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TITLE:

An Observational, Cross-Sectional Study Investigating the Prevalence of Vertebral Fractures among Community-Dwelling Postmenopausal Women in China (The *Chi*nese *V*ertebral *O*steoporosis *S*tudy, ChiVOS)

Table of Contents

List of Abbreviations

AE	Adverse event
AUC	Area Under the Curve
BMD	Bone Mineral Density
BMI	Body Mass Index
CI	Confidence Interval
COPD	Chronic Obstructive Pulmonary Disease
CSR	Clinical Study Report
CV	Coefficients of Variation
DXA, DEXA	Dual-energy X-ray Absorptiometry
ESPp	European Spine Phantom prototype
FDA	Food and Drug Administration
HRT	Hormone Replacement Therapy
IEC	Independent Ethics Committee
IOF	International Osteoporosis Foundation
NHANES	National Health and Nutrition Examination Survey
NPV	Negative Predictive Value
PASS	Post-Authorization Safety Surveillance
PPV	Positive Predictive Value
ROC	Receiver Operating Characteristic
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
VF	Vertebral Fracture
WHO	World Health Organization

List of Definitions

Vertebral Fracture	The presence of at least one vertebra morphometrically classified as grade 1, 2, or 3 on Genant's score as agreed by the both radiographic assessments
Osteoporosis	A BMD T-score ≤ -2.5 in at least one of the anatomic sites including the lumbar spine, the femoral neck, and the total hip OR A proven prior non-pathological fragility fracture
Fragility Fracture	A fracture that occurred with minimal trauma at a typical site of osteoporotic fracture that would be unlikely to cause fracture in a non-osteoporotic adult.
Postmenopause	No menses for at least one year, OR 6 months of spontaneous amenorrhea with serum FSH levels >40 mIU/mL, OR at least 6 months after a surgical bilateral oophorectomy with or without hysterectomy.
Asthma	A disease characterized by recurrent attacks of breathlessness and wheezing, varying in severity and frequency from person to person, with spirometry showing the FEV1improves > 12% following administration of a bronchodilator.
Chronic Obstructive Pulmonary Disease	A lung disease characterized by chronic obstruction of lung airflow that interferes with normal breathing and is not fully reversible, as confirmed in spirometry by a 75-80% of the FVC comes out in the first second and a FEV1/FVC ratio < 70% with symptoms of the disease.
Diabetes Mellitus	A disease characterized by recurrent or persistent hyperglycemia, and is demonstrating any one of the following: 1. Fasting plasma glucose level ≥ 7.0 mmol/l (126 mg/dl); 2. Plasma glucose ≥ 11.1 mmol/l (200 mg/dl) 2 hours after a 75-g oral glucose load as in a glucose tolerance test; 3. Symptoms of hyperglycemia and casual plasma glucose ≥ 11.1 mmol/l (200 mg/dl); 4. Glycated hemoglobin (HbA1C) ≥ 48 mmol/mol (≥ 6.5 DCCT %).
Confounding	A confounding variable or a confounder is a variable other than the risk factor and outcome under study that is independently related both to the risk factor and to the outcome. A confounder can create an apparent association between the risk factor and outcome or mask a real one

PROTOCOL SUMMARY

Title	An Observational, Cross-Sectional Study Investigating the Prevalence of Vertebral Fractures among Community-Dwelling Postmenopausal Women in China (The Chinese Vertebral Osteoporosis Study, ChiVOS)
Vendor/Collaborator	Not applicable
Rationale	Osteoporosis leads to major fractures including vertebral fractures. Vertebral fractures are a strong predictor of any fracture risk and thus impact the screening of osteoporotic patients and pharmacological treatments. Epidemiological studies investigating the prevalence of vertebral fractures have been increasing in recent years; however, in China, has so far been few.
Primary Objective(s)	To investigate the prevalence of radiographic vertebral fractures in community-dwelling postmenopausal women in China
Study Design	Observational, population-based, cross-sectional design with a clustered simple randomization sampling
Study Population	Community-dwelling postmenopausal women aged 50 or over
Study Duration	A 6-9 month of enrollment period
Exposure and Outcome	VF as confirmed by radiology imaging; osteoporosis as suggested by DXA T-score or a proven fragility fracture
Statistical Methods	Prevalence rate by point estimate and 95% CI with model-based statistical analyses for VF risk factors
Sample Size and Power Calculations	A sample size of 2700 women in 5 regions in China. Sample size calculation based on age-specific VF prevalence.
Limitations	Incident VF cannot be assessed in a cross-sectional study; biases for interview-based questionnaire.

1 Background and Rationale

1.1 Background

Osteoporosis is a multi-factorial skeletal disease characterized by low bone mass and a structural deterioration of the macro and microarchitecture of bone tissue, leading to increased bone fragility and susceptibility to fracture [1]. Osteoporosis is considered a global public health concern, due to its prevalence worldwide. Yet its pathogenesis has not been clear. Osteoporosis affects numerous people, of both sexes and all races, and its prevalence increases as the population ages. Currently, it has been estimated that over 200 million people, including 75 million in the United States, Western Europe and Japan [2], have osteoporosis. Approximately 30% postmenopausal women are osteoporotic in the US and in Europe [2]. In China, an observational study has suggested a total of 54 million women aged 50 or above have osteoporosis, representing a prevalence of 27.3% in this affected population [3].

Osteoporosis is often called a 'silent disease'. Its diagnosis relies on a bone mineral density (BMD) value by dual-energy X-ray absorptiometry (DXA, DEXA) [1] and/or a proven fragility fracture at major skeletal sites [2, 3]. It has a significant clinical impact because of the association with an increased risk of fractures at major skeletal sites including the hip, the vertebrae, and the distal forearm. At least 40% of osteoporotic women [4] and 15-30% of men [5] experience one or more fragility fractures in their remaining lifetime. The combined lifetime risk of hip, forearm and vertebral fractures (VF) is 40%, being equivalent to the risk of cardiovascular diseases [6]. Moreover, an initial osteoporotic fracture by any type is a major risk factor for a new fracture [7, 8]. For instance, patients with a history of VF have a 2.3-fold increased risk of a future hip fracture and a 1.4-fold increase in risk of distal forearm fracture [8]. These fragility fractures lead to a substantial loss of quality of life [6, 9], an increased hospitalization [10, 11] and an excessive risk of mortality [12], and thus cause a tremendous socioeconomic burden. Currently, Chinese therapeutic guideline has recommended a routine screening program, consisting of blood chemistry, chest-waist spine radiology, and DXA, for the diagnosis and treatment of osteoporosis in various populations including postmenopausal women with or without other socioeconomic and/or clinical risks.

Vertebral fractures are the most common manifestation of osteoporosis [13]. The deformities of the vertebral bodies, identified with imaging of the lateral spine, are usually asymptomatic and may initially be felt or presented in the form of severe back pain, loss of height or spinal deformities such as kyphosis. Prevalent radiographic vertebral fractures, most commonly in the thoracolumbar transition zone or midthoracic region, can cause reduced mobility and disability [14-16], and thus reduced health-related quality of life [15] and a higher risk of death in the elderly [17]. Vertebral fractures are prevalent, which increases with age. In the US, the incidence of vertebral fractures accounts for 700,000 of the 1.5 million osteoporotic fractures annually [18]; in Europe, the overall prevalence of radiographic vertebral fracture is estimated at approximately 12% in osteoporotic women [10]. The prevalence among Caucasian women is as high as 30% in the population aged 80 years or elder [19]. Unlike other types of fractures, for

example, hip fractures, which are less in Asians, vertebral fractures have been reported to be as frequent in Asian women [20]. Based on separate local cross-sectional studies conducted in Beijing, shanghai and Chengdu, a total of 1.8 million people were estimated to have a vertebral fracture annually in China [3]; the prevalence is 15% in women who are 50 years of age or elder, and is between 36% and 39% in those who are 80 years of age or elder, respectively [3].

