Summary Table of Study Protocol

Title	Global burden of hip fractures – trends in incidence, post-fracture treatment, and mortality; a multi-country, observational study
Protocol version identifier	Version 1.0
Date of last version of the protocol	09 June 2020
EU Post Authorization Study Register No	NA
Active Substance	NA
Medicinal Product	NA
Device	NA
Product Reference	NA
Procedure Number	NA
Joint PASS	No
Research Question and Objectives	The aim is to characterize hip fractures by year among men and women aged 50 years and above within multiple countries. Primary objective is: • to estimate the annual incidence of hip fracture Secondary objectives are: • to estimate the proportion of patients having use of a pharmacological treatment for fracture prevention within 12 months following their initial hip fracture by year • to estimate the mortality rate within 12 months following patients' initial hip fracture by year
Countries of Study	**Asia**: China, Hong Kong, Korea, Singapore, Taiwan, Thailand, Japan **Oceania:** Australia, New Zealand **Europe**: Denmark, Finland, France, Germany, Italy, Netherlands, Spain, United Kingdom **North America:** United States, Canada **South America:** Brazil

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Marketing Authorization Holder

Marketing authorization holder	Amgen Inc.
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Investigator's Agreement

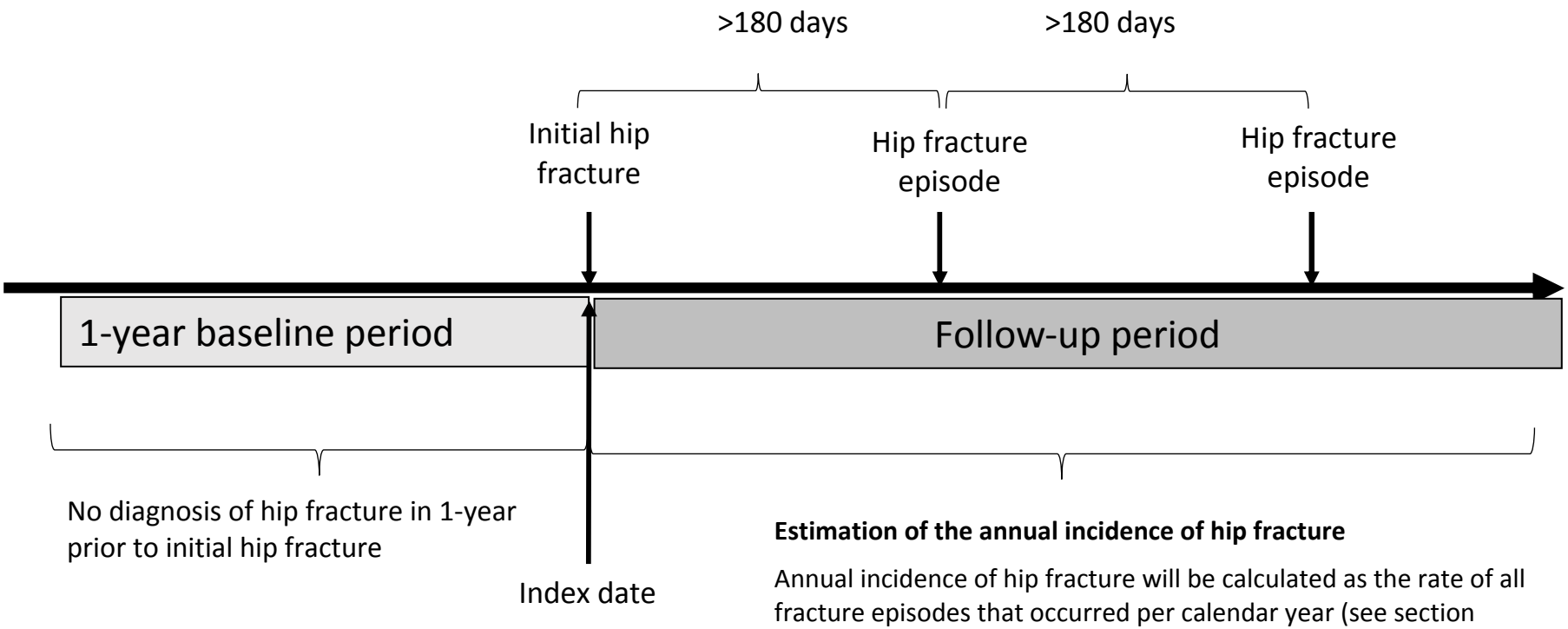
I have read the attached protocol entitled, "Global burden of hip fractures – trends in incidence, post-fracture treatment, and mortality; a multi-country, observational study" dated 09-June-2020, and agree to abide by all provisions set forth therein

