CLINICAL STUDY PROTOCOL

Artificial Intelligence-Guided Diagnosis for High-Risk Osteoporosis Populations: A Pragmatic Randomized Clinical Trial

VERSION 6.0

2026-4-9

Shih-Ann Chen, Kun-Hui Chen, Chia-Hui Tan, Xin-Hua Chen, Pin-Kuei Fu, Chia-En Lien, Cheng-Hung Lee, Chia-Hui Lin, Hsiao-Hung Chiang

Taichung Veterans General Hospital

Table of Contents

1. Synopsis

Protocol Title：

Artificial Intelligence-Guided Diagnosis for High-Risk Osteoporosis Populations: A Pragmatic Randomized Clinical Trial.

Study Objectives：

The overall objective of this study is to examine the clinical effectiveness, healthcare resource usage, and cost outcomes associated with the application of AI-guided diagnotic SaMD (software as medical device), VeriOsteo OP, compared with regular care among patients with high-risk or extremely high-risk osteoporosis. After identifying a patient with high-risk or extremely high-risk of osteoporosis, the intervention to treat the osteoporosis was either provided or not to the study group and control group among the study population.

The primary objective is to evaluate the clinical effectiveness of VeriOsteo OP in improving bone mineral density (BMD) after clinical intervention in patients with high-risk or extremely high- risk osteoporosis. The secondary objective will assess the risk of bone fractures and a composite outcome. Additionally, the exploratory objective is to analyze healthcare resource utilization and associated costs.

Investigational product(s)：

VeriOsteo OP, an AI-guided TFDA-approved tool for predicting of high risk of osteoporosis from standing posteroanterior view of chest X-ray, provided by the AcerMedical Inc.

Development Phase：☐ I ☐II ☐III ■IV ☐其它_____ ☐不適用

Study Design：

1. ■ Experimental Group
   ■ Control Group ： ■ Placebo
   ☐ Study Drug (Name、Dose、Usage) _____
   ☐ Other _____
2. Blinding：■ Open ☐ Evaluator-blind ☐ Single-blind(patient) ☐ Double-blind(patient+PI)
   ☐ Double Dummy ☐ Other _____
3. Randomization: ■ Yes ☐ No
4. ■ Parallel design ☐ Crossover design ☐ Other _____ ☐ Not applicable
5. Treatment Period：_____(days/weeks/months/years) ■ Not applicable
6. Study Period: _____1.5_____years (or From 01/04/2025 to 30/09/2026)
7. Dose adjustment：☐ Mandatory ☐ Selectively ☐ No ■ Not applicable
8. Study location：☐ Single ■ Multi-center ☐ Global

Endpoints (Outcome measure)：

1. **Primary endpoint:** effectiveness of VeriOsteo OP in improving bone mineral density after clinical intervention in patients at high and very high risk of osteoporosis
2. **Secondary endpoints:** incident bone fracture and composite outcomes
3. **Exploratory endpoints:** osteoporosis related healthcare resource utilization and costs

Inclusion/Exclusion Criteria：

Study population:

Patients between the ages of 40 and 80 identified as high-risk or extremely high-risk osteoporosis (defined by the OSTAi <-1** or MOSTAi ≦ 11**), without a diagnosis of

osteoporosis, hyperparathyroidism, or other metabolic bone disease will be enrolled. Participants will be randomized and enrolled between three hospitals (two medical centers and one regional hospital) in Taiwan.

** OSTAi : OSTAi =[body-weight (kg) – age (year)] x 0.2
MOSTAi : MOSTAi = MOSTAi = 0.3 x body weight (Kg) - 0.1 x age (year)

Inclusion criteria:

- Aged between 40 to 80 years old
- Identified as high-risk by the Osteoporosis Self-Assessment Tool for Taiwan Postmenopausal Women (OSTAi) <-1 or Male Osteoporosis Self-Assessment Tool for Taiwan (MOSTAi) ≦11 based on the individual's age and weight (kg)
- Had chest x-ray within one year

Exclusion criteria:

- Age < 40 years old
- Age >80 years old
- BMI< 18 kg/m^2 or >30 kg/m^2
- Pregnant in prior one year
- Recorded diagnosis of osteoporosis within the past two years
- History of prior DXA imaging (prior quantification of BMD) within 2 years
- History of metabolic bone disease

Study Procedures：

Potentially eligible participants will be identified by the EHR database of three hospital sites. Participants, starting with those at highest risk, will then be contacted by the site study coordinator until 1,181 have been recruited. Following informed consent, participants will be randomly assigned (2:1) to the intervention or control arm. A doctor will review the participants and the research nurse will record the baseline characteristics, disease history, and anthropometric details. All participants will be fully reimbursed a VeriOsteo OP test and a DXA examination at baseline to confirm whether they have osteoporosis. Participants in the intervention group will receive a report if they are at high-risk of osteoporosis which defined by VeriOsteo OP. All participants will be followed up with an interview at 6th, 12th month by telephone and will undergo a DXA examination and face-to-face interview at 18th month.