In the clinical setting, lateral thoracic and lumbar spinal radiographs are the standard procedure for the diagnosis and assessment of vertebral fractures. Several qualitative and quantitative approaches have been developed to adjudicate a vertebral fracture, including a widely accepted Genant's semi-quantitative technique [21, 22]. However, in contrast to other fractures, most vertebral fractures receive little clinical attention and remain undiagnosed at the time of occurrence or during the lifetime [6, 9, 13]. The reason may be that most (up to 75%) vertebral fractures are absent from clinical signs and symptoms [22], and even only one fourth to one third of incident radiographically identified vertebral fractures are clinically diagnosed [23, 24]. As indicated in a previous report in 2011, there were an estimated 9 million new osteoporotic fractures worldwide in a particular year, among which only 1.4 million were clinical vertebral fractures and thus were medically cared [25]. Nevertheless, vertebral fractures are proven a strong predictor of a future fracture risk, at any skeletal site, which is independent of BMD [13, 26]. Women who have 2 or more vertebral fractures may have a 7-fold risk in having another vertebral fracture within one year, a 2 to 3-fold risk in having a future non-vertebral fracture, and a 2-fold risk in having a hip fracture, respectively [27]. Based on therapeutic guidelines [1, 2], a vertebral fracture is consistent with a diagnosis of osteoporosis (BMD DXA T-score $\leq$2.5) [1, 2] in the absence of a bone density diagnosis by dual-energy X-ray absorptiometry (DXA, DEXA). An early diagnosis of vertebral fractures is indicated for subsequent pharmacological therapy for osteoporosis, which is critical to prevent an add-on osteoporotic fracture.

1.2 Rationale

Historically, population-based studies of vertebral fracture have been few. This may be due in part to the variable clinical presentation of vertebral deformity, as well as to variation in opinion as to the extent of deformity which constitutes a significant vertebral fracture. The development of morphometric and semi-quantitative visual techniques has enabled a number of studies to explore both the prevalence and incidence of vertebral fractures in the US [28] and Canada (CaMOS [29]), typical European communities (EPOS [30], EVOS [31], FRAVO [32]) and Japan [33], and in developing countries including Latin American countries [34], India [35], and China [36]. These studies have elucidated a global prevalence of vertebral fractures and provided a possible comparison of epidemiological data among different populations with varied geographic locations, environment and culture, and lifestyle. In contrast with hip fractures, the prevalence and incidence of vertebral deformities appears relatively homogeneous across different regions of the world. The prevalence tends to increase with age among men and women.

On the other hand, variations in sample size (CaMOS n=6433, EVOS n=17,342 FRAVO n=842; LAVOS n=1922, DeVOS n=808, Beijing Osteoporosis Project n=402), sampling methodology (age-stratified population-based sampling vs. simple survey sampling), and assessment criteria are seen across the studies. The extent to which these variations represent study bias remains uncertain. Notably, a fine comparison of VF epidemiology between Western societies and China is difficult. Among few population-based studies conducted in China, the Beijing Osteoporosis Project was the first well-documented epidemiology study. The study group performed a randomized sampling and previously validated assessment from the US [36]. However, this study was in a relatively small scale and only represented a local population from the city of Beijing. Another study was the Hong Kong Osteoporosis Study, in which 2178 postmenopausal women have been enrolled [37]. Considering geographic location, lifestyle, and clinical practice, study results may not be generalized to the entire Chinese population. Other cross-sectional studies investigating osteoporosis and fractures neither aimed at a primary collection of VF epidemiology data [39], nor designed adequately to minimize study bias [40]. Therefore, a well-designed, nationwide, population-based epidemiological investigation of the prevalence of vertebral fractures and related risk factors in China is necessary.

2 Objectives and Hypotheses

2.1 Primary Objective(s) & Hypothesis(es)

To investigate the prevalence of vertebral fractures in community-dwelling postmenopausal women in China

2.2 Secondary Objective(s)

1. To investigate the prevalence of osteoporosis in community-dwelling postmenopausal women in China;
2. To identify risk factors for prevalent vertebral fractures in community-dwelling postmenopausal women in China;
3. To identify risk factors for densitometric osteoporosis in community-dwelling postmenopausal women in China.

2.3 Exploratory Objective(s)

1. To assess the diagnostic accuracy of onsite radiology imaging for vertebral fractures in China's local clinical practice;
2. To assess the diagnostic role of vertebral imaging for the screening of osteoporosis and pharmacological treatment in China's local clinical practice.

3 METHODOLOGY

3.1 Summary of Study Design

This study will be designed as an observational, population-based, cross-sectional study. A total of 2700 postmenopausal women over age of 50 inclusive and physically living in a community will be included in the study. As suggested by Chinese local guideline, postmenopausal women are eligible for a subsidized screening program (blood chemistry, radiology and/or DXA assessment) for osteoporosis clinical management. A cluster sampling (two-stage random sampling) by age and geographic region will be performed represent a geographically generalized Chinese population with specific gender and age groups relevant to postmenopausal osteoporosis and VF prevalence. Subject recruitment will be based on various local demographic records including Government resident lists, local population lists, electoral registers, and health registers by a study invitation and a referral to the investigators at each study center. By 1 onsite visit, an interview, DXA measurement, and thoracic/lumbar spine X-ray will be performed to collect a set of data regarding socioeconomic/medical (interview-based questionnaire), VF assessment (radiographs), and specific densitometric information (BMD DXA) from the participant. No any follow-up visit is required for this cross-sectional study unless a spine imaging and/or BMD measurement cannot be made during the visit due to a particular reason in the study or from the subject. The recruitment period is estimated between 6 and 9 months and initiated at any time point during a calendar year, because a seasonal or social impact on the data of interest is minimal. Analyses will be based on epidemiological data and then be expanded to establish a vertebral fracture risk assessment model.

3.2 Study Population

This study will include approximately 2700community-dwelling postmenopausal women aged50 or above at 8 - 10 participating sites throughout China. A two-stage cluster sampling will be performed for the study. Firstly, geographic regions are divided into 'clusters' and then a randomized stratified sampling will be performed by age group using a computerized random selection on various demographic records (as indicated in Section 3.1) from the participating sites and the communities by which they cover. All subjects are expected to have an interview for questionnaire, vertebral imaging and BMD measurement. To be eligible for the study, participants must fulfill the following inclusion and exclusion criteria (Section 3.3 and 3.4):

3.3 Inclusion Criteria

All inclusion and exclusion criteria will be reviewed by the investigator or qualified designee to ensure that the subject qualifies for the study.

For an inclusion of the study, participant must:

1. Be age of 50 or above at the time of consent;
2. Live in an urban community in China for over 6 months;
3. Be postmenopausal;

   Postmenopause *is defined as no menses for at least one year, OR 6 months of spontaneous amenorrhea with serum FSH levels >40 mIU/mL, OR at least 6 months after a surgical bilateral oophorectomy with or without hysterectomy.*
4. Be willing to participate by giving informed consent.

3.4 Exclusion Criteria

The participant may not be eligible for the study if one of the followings is met:

1. Race other than Asian;
2. Unwillingness to participate;
3. Cognitive impairment or physical impediment to affect completion of any study procedure;
4. Other potential reasons, in the investigator's discretion, to confound or affect completion of study procedure.

3.5 Stratification

The subjects will be sampled and stratified according to the following factors:

1) Age;

   Seven (7) age groups: 50 - 54, 55 - 59, 60 - 64, 65 - 69, 70 - 74, 75 - 79, 80 or above;

2) Geographic region;

   Five (5) regions in China: North, South, Southeast, Southwest, and Central

4 Variables and Epidemiological Measurements

All eligible participants will be included in the study to an endocrinologist, or other specialist, whenever appropriate, for the collection of all clinical and radiological information by 1 onsite study visit in a cross-sectional fashion. Spine radiograph and/or DXA may be separated from onsite interview by a follow-up visit as determined by the investigator.

