Taiwan (Lin TC et al, 2011; Lin TC et al, 2014) and in Tianjin (Liu R et al, 2018; 中国骨质疏松杂志2014 年7 月第20 卷第7 期) and in ShanDong (China Health Standard Management, vol 7, no. 20) ; 3) the lifestyle risk factors for osteoporosis (e.g., smoking, alcohol use, and exercise) in the general population, based on similar methods for data collection in a health interview survey, between Taiwan (http://nhis.nhri.org.tw/) and Shanghai (实用预防医学 2018 年2 月 第 25 卷 第 2 期).

10. Protection of Human Subjects

10.1 Informed Consent

Informed consent will not be required for a study containing only de-identified secondary data.

10.2 Institutional Review Board (IRB)

The study protocol will be reviewed by the IRB of National Cheng Kung University (ID: #107-103) in Taiwan and by the pertinent IRB in Hong Kong.

11. Collection, Recording, and Reporting of Safety Information

This study is analyzing secondary data from NHIRD and CDARS. The safety outcomes that are listed in section 9.3.3.1 will be analyzed in this study. These will be reported in aggregate in the final study report as rates. See section 9.3.3.1 for safety outcomes and definitions. Submission of safety outcomes as individual safety reports to Amgen is not

required. Safety events suspected to be related to any medicinal product should be reported to the local authority in line with the local country requirements.

12. Administrative and Legal Obligations

12.1 Protocol Amendments and Study Termination

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

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

13. Plans for Disseminating and Communicating Study Results

The study protocol and the Observational Research Study Report (ORSR) of results will be submitted to the China Center for Drug Evaluation.

The study will be submitted for publication.

13.1 Publication Policy

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

Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published and (4) agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are investigated and resolved. Authors should meet conditions 1, 2, and 3 and 4.

- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group alone does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

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15. Appendices

Appendix A. Covariates

Variable	Code types
Age	continuous
Income level	categorical
Urbanization levels	categorical
Health resource utilization	
ER visits	continuous
Outpatient visits	continuous
Hospitalizations	continuous
Comorbid conditions	
Hip fracture history	Dichotomous
Vertebral fracture history	Dichotomous
Nonvertebral fracture history	Dichotomous
Hypertension	Dichotomous
Diabetes	Dichotomous
Dyslipidemia	Dichotomous
GI bleeding	Dichotomous
Peptic ulcer	Dichotomous
Pneumonia	Dichotomous
COPD	Dichotomous
Ischemic heart disease	Dichotomous
Chronic heart disease	Dichotomous
Ischemic stroke	Dichotomous
Hemorrhagic stroke	Dichotomous
Osteoarthritis	Dichotomous
Rheumatic arthritis	Dichotomous
Renal failure	Dichotomous
Parkinsonism	Dichotomous
Dementia	Dichotomous
Depression	Dichotomous
Schizophrenia	Dichotomous
Glaucoma	Dichotomous
Cataract	Dichotomous
Osteoporosis medications - history	
Bisphosphonates	Dichotomous
Alendronate	Dichotomous
Ibandronate	Dichotomous
Risedronate	Dichotomous
Zolendronate	Dichotomous

Teriparatide	Dichotomous
Calcitionin	Dichotomous
Raloxifene	Dichotomous
Medication history	
Steroid	Dichotomous
Alpha blocker	Dichotomous
Antiarrhythmic	Dichotomous
Calcium channel blockers	Dichotomous
Beta blocker	Dichotomous
Diuretic	Dichotomous
RAS inhibitors	Dichotomous
Hypoglycemic agents	Dichotomous
Lipid lowering agents	Dichotomous
Anti-acids	Dichotomous
Propulsive agents	Dichotomous
Antihistamine	Dichotomous
NSAID	Dichotomous
Antigout	Dichotomous
antiplatelet	Dichotomous
Antithrombotics	Dichotomous
Bronchodilators	Dichotomous
Antiparkinson	Dichotomous
Antipsychotics	Dichotomous
Antidemantia	Dichotomous
Antidepressant	Dichotomous
Benzodiazepines	Dichotomous
Hormone replacement therapy	Dichotomous

Appendix B. Codes for Osteonecrosis of Jaw

ICD-9-CM (Taiwan and Hong Kong)	Description
525.9	Unspecified disorder of the teeth and supporting structure
526.4	Inflammatory conditions of jaw
526.89	Other specified diseases of the jaws
526.9	Unspecified disease of the jaws
528.9	Other and unspecified diseases of the oral soft tissues
730.00	Acute osteomyelitis, site unspecified
730.08	Acute osteomyelitis involving other
730.10	Chronic osteomyelitis, site unspecified
730.18	Chronic osteomyelitis involving other specified sites
730.20	Unspecified osteomyelitis, site unspecified
733.40	Aseptic necrosis of bone, site unspecified
733.45	Osteonecrosis of the jaw
733.49	Aseptic necrosis of other bone sites
733.90	Disorder of bone and cartilage, unspecified
ICD-10-CM (Taiwan)	**Description**
M27.2 (K10.2)	Inflammatory conditions of jaws
M27.3 (K10.3)	Alveolitis of jaws
M87.180	Osteonecrosis due to drugs, jaw
M87.08 M87.28 M87.38 M87.88	Idiopathic aseptic necrosis of bone, other site; Osteonecrosis due to previous trauma, other site; Other secondary osteonecrosis, other site; Other osteonecrosis, other site;
(K10.8)	Other specified disease of jaws

Note: Code at any position of diagnosis, hospitalization or outpatient care

Appendix C. Codes for subtrochanteric or shaft of femur fracture

ICD-9-CM (Taiwan and Hong Kong)	Description
820.22	Closed fracture of subtrochanteric section of neck of femur
821.00	Closed fracture of unspecified part of femur
821.01	Closed fracture of shaft of femur
ICD-10-CM (Taiwan)	**Description**
S72.2--A	Closed subtrochanteric fracture of femur -- initial encounter
S72.3--A	Closed fracture of shaft of femur -- initial encounter

Note: Code at any position of diagnosis, hospitalization. Fractures due to a motor vehicle accident (see Appendix I) on the same date were not included as endpoints.