Signature

Name of Coordinating Investigator Date

Study Design Schema for study objective #1

Study period: 01 Jan 2005 to 31 Dec 2018



Estimation of the annual incidence of hip fracture

Annual incidence of hip fracture will be calculated as the rate of all fracture episodes that occurred per calendar year (see section 8.6.5.4 for details).

Hip fracture episodes include the initial hip fracture plus episodes after the initial fracture (contralateral or ipsilateral). Episodes after the initial hip fracture must be separated by a wash-out period of at least 180 days.

1. Table of Contents

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2. List of Abbreviations

Abbreviation or Term	Definition/Explanation
ACDM	Analytic Common Data Model
ATC	Anatomical Therapeutic Chemical classification system
BMD	Bone Mass Density
CI	Confidence Interval
CPRD	Clinical Practice Research Datalink
DDT	Data definition table
EMR	Electronic medical record
HKU	University of Hong Kong
ICD	International Classification of Diseases
IR	Incidence rate
OBP	Oral bisphosphonates
OP	Osteoporosis
SAP	Statistical Analysis Plan
WHO	World Health Organisation

3. Responsible Parties

See Appendix C

4. Abstract

- *Study Title*:

  Global burden of hip fractures – trends in incidence, post-fracture treatment, and mortality; a multi-country, observational study

- *Study Background and Rationale*:

  Hip fracture is a public health burden leading to high morbidity and mortality. To inform health initiatives for improving patient outcomes, longitudinal and cross-geographical comparisons of health data can provide insights on aetiology, risk factors, and effectiveness of healthcare practices. Globally, there is wide variation in the incidence of hip fracture among adults, ranging from an age-standardized rates of 500 cases per 100,000 (e.g. Denmark) to 100 cases per 100,000 (e.g. South Africa). Following a hip fracture, individuals are at increased risk of a subsequent osteoporotic fracture. To reduce the risk of the subsequent fracture, clinical guidelines recommend pharmacological treatment. Irrespective of guidelines, treatment rates in the post-fracture population have been reported to be low in several geographies.

  Global reports of disease are typically systematic reviews based upon many studies representing a heterogeneity of methods, sample sizes, and study periods; thus making it a challenge to interpret the between country variation often seen in these reports. We propose a study of hip fractures using a standardized methodology applied to large databases of health records within geographies of Asia, Oceania, North and South America, Western and Northern Europe.

- *Research Question and Objectives*

  The aim is to characterize hip fractures by year among men and women aged 50 years and above within multiple countries.

Objectives	Outcomes
Primary	
To estimate the annual incidence of hip fracture	Hip fracture episodes (including the initial hip fracture or another hip fracture -- contralateral or ipsilateral)
Secondary	
To estimate the proportion of patients having use of a pharmacological treatment for fracture prevention within 12 months following their initial hip fracture by year	Pharmacological treatment for fracture prevention (including medications recommended for the secondary prevention of osteoporotic fragility fractures)
To estimate the mortality rate within 12 months following patients' initial hip fracture by year	Death

- *Hypothesis*

  This is a descriptive study; no hypothesis will be tested.

- *Study Design*

  Retrospective cohort study, using a common protocol and an analytical common data model (ACDM) to obtain aggregated data from each database. The study will consist of annual cohorts of hip fracture patients from each database.

- *Data Source*

  This study will use patient-level electronic health data derived from the respective national or regional administrative databases, clinical databases or registry databases. The study period will be from 1st January 2005 to 31st December 2018, subject to data availability for each database.