Questionnaire

All demographic data, socioeconomic status, lifestyle information, and clinical features including medical history/concomitant medications, will be collected by an interviewer-administered questionnaire performed by the investigator. The questionnaire will be designed to adapt China's cultural and clinical practice. The analyzable variables derived from the questionnaire include (but not limited to):

- Age (absolute value and category);
- Place of birth and dwelling geographic region;
- BMI (height and weight, as measured in the site);
- Social status and lifestyle (educational level, occupation, monthly income, physical exercise, diet, smoking, alcohol intake, diet, calcium intake);
- Clinical features (age and years of menopause, medical history, history of osteoporosis and parental osteoporosis, any prior fractures, prior and concomitant medication, antiresorptive treatment, glucocorticoid treatment, other treatment reducing bone mass);
- FRAX score (as determined by self-reported fracture and radiology evidence and calculated based on the information from questionnaire with/without BMD).

BMD Measurement

The subject's densitometric measurement will be performed by DXA onsite. Different DXA scanners from manufacturers including Hologic, Lunar and Norland will be used onsite upon availability. The BMD of three skeletal locations, the lumbar spine, the femoral neck, and the total hip, will be determined and presented as absolute value, T-score. The definitions of normal ($\geq$ -1.0 SD compared to young adult women), osteopenia (between -1 to -2.5 SD compared to young adult women) and of osteoporosis ($\leq$ -2.5 SD compared to young adult women) will be applied for both locations in the study, by assessing densitometric readings based on the World Health Organization(WHO)classification [41]. Reference databases for the calculation of the T-score include the National Health and Nutrition Examination Survey (NHANES) III database for the hip and the manufacturer's database for the spine [42]. The US reference database in DXA devices provided by the manufacturers has been adopted in local China's clinical practice [3] and validated in published Chinese studies [36, 39]. No

single local reference database will be applied for a recalculation of T-score due to its relatively smaller sample size and lack of an extensive validation across Asian populations.

DXA has been established as a reliable method providing acceptable precision and accuracy. For lumbar spine, coefficients of variation (CV) in measurements have been reported between 0.26 and 1.5% in short-term studies [43-46], and between 0.8 and 2.6% in long-term studies [43-46]. Precision results for spine phantom measurements using DXA were reported between 0.4 and 0.67% and in long-term studies between 0.23% and 1.0% [43, 45-47]. The DXA measurement for the lumbar spine has a satisfactory diagnostic profile in terms of sensitivity and specificity (ROC AUC 94%) [45].

DXA Quality Control

All participating sites will be organized to have an investigator meeting at which principles and procedures for performing densitometry and densitometric analyses will be agreed for quality monitoring. Study and procedure training, for instance, patient positioning, will be provided for relevant site personnel. Day-to-day quality control will be executed by the participating site personnel. Measurement stability will be ensured by daily or alternate daily calibrations with brand-specific phantoms. The short-term measurement precision will be calculated based on individual site quality control program and alerted to the study team if coefficient of variation reaches 3.0%. Moreover, quality control in densitometry will be performed and enhanced by regular visits to sites by the Sponsor and its delegate. A periodic review of specimen analyses will be made by the investigators and the Sponsor.

DXA Machine and Cross-Calibration

DXA machines [Hologic (Waltham, MA, U.S.A.), Lunar (Madison, WI, U.S.A.), and Norland (Fort Atkinson, WI, U.S.A.)] in each site will be cross-calibrated for these beamed machines after observed BMD measurements are made. A two-step approach will be applied to calibrate BMD readings for all machines involved in the study. For each machine type in the study, the standardized BMD measurements will be derived from observed BMD in the manufacturer's own units using the equation by Pearson and colleagues [48] as below:

$$Observed\ measurement = \alpha * [1 - exp(-\beta * standardized\ BMD)] + \varepsilon i$$

Where α is the asymptote and β is the slope when the standard BMD measurement is small. This curve-fitting formula was found by Pearson and colleagues to provide a better fit than the linear regression formula. When the exponential fit was employed the standardized BMD will be obtained by a re-arrangement to give:

$$Standardized\ BMD = \delta * ln(\alpha) - \delta * In(\alpha - Observed\ BMD)$$

Where $\delta = 1/\beta$ and ln is the natural logarithm.

This procedure will cross-calibrate machines of the same brand in the study. The second step is to cross-calibrate between brands to remove between-brand differences, by using equations developed by the International Committee for Standardization of Densitometry as following [47]:

Cross-Calibration for Lumbar Spine BMD

Hologic	= (0.906 * Lunar) - 0.025	= (0.912 * Norland) + 0.088
Lunar	= (1.074 * Hologic) + 0.054	= (0.995 * Norland) + 0.135
Norland	= (0.983 * Lunar) - 0.112	= (1.068 * Hologic) - 0.070

Cross-Calibration for Femoral Neck BMD

Hologic	= (0.836 * Lunar) - 0.008	= (0.836 * Norland) + 0.051
Lunar	= (1.013 * Hologic) + 0.142	= (0.945 * Norland) + 0.115
Norland	= (0.961 * Lunar) - 0.037	= (1.030 * Hologic) + 0.058

Alternatively, BMD cross-calibration may be made using other standards and equations, for example, European Spine Phantom prototype (ESPp) for spine [49] as well as the femoral neck and trochanter [50]. Cross-calibration results made by other standards and verifications for original calibrated results may be made and included in the statistical analysis plan (SAP) and clinical study report (CSR), if deemed necessary by the principal investigators and Merck's study team.

Vertebral Radiology

Lateral thoracic and lumbar spinal radiographs will be performed to assess any vertebral fractures in the study. The diagnosis of vertebral fractures will be standardized by the Genant semi-quantitative approach [51], based on recommendations of the International Osteoporosis Foundation. This visual method uses the qualitative features of vertebral shape and degree of reduction in vertebral height in the anterior, middle, or posterior vertical dimension to grade a vertebral body as normal, uncertain, or characterized by a mild, moderate, or severe fracture. The Genant's five grades for vertebrae T4 to L4 are listed as below:

- Grade 0 **normal**

  Height of anterior, middle, and/or posterior is preserved;

- Grade 0.5 **borderline**

15-19.9% reduction in anterior, middle, and/or posterior height

- Grade 1 **mild**

  20-25% reduction in anterior, middle, and/or posterior height and a reduction of area 10-20%

- Grade 2 **moderate**

  25-40% reduction in any height and a reduction in area 20-40%

- Grade 3 **severe**

  40% reduction in any height and area

In the study, vertebral fracture is defined as the presence of at least one vertebra morphometrically classified as grade 1, 2, or 3 on Genant's score as agreed by the both radiographic assessments in the study. Two (2) experienced radiologists who are blinded to the study will separately review the vertebral morphology and grade Genant's Score as per protocol. Radiologists will receive additional training to reduce variability between inter-observer interpretations. Prior to the study, each site will forward sample radiographs to the radiology coordination site for quality assessment and to check compliance with the protocol and technical standard. Intra- and inter-observer reliabilities will be tested using first 100 X-ray images from any study site before the adjudication starts. If there is a disagreement in terms of Genant's grading between two study radiologists, a third party radiological review will give a final decision.

The Genant semi-quantitative approach has been established a reliable and reproducible assessment in radiographic vertebral fracture. The intra-observer agreement for prevalent vertebral fracture was generally between 93 and 97% ($\varkappa = 0.73 - 0.89$) [51], regardless of the radiologist's experience. As compared with reviewer's experience and other quantitative methods, an inter-observer agreement by difference in experience and method was between 92 and 94% ($\varkappa = 0.65 - 0.74$) [51].

Definitions of Osteoporosis

In the study, osteoporosis is defined [3, 41] if the subject has at least one of the following as:

- A BMD T-score $\leq$ -2.5 in at least one of the anatomic sites including the lumbar spine, the femoral neck, and the total hip;
- A proven prior non-pathological fragility fracture.