Appendix D. Codes for hypocalcemia

ICD-9-CM (Taiwan and Hong Kong)	Description
275.41	Hypocalcemia
ICD-10-CM (Taiwan)	**Description**
E83.51	Hypocalcemia

Note: Code at primary diagnosis position, hospitalization or emergency room visit

Appendix E. Codes for hip fracture

ICD-9-CM (Taiwan)	Description
820.0	Closed transcervical fracture
820.2	Closed pertrochanteric fracture of femur
820.8	Closed fracture of unspecified part of neck of femur
733.14	Pathologic fracture of neck of femur
ICD-9-CM (Hong Kong)	**Description**
820.xx	Fracture of neck of femur
ICD-10-CM (Taiwan)	**Description**
S72.0--A	Closed fracture of head or neck of femur -- initial encounter
S72.1--A	Closed pertrochanteric fracture -- initial encounter
S72.2--A	Closed subtrochanteric fracture of femur -- initial encounter
M80.051A, M80.052A, M80.059A	Age-related osteoporosis with current pathological fracture; right, left, or unspecified femur -- initial encounter
M84.451A, M84.452A, M84.453A, M84.459A	Pathological fracture; right, left, or unspecified femur or unspecified hip -- initial encounter

Note: Code at any position of diagnosis, hospitalization. Fractures due to a motor vehicle accident (see Appendix I) on the same date were not included as endpoints.

Appendix F. Codes for vertebral fracture

ICD-9-CM (Taiwan)	Description
805.0	Closed fracture of cervical vertebra
805.2	Closed fracture of thoracic vertebra
805.4	Closed fracture of lumbar vertebra
805.8	Closed fracture of unspecified vertebral column
733.13	Pathologic fracture of vertebrae
ICD-9-CM (Hong Kong)	**Description**
805.xx	Fracture of vertebral column
ICD-10-CM (Taiwan)	**Description**
S12.---A	Closed fracture of cervical vertebra -- initial encounter
S22.0--A	Closed fracture of thoracic vertebra -- initial encounter
S32.0--A	Closed fracture of lumbar vertebra -- initial encounter
M48.50XA, M48.52XA, M48.53XA, M48.54XA, M48.55XA, M48.56XA, M48.57XA	Collapsed vertebra (sites: unspecified, cervical, cervicothoracic, thoracic, thoracolumbar, lumbar, lumbosacral) -- initial encounter
M80.08XA	Age-related osteoporosis with current pathological fracture, vertebra -- initial encounter

Note: Code at primary position of diagnosis, hospitalization. Fractures due to a motor vehicle accident (see Appendix I) on the same date were not included as endpoints.

Appendix G. Codes for humerus fracture

ICD-9-CM (Taiwan)	Description
812.0	Closed fracture of upper end of humerus
812.2	Closed fracture of shaft or unspecified part of humerus
812.4	Closed fracture of lower end of humerus
733.11	Pathologic fracture of humerus
ICD-10-CM (Hong Kong)	**Description**
812.xx	Fracture of humerus
ICD-9-CM (Taiwan)	**Description**
S42.2--A	Closed fracture of upper end of humerus -- initial encounter
S42.3--A	Closed fracture of shaft of humerus -- initial encounter
S42.4--A	Closed fracture of lower end of humerus -- initial encounter
M80.021A, M80.022A, M80.029A	Age-related osteoporosis with current pathological fracture; right, left, or unspecified humerus -- initial encounter
M84.421A, M84.422A, M84.429A	Pathological fracture; right, left, or unspecified humerus or unspecified hip -- initial encounter

Note: Code at any position of diagnosis, hospitalization. Fractures due to a motor vehicle accident (see Appendix I) on the same date were not included as endpoints.

Appendix H. Codes for wrist fracture

ICD-9-CM (Taiwan)	Description
813.4	Closed fracture of lower end of radius or ulna
813.5	Open fracture of lower end of radius or ulna
733.12	Pathologic fracture of distal radius or ulna
ICD-10-CM (Hong Kong)	**Description**
813.xx	Fracture of radius or ulna
814.xx	Fracture of carpal bones
ICD-9-CM (Taiwan)	**Description**
S52.5--A, S52.5--B, S52.5--C	Fracture of lower end of radius (right, left, or unspecified) -- initial encounter
S52.6--A, S52.6--B, S52.6--C	Fracture of lower end of ulna (right, left, or unspecified) -- initial encounter
M80.031A, M80.032A, M80.039A	Age-related osteoporosis with current pathological fracture; right, left, or unspecified forearm -- initial encounter
M84.431A, M84.432A, M84.433A, M84.434A, M84.439A	Pathological fracture; right or left ulna, right or left radius, or unspecified ulna and radius -- initial encounter

Note: Code at any position of diagnosis, hospitalization

Appendix I. Codes for major trauma

ICD-9-CM (Taiwan and Hong Kong)	Description	ICD10 (Taiwan)
E800-E848	Railway accidents, motor vehicle accidents, other road vehicle accidents; water transport accidents; air transport accidents; other vehicle accidents	V00 – V99