- *Patient Eligibility Criteria*

  Inclusion

  - aged 50 years or above AND
  - hospitalized due to hip fracture during the study period between 1st January 2005 and 31st December 2018

Exclusion

- diagnosis of hip fracture within 12 months before the initial fracture
- missing sex or age
- less than 12 months in the data source before the initial hip fracture

- *Follow-up*

  For the primary objective of hip fracture incidence, there is no follow-up of patients.

  For the secondary objectives of post-fracture treatment and mortality, each patient will be followed from date of initial hip fracture (index date) until another hip fracture episode, 12 months, death, loss to follow-up, 31st December 2018 or the end of data available in a database; whichever earliest.

- *Variables*

  Outcome Variables

  - Hip fracture episodes: Defined by an inpatient diagnosis for hip fracture identified with database-specific coding (ICD-9/-10 codes or equivalent codes). Episodes include a patient's initial hip fracture (the first occurrence of hip fracture without any hip fracture diagnosis in the 1-year prior), plus any hip fracture episodes after the initial fracture. A hip fracture episode can include the initial hip fracture or another hip fracture (contralateral or ipsilateral). New episodes are defined by no hip fracture diagnosis in the 180-days prior [i.e., wash-out period].
  - Pharmacological treatment for fracture prevention: Defined by medications recommended for the secondary prevention of osteoporotic fragility fractures identified with database-specific coding (WHO Anatomical Therapeutic Chemical (ATC) Classification System codes or equivalent codes).
  - Mortality: death date and the cause of death, if available, based upon database-specific coding (ICD-9/-10 codes or equivalent codes).

  Exposure Variable

  NA

  Covariates

  - Demographics: Sex and date of birth (or age at index date).

- *Study Sample Size*

  Each database is estimated to provide several hundred hip fractures per year and up to tens of thousands of hip fractures per year. For example, the data source for Hong Kong, a region of 7.2 million people with 2.8 million adults aged 50+, has ≈9300 hip fractures per year in adults aged 50+ (a crude rate of 330 fractures per 100,000). The protocol includes estimated samples sizes for each database and precision estimates for the study endpoints.

- *Data Analysis*

  For the primary objective:

- the annual incidence of hip fracture will be calculated by the total number of hip fracture episodes in a calendar year divided by the population at risk.

For the secondary objectives:

- Kaplan-Meier method will be used to estimate the postfracture treatment proportion within 3, 6 and 12 months of fracture and 95% confidence intervals (CI), censoring patients on another hip fracture episode, 12 months, death, loss to follow-up, 31st December 2018 or the end of data available in a database; whichever earliest.
- the mortality rate will be calculated by the number of patients who died within the 12-months of initial hip fracture divided by the number of patients with a hip fracture in a calendar year.

Each database will be analyzed and reported individually (i.e., will not be pooled).

5. Amendments and Updates

None

6. Rationale and Background

6.1 Diseases and Therapeutic Area

Hip fracture is a public health burden leading to high mortality (≈ 22% mortality rate at one year) (Downey et al., 2019) and morbidity (30% - 50% of patients lose functional independence) (Johnell et al., 2004; Ballane et al., 2014). Globally, there is wide variation in the incidence of hip fracture in the population at age 50 years or above (Kanis et al., 2012), ranging from an age-standardized rate of over 500 cases per 100,000 adults (e.g. Denmark) to less than 100 cases per 100,000 adults (e.g. South Africa). Secular trends in the incidence of hip fracture have been suggested to follow the level of urbanization (Ballane et al., 2014).

Following a hip fracture, individuals are at greater risk of another osteoporotic fracture relative to those without a fracture. For example, in a study included over 96,000 U.S. postmenopausal women who sustained a hip fracture, 8% had another clinical fracture within 1 year, 15% within 2 years, and 25% within 5 years. (Balasubramanian et al, 2019). To reduce the risk of a subsequent fracture, clinical guidelines recommend a pharmacological treatment after a hip fracture (ASBMR 2018; Kanis et. al., 2019). Irrespective of guidelines, treatment rates in the post-fracture population have been reported to be low in several geographies (16 – 21% of patients receiving pharmacological treatment) (Solomon et al., 2014; Kim et al., 2015) and appear to be decreasing in both the U.S. (Desai et al., 2018) and Europe (Hernlund et al., 2013). Given that pharmacological treatments have demonstrated a 30%-50% reduction in