A fragility fracture is defined as a fracture that occurred with minimal trauma at a typical site of osteoporotic fracture that would be unlikely to cause fracture in a non-osteoporotic adult. This assessment will be made based on self-reported fracture section included in the questionnaire and a review of medical history/documents/physical examination, or as suggested by the radiographic imaging in the study.

5 Study Flow Chart

Study Period:	Enrollment		Observation	Follow-Up
Visit Number/ Title:	Invitation[#]	Screening[△]	Study Visit[**]	Unscheduled Visit[***]
Study Day	NA	1	1	NA
Informed Consent		X		
Medical History [※]		X		
Inclusion/Exclusion Criteria		X		
Investigator-administered Questionnaire [¶]			X	
Physical Examination*				
DXA Measurement [§]			X	X
Spine Radiography [&]			X	X

#All available resources recording participant's demographic information will be used to randomly select invitees; a letter will be sent out to explain the study. The receipt and acceptance of invitation by the participant will be directly to the investigator; △ Informed consent, review of inclusion/exclusion criteria must be onsite, after the acceptance of study invitation from the participant; All eligible subjects will be allocated to a study ID number for all procedures;

**An onsite study visit will be conducted at the same day when the subject's eligibility to the study is determined.

*** An unscheduled follow-up may be performed by the investigator if the subject cannot have DXA measurement and/or spine X-ray on the study visit due to clinical and/or other unexpected (i.e. DXA device failure) reason; ※ A brief review of the subject's medical history, including menstrual history, physical ability and cognitive status will be performed to determine study eligibility at the screening;

¶ The questionnaire is an interview-based session administered by the investigator with Chinese official written language. Same individual investigator (s) will perform questionnaire interviews for all subjects at each study site; The questionnaire will collect self-reported data on demographics, gynecological history, socioeconomic status, life style factors, and clinical risk factors for osteoporosis. Standing height (centimeters) by a stadiometer and weight (kilograms) by a regularly calibrated scale will be determined at each site before the questionnaire;

* Include height and weight, and fracture-related physical examination;

§Central DXA scanners from different manufacturers including Hologic, Lunar and Norland will be used to measure the BMD of the spine, the femoral neck, and the total hip. The subject's DXA measurement may be made on an unscheduled follow-up for any compelling reason (i.e. injected contrast material or device failure);

& Two radiographies centered on T7 and L2 will be performed. Radiographs will be taken with the patient in the left lateral position and the subject will be required to breathe by instructions to allow blurring of the overlying ribs and lung detail by motion.

6 STUDY PROCEDURES

6.1 Study Procedures

The Study Diagram in Section 5 summarizes the study procedures to be performed at each visit. Individual study procedures are described in detail below. It may be necessary to perform these procedures at unscheduled time points if deemed clinically necessary by the investigator. Furthermore, additional evaluations/testing may be deemed necessary by the Sponsor for reasons related to subject safety.

6.1.1 Administrative Procedures

6.1.1.1 Randomization and Study Invitation

In the study, 5 geographic regions will be identified as 'clusters' at the first stage. Within a region, a computer-generated randomization list by stratum (age) will then be produced separately in each participating site to identify and select specific invitees. All possible resources securing the participant's bio-information and contact details will be utilized to generate a full list of potential invitees. These resources include, but not limited to, Government resident lists, community-dwelling records, city council records, primary care health records and/or local health insurance records. Based on the sequence of the list, a numbered letter will be sent out to all women who are 50 years of age (inclusive) or above from the investigator to enquiry of their wish to attend the study. The letter to the women selected will explain the nature, the objectives and the study elements of the study. The receipt and acceptance of invitation will direct to the investigators by telephone, email, return of letter, or showcase the letter at the time of onsite screening. An advance notification by telephone or email may be practiced by the site investigator and/or study authorized staff to increase the rate of invitation acceptance.

6.1.1.2 General Informed Consent

Consent must be documented by the subject's dated signature or by the subject's legally acceptable representative's dated signature on a consent form along with the dated signature of the person conducting the consent discussion.

A copy of the signed and dated consent form should be given to the subject before participation in the study.

The initial informed consent form, any subsequent revised written informed consent form and any written information provided to the subject must receive the IRB/ERC's approval/favorable opinion in advance of use. The subject or his/her legally acceptable representative should be informed in a timely manner if new information becomes available that may be relevant to the subject's willingness to continue participation in the study. The communication of this information will be provided and documented via a revised consent form or addendum to the original consent form that captures the subject's dated signature or by the subject's legally acceptable representative's dated signature.

Confidential

Specifics about a study and the study population will be added to the consent form template at the protocol level.

The informed consent will adhere to IRB/ERC requirements, applicable laws and regulations and Sponsor requirements.

6.1.1.3 Medical History

A medical history will be obtained by the investigator or qualified designee. A brief review of the subject's medical history, including menstrual history, physical ability and cognitive status, based on the subject's medical records and physical examination, will be performed to determine study eligibility at the screening.

6.1.1.4 Assignment of Screening Number

All consented subjects will be given a unique screening number that will be used to identify the subject before all study-related procedures. Each subject will be assigned only one screening number. Screening numbers must not be re-used for different subjects. Any subject who is screened multiple times will retain the original screening number assigned at the initial screening visit. No separate study ID number will be allocated to the eligible participants.

6.1.2 Clinical Procedures/Assessments

6.1.2.1 Questionnaire and Physical Examination

The study's questionnaire will be developed based on questionnaires of previous large studies [29-34] and is attached in the Section 11 Appendices. During the investigator's meeting and training session, the questionnaire will be reviewed and discussed in order to clarify terms, country features, and standardization. The investigator will have training in understanding the questionnaire before the study enrollment. The questionnaire will be delivered by Chinese simplified written language. In order to minimize variability, it is preferred that the same individual investigator (s) perform questionnaire interviews for all subjects at each study site.

The questionnaire will collect self-reported data on demographics, gynecological history, socioeconomic status, life style factors, and clinical risk factors for osteoporosis. Commercial calcium supplement and vitamin D intake will be calculated according to names and daily doses reported by participants. Alcohol intake will be calculated in grams per day and be categorized according to the WHO as: never, for the subject who does not report alcohol intake; mild, from 1 to 10 grams per day; moderate, from 11 to 40 grams per day; and severe, for more than 40 grams per day. For smoking history, information on time and average number of cigarettes (and any other type of tobacco) consumed will be obtained. Physical activity will be assessed in minutes per day according to time spent on various activities including walking, dancing, and other Chinese specific outdoor activities.

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All other major risk factors will be based on self-reported during the interview administered by the investigator. The subject's symptoms/signs and medical records will be reviewed for possible medical history. Comorbidities including asthma, chronic obstructive pulmonary disease (COPD), and diabetes mellitus are defined in the study (Refer to 'List of Definitions') and all definitions of diseases will be provided and further explained by the investigator during the interview. A detailed history of any fracture (after age of 40, anatomical site and the level of trauma) and height loss will be collected; prior and concomitant medications regarding steroids use, hormone replacement therapy (HRT), and any use of antiresorptive drugs will be recorded for medication name, daily dose and treatment duration.

Standing height (centimeters) will be determined by means of a stadiometer and weight (kilograms) assessed with a regularly calibrated scale at each site. The stadiometer should be adequate to measure height within 4 mm. Patients will be weighed without shoes or jackets. The BMI will be computed as weight (kilograms) divided by the square of the height (square meters) and defined as underweight≤18.5, normal (18.5–24.9 kg/m^2), overweight (25 to 29.9 kg/m^2), and obese (> 30 kg/m^2). The subject will be asked to recall and report the height and weight at the age of 25. In addition, a fracture-related physical examination will be performed for the subject who has reported a fracture history, based on the investigator's discretion.

The questionnaire should also be reviewed by the investigators for any SAEs/drug-related AEs that need to be reported per the protocol.

6.1.2.2 DXA Examination

All subjects are expected to have BMD measurement upon a successful completion of questionnaire. Densitometric measurement will be performed by a central dual-energy x-ray absorptiometry device at each site. DXA scanners from different manufacturers including Hologic, Lunar and Norland will be used onsite upon availability. A peripheral DXA on mobile health van must not be used in the study. BMD from all subjects included in a particular site will be measured by the same DXA machine or, at least, a machine from the same manufacturer. All BMD results from different machines will be quality controlled during the study.

On the day of the exam, the subject will be instructed to position and wear properly under a low X-ray radiation exposure. The subject will lie on a padded table, where legs will be supported on a padded box to flatten the pelvis and lumbar spine, and foot be placed in a brace that rotates the hip inward. Detailed positioning and other instructions will be suggested by the study DXA technicians according to the manufacturer's operation manual.

At the investigator's discretion, the subject's DXA measurement may be made on an unscheduled follow-up if there is any compelling reason (i.e. injected contrast materials or device failure) precluding the examination on the day of the study visit. The subject's BMD results from any institution 28 days prior to screening may be deemed appropriate for the study if such measurements are made per protocol as assessed by the investigator and discussed with the Sponsor. Subjects with known spine deformities will be required

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to have densitometric measurement unless a waiver is made by the investigator after a consultation with the Sponsor.

6.1.2.3 Radiology and Fracture Diagnostic Procedure

The subject will be required to have an examination on the spine. The radiographs will be obtained using a standardized technique in the all participating sites. Two lateral radiographies centered on T7 and L2 will be performed. Radiographs may be taken with the patient in the left lateral position. For the lateral thoracic spine the cassette is positioned with the top above the subject's shoulders. To maintain lateral position, the subject's shoulders, hips, knees and ankles will be superimposed with padding between the elbows and knees. A radiolucent pad may be required under the lumbar spine at waist level to straighten the lower thoracic spine. For thoracic film taking, the subject will be required to breathing by instructions to allow blurring of the overlying ribs and lung detail by motion. The quality of the radiograph is improved further by placing a sheet of lead rubber on the X-ray table posterior to the spine. For the lateral lumbar spine view, T12 to S1 should be visualized on the radiograph in the true lateral position without rotation or obliquity. As with the lateral thoracic view, the subject's shoulders, hips, knees and ankles will be superimposed, padding between the elbow, knees and ankles. The lumbar spine must also be parallel to the film. Radiolucent pads may be placed under the upper part of the lumbar spine to correct an oblique direction from L1 to L5. Alternatively, the X-ray tube can be angled toward the feet so that the X-ray beam is perpendicular to the spine.

The Genant semiquantitative method will be used to standardize the diagnosis of fractures, as recommended by the IOF. Prior to the study, each site will forward sample radiographs to the radiology coordination site, as nominated by the Sponsor, for quality assessment and to check compliance with the protocol and technical standard. Two experienced radiologists, blinded to the study, will perform the adjudicative evaluation of the radiographs. Intra- and inter-observer reliabilities will be tested using first 100 X-ray images from any study site before the results interpretation. In case there is a disagreement in terms of Genant's grading between experienced radiologists, a third party radiological review will be performed to give a final decision.

6.1.3 Other Procedures

6.1.3.1 Withdrawal/Discontinuation

When a subject discontinues/withdraws prior to trial completion, all applicable activities scheduled for the final trial visit should be performed at the time of discontinuation. In the study, the subject will have one scheduled visit and have the right to discontinue at any time of the study, which is included in the letter of invitation and informed consent. No specific activities for the subject will be arranged at the time of the subject's withdrawal.

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6.1.4 Visit Requirements

Visit requirements are outlined in Section 5 – Study Diagram. Specific procedure-related details are provided above in Section 6.1 – Study Procedures.

6.1.4.1 Screening

Participants will be evaluated to determine that they fulfill the entry requirements as set forth in Sections 3.3-3.4. Screening procedures may be repeated after consultation with the Sponsor.

7 Safety Reporting and Related Procedures

7.1 Definition of Adverse Event

An adverse event is defined as any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product or who undergoes a protocol-specified procedure and which does not necessarily have to have a causal relationship with this treatment or procedure. An adverse event can therefore be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product or protocol-specified procedure, whether or not considered related to the medicinal l product or protocol-specified procedure. Any worsening (i.e., any clinically significant adverse change in frequency and/or intensity) of a preexisting condition that is temporally associated with the use of the Sponsor's product, is also an adverse event.

Changes resulting from normal growth and development that do not vary significantly in frequency or severity from expected levels are not to be considered adverse events. Examples of this may include, but are not limited to, teething, typical crying in infants and children and onset of menses or menopause occurring at a physiologically appropriate time.

Sponsor's product includes any pharmaceutical product, biological product, device, diagnostic agent or protocol-specified procedure, whether investigational (including placebo or active comparator product) or marketed, manufactured by, licensed by, provided by or distributed by the Sponsor for human use.

Adverse events may occur during the course of the use of the Sponsor's product in studies or within the follow-up period specified by the protocol, or prescribed in clinical practice, from overdose (whether accidental or intentional), from abuse and from withdrawal.

7.2 Definition of Serious Adverse Event

"Serious Adverse Event" (SAE) means an adverse event which is fatal or life threatening, results in persistent or significant disability/incapacity, requires inpatient hospitalization, prolongation of existing inpatient hospitalization, or is a congenital anomaly/birth defect, cancer, the result of an overdose or is another important medical event. Other important medical events that may not result in death, may not be life-threatening, or may not require hospitalization may be considered a Serious Adverse Event when, based upon appropriate medical judgment, they may jeopardize the patient or subject and may require medical or surgical intervention to prevent one of the other outcomes listed previously. Examples of such medical events include allergic bronchospasm requiring intensive treatment in an emergency room or at home and blood dyscrasias or convulsions that do not result in inpatient hospitalization.

7.2.1 Other Relevant Safety Information

The following events are considered important safety information and should be collected/reported using the same timeframes and reporting methods as SAEs:

- Exposure to product during pregnancy or lactation
- Lack of effect

7.3 Causality Assessment

A causality assessment (attribution) must be performed and recorded for each SAE/non-serious AE in relationship to a Sponsor's product. During studies with direct patient contact (visits), the assessment of causality will be determined by an investigator who is a qualified physician according to his/her best clinical judgment. Use the following criteria as guidance (not all criteria must be present to be indicative of causality to a Sponsor's product: There is evidence of exposure to the Sponsor's product; the temporal sequence of the AE onset relative to the administration of the Sponsor's product is reasonable; and the AE is more likely explained by the Sponsor's product than by another cause. In studies without direct patient contact, the assessment of causality would be determined by a notation of attribution in medical records. Causality can be assigned by the investigator or the Sponsor. Examples include a drug-induced rash that an investigator attributes to a specific product, or a clinical notation that a product was discontinued because it caused insomnia.

7.4 Adverse Event Reporting

Any Serious Adverse Event (SAE), regardless of causality, which occurs in any study subject within 2 days following a protocol-specified procedure, must be recorded in the study database and also must be submitted to Global Safety. Additionally, any SAE brought to the attention of an investigator at any time after the above specified time period must be recorded in the study database and also must be submitted to Global Safety if the event is felt to be possibly related to a protocol-specified procedure. All subjects with SAEs related to protocol-specified procedures must be followed up for outcome. All non-serious AEs which are felt to be possibly related to the protocol-specified procedure must be recorded in the study database and also must be submitted to Global Safety. In such cases, the INVESTIGATOR will complete an Adverse Event report form (attachment) in English and submit SAEs within 24 hours and non-serious AEs within 10 calendar days to the Vendor Sponsor Contact by Fax or e-mail. Vendor Sponsor Contact will submit AE form to Merck Global Safety at AER FAX # 215-993-1220 (US), or toll-free fax 1-800-547-5552 (ex-US and US availability)within 2 business days (SAEs) and 10 calendar days (AEs) of receipt for reporting to worldwide regulatory agencies as appropriate.

In addition, if through the conduct of this study, an investigator becomes aware of any Serious Adverse Event (SAE), regardless of causality, or non-serious AE, that is felt to be

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causally related, to any investigational or marketed product manufactured by Merck the event must be reported. In such cases, the INVESTIGATOR will complete an Adverse Event report form (attachment) in English and submit SAEs within 24 hours and non-serious AEs within 10 calendar days to the Vendor Sponsor Contact by Fax or e-mail. Vendor Sponsor Contact will submit AE form to Merck Global Safety at AER FAX # 215-993-1220 (US), or toll-free fax 1-800-547-5552 (ex-US and US availability)within 2 business days (SAEs) and 10 calendar days (AEs) of receipt for reporting to worldwide regulatory agencies as appropriate.
The end of study report summarizing SAEs and non-serious AEs to study procedures will be provided to regulatory agencies as required.

Spontaneously reported SAEs and non-serious AEs following the use of OTHER investigational or marketed products manufactured by Merck, regardless of causality, will be collected and reported to regulatory agencies as individual cases as required but will not be included in the end of study report.

7.5 Sponsor Responsibility for Reporting Adverse Events

All adverse events will be reported to regulatory agencies, IRB/IECs and investigators in accordance with all applicable global laws and regulations.

8 Statistical Analysis Plan

8.1 Statistical Methods

This section outlines the statistical analysis strategy and procedures for the study. If, after the study has begun, changes are made to primary and/or key secondary hypotheses, or the statistical methods related to those hypotheses, then the protocol will be amended. Changes to exploratory or other non-confirmatory analyses made after the protocol has been finalized, along with an explanation as to when and why they occurred, will be listed in the CSR for the study. Post hoc exploratory analyses will be clearly identified in the CSR. A separate SAP will be created for this study.

8.1.1 Primary Objective(s): Calculation of Epidemiological Measure(s) of Interest (e.g. descriptive statistics, hazard ratios, incidence rates, test/retest reliability)

The study's primary objective is to investigate the prevalence of radiographic vertebral fractures in community-dwelling postmenopausal women in China. Descriptive statistics will be made to statistically address this objective. No hypothesis testing will be applied in the study for this primary objective.

Point estimates (percentage) of prevalence by overall study population and by age group and/or geographic region will be calculated and displayed. A fracture case is defined and counted as the subject with the presence of at least one vertebra classified as grade 1, 2, or 3 semi-quantitatively by Genant's score as agreed by both study radiologists.

Point estimates of prevalence rates by overall and geographic region will be adjusted by a nationwide age distribution using the database from Basic Statistics on National Population Census 2010, National Bureau of Statistics of China [53]. A direct method of adjusting rates will be made to give age-standardized prevalence. Age-standardized rate by regional age distribution data may be calculated subject to site location and will be specified in the SAP before database lock and study analyses.

A corresponding two-sided 95% confidence interval (CI) for each individual point estimate will be given. This 95% CI is based on a direct calculation of the exact binomial distribution. A more conservative method, the Wilson Score CI [52], will be applied to give 95% CIs for all point estimates and compared with the exact binomial distribution.

To test reproducibility for fracture adjudication, intra- and inter-observer reliabilities will be tested using a sample of first 100 X-ray films from any participating site in the study. Intra-observer and inter-observer agreement will be calculated by kappa statistic. A κ is 0.81 or above suggests very good agreement.

The statistical analyses for primary objective are summarized in Table 8.1.1.1.

Table 8.1.1.1 Statistical Analysis Approaches on Primary Objective

VF Prevalence	Rate	Estimate*
Overall	Crude/Age-Standardized Rate	Point and 95% CI
Age Group§	Crude Rate	Point and 95% CI
Region^	Crude/Age-Standardized Rate	Point and 95% CI
Age Group and Region△	Crude Rate	Point and 95% CI
Genant's Grade※	Crude Rate	Point and 95% CI

* Based on exact binomial distribution 95% CI and Wilson Score 95% CI;
§ Age group will be given by 50 – 54, 55 – 59, 60 – 65, 65 – 69, 70 – 74, 75 – 79, and 80+; and by < 65 and ≥65;
^ Participating sites will be grouped by 5 regions in China: North, South, Southeast, Southwest, and Central;
△ Prevalence rate will be presented by all age groups and overall in individual regions in China;
※ Genant's Grade by 1, 2 or 3.

8.1.2 Secondary Objective(s): Calculation of Epidemiological Measure(s) of Interest (e.g. hazard ratios, incidence rates, test/retest reliability)

8.1.2.1 Prevalence of Osteoporosis

In the study, prevalence of osteoporosis in community-dwelling postmenopausal women in China will be investigated as a secondary objective. Descriptive statistics will be made to statistically address this objective. Point estimates (percentage) and corresponding 95% CI (exact binomial and Wilson score) will be presented for each analysis category and will be adjusted by age distribution in China [53]. Prevalence rates will also be given by age group and geographic region. A case with osteoporosis is counted based on the definition in Section 4.

The prevalence of osteoporosis will be presented as overall and by different diagnostic criteria and will be listed separately to allow an evaluation on the frequency distribution of each individual diagnostic setting in the study population.

The analysis of osteoporosis prevalence is displayed in the Table 8.1.2.1.

Table 8.1.2.1 Statistical Analysis Approaches on the Prevalence of Osteoporosis

Osteoporosis	Rate*	Estimate**	Frequency***
Overall	Crude/Age-Standardized	Point and 95% CI	Percent
By DXA BMD^	Crude/Age-Standardized	Point and 95% CI	Percent
By Fragility Fracture△	Crude/Age-Standardized	Point and 95% CI	Percent & Cumulative

* Prevalence rates will be sub-analyzed by age group (50 - 54, 55 - 59, 60 - 65, 65 - 69, 70 - 74, 75 - 79, and 80+; and by < 65 and ≥65) and/or geographic region (North, South, Southeast, Southwest, and Central);
** Based on exact binomial distribution 95% CI and Wilson Score 95% CI;
*** Calculation of frequency is relative to overall percent (100%);
^ the subject with a T-score ≤ -2.5 as suggested by a DXA measurement
△ The subject with DXA measurement with a proven non-pathological major fracture as reported by the medical history or as suggested by radiology.

8.1.2.2 Risk Factors for Radiographic Vertebral Fracture or Densitometric Osteoporosis

As secondary objectives, all possible factors including socioeconomic status, lifestyle and clinical parameters will be assessed to identify if they are the risk factors of a prevalent vertebral fracture or densitometric osteoporosis in Chinese postmenopausal women.

A two-step statistical modeling will be established to assess the potential risks against the response of analysis interest (dependent variable). Initially, a single logistic regression for bivariate analysis will be used to give a percentage tabulation presenting proportions of case (morphometric vertebral fracture or densitometric osteoporosis) versus control by each analysis parameter. An odds ratio and associated probability (P value) will be given to examine the statistical significance of this independent variable in the model. A P value of 0.25 or less will be the criterion [54] for an entry into a multivariate logistic model for all estimated variables. Also, all clinically relevant variables, regardless of a probability level, will be included in the final model at the discretion of the study team.

Finally, a multivariable logistic regression model will be constructed for both dependent variables. A stepwise backward method to eliminate non-significant variables will be performed until all remaining variables in the model have a P value less than 0.1. The goodness-of-the-fit will be evaluated by using deviance and likelihood ratio tests and Hosmer–Lemeshow test [55] to assess if there is any single important variable missing from the model.

In the bivariate and multivariate analysis, age, BMD, and BMI will be fitted as continuous variables. Geographic region grouping study sites will be fitted as a categorical variable. Due to potential collinearity of BMD to vertebral fracture, BMD will also be introduced as a dichotomic variable (osteoporosis vs. normal and osteopenia). BMI may vary among study sites in the study, odds ratio per unit BMI instead of per standard deviation to minimize the biases upward.

8.1.3 Exploratory Objective(s): Calculation of Epidemiological Measure(s) of Interest (e.g. hazard ratios, incidence rates, test/retest reliability)

The diagnostic accuracy of onsite vertebral imaging will be tabulated by a simple 2*2 contingency table against blinded adjudication. Sensitivity, specificity, positive predictive value (PPV), negative predictive value (NPV), and likelihood ratio will be given with a corresponding 95% CI. Kappa test for inter-observer agreement between onsite and blinded experienced radiologists will be calculated and presented. Logistic regression model will also be used to assess the probability of a subject with adjudicated vertebral fracture will have the vertebral fracture as diagnosed onsite. The area under the Receiver Operating Characteristic (ROC) curve will be given to evaluate the degree of discrimination for the probability of interested response. Effects of age, region, and/or other analysis variables will be adjusted in the model whenever statistically appropriate.

Assessment in the diagnostic role of vertebral imaging for the screening of osteoporosis will be explored by a simple binary diagnostic test. An osteoporosis diagnosis in the study will be deemed as 'true condition' whereas the blinded vertebral imaging outcome will be the diagnostic tool. Sensitivity, specificity, PPV, NPV, and likelihood ratio will be presented with a corresponding 95% CI. Similarly, logistic regression model will also be used to assess the probability of a subject with adjudicated vertebral fracture will have densitometric osteoporosis. The area under the ROC curve will be given to evaluate the degree of discrimination for the probability of interested response. Effects of age, region, and/or other analysis variables will be adjusted in the model whenever statistically appropriate.

8.1.4 Summaries of Baseline Characteristics, Demographics, and Other Analyses

Demographic variables (i.e. age, gender), socioeconomic variables, prior and concomitant therapies, and BMD absolute values (including FRAX® score) will be summarized overall and by age and/or region, and presented either by descriptive statistics (i.e. mean+/- standard deviation for normal distribution or median for skewed variables) or categorical tables (number and proportion).

For all study variables, **no imputation** will be made for any missing values. In terms of FRAX calculation, missing values will be imputed as 'normal'.

8.2 Bias

8.2.1 Methods to Minimize Bias

A two-stage randomized cluster sampling for the study with all demographic resources may minimize volunteer effect, for example, participants with older age and pre-existing fractures; nonresponse bias may be lessened by endeavours by the investigator for advance notification and follow-up with the study invitation. Recall bias may occur in all subjects especially women without a fracture or osteoporosis history (easily forget part of

clinically relevant medications, i.e. commercial calcium supplements or vitamin D preparations). Self-reporting fracture history may be validated by document and/or physical examination, if it is involved in the diagnosis of osteoporosis. The investigator may encourage the subject recall health status and collect all possible evidence documents to verify the subject's claims in the questionnaire. These documents may be from, but not limited to, the subject's medical records, hospital records/database, and/or private insurance documents. Measurement biases will be minimized by DXA machine calibration, quality control by the site and study team, and blinded fracture adjudication by experienced radiologists. For reliability and validity, a pilot testing of the questionnaire will be performed. Moreover, statistical methodology will be appropriately selected to avoid analysis biases in terms of variability in variables including BMI and BMD.

8.2.2 Adjustment for Multiple Comparisons

This is no adjustment for multiple comparisons for study analyses.

8.2.3 Limitations

Despite methods to minimize potential biases or imprecision in the study, there are several limitations of the study. Due to a cross-sectional design, a snapshot in time of the disease is given and thus the incident of vertebral fractures over time cannot be assessed. Although random sampling method is adopted in the study, concerns in a low response to study invitation, subject dropout and random errors may still exist, which may confound the study results and interpretations.

8.3 Sample Size and Power Calculations

The sample size of the study was calculated based on prevalence data per age group several large epidemiological studies [29-32, 36]. As the prevalence of vertebral fractures increases with age, the sample size will be determined as per age group by setting a lower limit for each assumed age-based prevalence rate (Table 8.3.1), using Clopper-Pearson exact method [52] to compute the lower bound of the corresponding 95% CI at a 5% precision. A sample size of 545 at each geographic region will be statistically sufficient to cover all age groups in detecting the prevalence of vertebral fractures, assuming a 5% withdrawal rate for the spinal radiographs in the study. Considering geographic distribution (5 regions), a total sample size of approximately 2700 postmenopausal women aged 50 or above will be enrolled for the study. In addition, this sample size will yield a generally over 90% power at a 0.05 significance level to detect a geographic impact for the fracture prevalence by an odd ratio at 1.40 or 1.50, by using a univariate logistic model in estimating the change in probability.

Assuming a 40% nonresponse rate in population-based studies [56] and 5% ineligibility rate [32], invitation letters will be posted to approximately 4750 women in all regions.

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Table 8.3.1 Sample Size Calculation by Age Group based Prevalence

Age group	Sample size	Assumed Prevalence	95% CI Lower Limit
50 - 54	44	5.0%	1.0%
55 - 59	81	7.0%	3.0%
60 - 64	100	12.0%	6.0%
65 - 69	90	16.0%	10.0%
70 - 74	80	20.0%	12.0%
75 - 79	70	23.0%	15.0%
>80	53	37.0%	26.0%

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9 ADMINISTRATIVE AND REGULATORY DETAILS

9.1 Confidentiality

9.1.1 Confidentiality of Data

By signing this protocol, the investigator affirms to the Sponsor that information furnished to the investigator by the Sponsor will be maintained in confidence, and such information will be divulged to the Institutional Review Board, Ethics Review Committee or similar or expert committee; affiliated institution and employees, only under an appropriate understanding of confidentiality with such board or committee, affiliated institution and employees. Data generated by this study will be considered confidential by the investigator, except to the extent that it is included in a publication as provided in the Publications section of this protocol.

9.1.2 Confidentiality of Subject Records

By signing this protocol, the investigator agrees that the Sponsor (or Sponsor representative) or Institutional Review Board/Independent Ethics Committee (IRB/IEC), may consult and/or copy study documents in order to verify worksheet/case report form data. By signing the consent form, the subject agrees to this process. If study documents will be photocopied during the process of verifying worksheet/case report form information, the subject will be identified by unique code only; full names/initials will be masked prior to transmission to the Sponsor.

By signing this protocol, the investigator agrees to treat all subject data used and disclosed in connection with this study in accordance with all applicable privacy laws, rules and regulations.

9.1.3 Confidentiality of Investigator Information

By signing this protocol, the investigator recognizes that certain personal identifying information with respect to the investigator, and all subinvestigators and study site personnel, may be used and disclosed for study management purposes, as part of a regulatory submissions, and as required by law. This information may include:

- name, address, telephone number and e-mail address;
- hospital or clinic address and telephone number;
- curriculum vitae or other summary of qualifications and credentials; and
- other professional documentation.

Consistent with the purposes described above, this information may be transmitted to the Sponsor, and subsidiaries, affiliates and agents of the Sponsor, in your country and other countries, including countries that do not have laws protecting such information. Additionally, the investigator's name and business contact information may be included when reporting certain serious adverse events to regulatory agencies or to other investigators. By signing this protocol, the investigator expressly consents to these uses and disclosures.

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If this is a multicenter study, in order to facilitate contact between investigators, the Sponsor may share an investigator's name and contact information with other participating investigators upon request.

9.2 Compliance with Financial Disclosure Requirements

Financial Disclosure requirements are outlined in the US Food and Drug Administration Regulations, Financial Disclosure by Clinical Investigators (21 CFR Part 54). It is the Sponsor's responsibility to determine, based on these regulations, whether a request for Financial Disclosure information is required. It is the investigator's/subinvestigator's responsibility to comply with any such request.

The investigator/subinvestigator(s) agree, if requested by the Sponsor in accordance with 21 CFR Part 54, to provide his/her financial interests in and/or arrangements with the Sponsor to allow for the submission of complete and accurate certification and disclosure statements. The investigator/subinvestigator(s) further agree to provide this information on a Certification/Disclosure Form, commonly known as a financial disclosure form, provided by the Sponsor or through a secure password-protected electronic portal provided by the Sponsor. The investigator/subinvestigator(s) also consent to the transmission of this information to the Sponsor in the United States for these purposes. This may involve the transmission of information to countries that do not have laws protecting personal data.

9.3 Compliance with Law, Audit and Debarment

By signing this protocol, the investigator agrees to conduct the study in an efficient and diligent manner and in conformance with this protocol; generally accepted standards of Good Pharmacoepidemiology Practice; and all applicable local laws, rules and regulations relating to the conduct of the clinical study.

The investigator also agrees to allow monitoring, audits, Institutional Review Board/Independent Ethics Committee review and regulatory agency inspection of study-related documents and procedures and provide for direct access to all study-related source data and documents.

The investigator agrees not to seek reimbursement from subjects, their insurance providers or from government programs for procedures included as part of the study reimbursed to the investigator by the Sponsor.

The Investigator shall prepare and maintain complete and accurate study documentation in compliance with Good Pharmacoepidemiology Practice, standards and applicable local laws, rules and regulations; and, for each subject participating in the study, provide all data, and, upon completion or termination of the study, submit any other reports to the Sponsor as required by this protocol or as otherwise required pursuant to any agreement with the Sponsor.

Study documentation will be promptly and fully disclosed to the Sponsor by the investigator upon request and also shall be made available at the investigator's site upon request for inspection, copying, review and audit at reasonable times by representatives of the Sponsor or any regulatory agencies. The investigator agrees to promptly take any reasonable steps that are requested by the Sponsor as a result of an audit to cure deficiencies in the study documentation and worksheets/case report forms.

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The investigator must maintain copies of all documentation and records relating to the conduct of the study in compliance with all applicable legal and regulatory requirements. This documentation includes, but is not limited to, the protocol, worksheets/case report forms, advertising for subject participation, adverse event reports, subject source data, correspondence with regulatory authorities and IRBs/ERCs, consent forms, investigator's curricula vitae, monitor visit logs, laboratory reference ranges, laboratory certification or quality control procedures and laboratory director curriculum vitae. All study documents shall be made available if required by relevant regulatory authorities. The investigator must consult with the Sponsor prior to discarding study and/or subject files.

The investigator will promptly inform the Sponsor of any regulatory agency inspection conducted for this study.

Persons debarred from conducting or working on studies by any court or regulatory agency will not be allowed to conduct or work on this Sponsor's studies. The investigator will immediately disclose in writing to the Sponsor if any person who is involved in conducting the study is debarred or if any proceeding for debarment is pending or, to the best of the investigator's knowledge, threatened.

In the event the Sponsor prematurely terminates a particular study site, the Sponsor will promptly notify that site's IRB/IEC.

According to European legislation, a Sponsor must designate an overall coordinating investigator for a multi-center study (including multinational). When more than one study site is open in an EU country, Merck, as the Sponsor, will designate, per country, a national principal coordinator (Protocol CI), responsible for coordinating the work of the principal investigators at the different sites in that Member State, according to national regulations. For a single-center study, the Protocol CI is the principal investigator. In addition, the Sponsor must designate a principal or coordinating investigator to review the study report that summarizes the study results and confirm that, to the best of his/her knowledge, the report accurately describes the conduct and results of the study in the study's final report. The Sponsor may consider one or more factors in the selection of the individual to serve as the Protocol CI and or CSR CI (e.g., availability of the CI during the anticipated review process, thorough understanding of study methods, appropriate enrollment of subject cohort, timely achievement of study milestones). The Protocol CI must be a participating study investigator.

9.4 Compliance with Study Registration and Results Posting Requirements

Guidance: Registration is only required for PASS studies (safety and/or efficacy).
Under the terms of the Food and Drug Administration Modernization Act (FDAMA) and the Food and Drug Administration Amendments Act (FDAAA), the Sponsor of the study is solely responsible for determining whether the study and its results are subject to the requirements for submission to the Clinical Trials Data Bank, www.clinicaltrials.gov. Merck, as Sponsor of this study, will review this protocol and submit the information necessary to fulfill these requirements. Merck entries are not limited to FDAMA/FDAAA mandated studies. Information posted will allow subjects to identify potentially appropriate studies for their disease conditions and pursue participation by calling a central contact number for further information on appropriate study locations and site contact information.
By signing this protocol, the investigator acknowledges that the statutory obligations under FDAMA/FDAAA are that of the Sponsor and agrees not to submit any information about this study or its results to the Clinical Trials Data Bank.

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9.5 Quality Management System

By signing this protocol, the Sponsor agrees to be responsible for implementing and maintaining a quality management system with written development procedures and functional area standard operating procedures (SOPs) to ensure that studies are conducted and data are generated, documented, and reported in compliance with the protocol, accepted standards of Good Pharmacoepidemiology Practice, and all applicable federal, state, and local laws, rules and regulations relating to the conduct of the study.

9.6 Data Management

The investigator or qualified designee is responsible for recording and verifying the accuracy of subject data. By signing this protocol, the investigator acknowledges that his/her electronic signature is the legally binding equivalent of a written signature. By entering his/her electronic signature, the investigator confirms that all recorded data have been verified as accurate.

Detailed information regarding Data Management procedures for this protocol will be provided by the Sponsor.

10 List of References

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11 Appendices

1. Questionanire Sample Form

12. References

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13 Attachments

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14 PROTOCOL APPROVAL PAGE

TITLE: An Observational, Cross-Sectional Study Investigating the Prevalence of Vertebral Fractures among Community-Dwelling Postmenopausal Women in China (The *Chi*nese *V*ertebral *O*steoporosis *S*tudy, ChiVOS)

PROTOCOL NUMBER: MK-0217A-911
PROTOCOL VERSION & DATE: Version 1.0 dated 28-Mar-2016

SPONSOR: Merck Sharp & Dohme Corp., a subsidiary of Merck & Co., Inc.
(hereafter referred to as the Sponsor or Merck)
One Merck Drive
P.O. Box 100
Whitehouse Station, NJ 08889-0100, U.S.A.

Protocol Approved by:

TYPED NAME/TITLE	SIGNATURE	DATE

15 PROTOCOL ACCEPTANCE FORM

TITLE: An Observational, Cross-Sectional Study Investigating the Prevalence of Vertebral Fractures among Community-Dwelling Postmenopausal Women in China (The *Chi*nese *V*ertebral *O*steoporosis *S*tudy, ChiVOS)

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One Merck Drive
P.O. Box 100
Whitehouse Station, NJ 08889-0100, U.S.A.

Investigator

I agree to conduct this study in accordance with the design outlined in this protocol and to abide by all provisions of this protocol (including other manuals and documents referenced from this protocol); deviations from the protocol are acceptable only with a mutually agreed upon protocol amendment. I agree to conduct the study in accordance with generally accepted standards of Good Pharmacoepidemiology Practice. I also agree to report all information or data in accordance with the protocol and, in particular, I agree to report any serious adverse experiences as defined in Section 7 – Safety Reporting and Related Procedures. I understand that information that identifies me will be used and disclosed as described in the protocol, and that such information may be transferred to countries that do not have laws protecting such information. Since the information in this protocol and the referenced Investigator's brochure is confidential, I understand that its disclosure to any third parties, other than those involved in approval, supervision, or conduct of the study is prohibited. I will ensure that the necessary precautions are taken to protect such information from loss, inadvertent disclosure, or access by third parties.

_____	_____	_____
Principal Investigator's Name (Print)	**Signature**	**Date**

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