Concomitant Treatments： ■Not applicable

1. Concomitant Therapy：Not applicable

2. Prohibited Therapy：Not applicable

Statistical Methods：

1. Main study Hypothesis：☐ Equality ☐ Superiority ☐ Non-inferiority ■ Equivalence ☐ Other _____

2. Estimated Sample Size：整個試驗預計納入人數 1,181 ，整個試驗可評估人數 886
本中心預計納入人數 900 ，本中心可評估人數 750

3. Efficacy assessment group： ■ Intent-to-treat (ITT) ☐ Per-Protocol (**PP**) ☐ Other _____

附註：意圖治療：Intent-to-treat (ITT)；依計畫書：Per-Protocol (**PP**)

4. Interim analysis： ■ Yes ☐ No

5. Statistical methods：

The primary endpoint is the improvement in BMD (T-score). The modified intention-to-treat (mITT) analysis will be conducted including all randomized patents. Sensitivity analysis using per-protocol (PP) analysis will be conducted for those who completed follow-up.

The independent t-test will be used and the ANCOVA analysis adjusting for baseline T-score, age, sex and other covariates will use to examine the improvement between two groups. The Kaplan-Meier survival analysis and log-rank test will be used to compared the risk of bone fracture and all-cause death between two groups. Cox proportional hazard model adjusting for baseline confounders will be used to compare the risk of bone fracture and all-cause death.

6. Handling of Missing Data：

When the physicians participating in the trial screen and assess the reference standards, they will enter their interpretation results into the information system. The physicians must complete the interpretation of all data, meaning that no form fields can be left blank. If no data is entered, the system will issue a reminder and cannot be closed.

2. Introduction and Rationale

Osteoporosis, defined as a bone mineral density (BMD) of 2.5 or more standard deviations below the peak bone mass (e.g., T-score ≤-2.5), is a serious condition characterized by a decrease in bone density and the weakening of bone structure, leading to a significantly higher risk of fragile fractures[1]. Fracture risk increases with age due to declining skeletal strength and a higher likelihood of falls. Early intervention through lifestyle modification related to fall prevention and bone health, along with medications that help preserve bone, can lower the chances of primary fragility fractures and, as a result, lessen the financial burden on the healthcare system.[2]

According to clinical guidelines[3], females and males aged 50–64 years with two or more risk factors, 65–69 years with one risk factor, or 70 years or older with no risk factors have a 15–20% risk of fracture within 10 years. An observational study using large clinical registry data reported that a 20% intervention threshold for 10-year major fracture risk (measured by FRAX or CAROC) was identified as a highly ranked strategy among females aged 50 years and older[4].

However, under the current reimbursement criteria of Taiwan's National Health Insurance (NHI), pharmacologic interventions are only reimbursed for patients with a T-score of ≤ -2.5 and at least one vertebral compression fracture or hip fracture, or those with a -2.5≤ T-score ≤-1 who have at least two vertebral compression fractures or a hip fracture.

The current gold standard for assessing bone density and calculating fracture risk is Dual-Energy X-ray Absorptiometry (DXA). While DXA provides a low-radiation method for measuring bone mineral density (BMD), individuals at high risk of osteoporosis may remain unaware of their condition and are often underdiagnosed. Furthermore, DXA referrals often occur too late for early intervention, as most patients are referred only after experiencing their first fragility fracture. Despite the known high prevalence of osteoporosis and osteopenia, DXA scan are often limited due to accessibility, cost, and potential risk of additional radiation exposure[5]. Since osteoporosis often presents without obvious symptoms, evaluating risk factors in combination with a non-invasive diagnostic tool can be a crucial first step. Several clinical guidelines even recommend conducting a fracture risk assessment before performing a BMD test[6].

To address these challenges in osteoporosis diagnostics and unmet medical need, Taichung Veterans General Hospital (TCVGH) in cooperation with AcerMedical Inc., had developed

VeriOsteo OP, a software as medical device (SaMD) solution that estimates real BMD (i.e., T-score) from standing posteroanterior (PA) view of chest X-ray. This software aims to facilitate opportunistic screening of patients undergoing routine chest PA X-rays, enabling earlier identification of osteoporosis risk without waiting for a fracture to necessitate DXA.

Research indicates that patients are more likely to adhere to treatment and medication guidelines when an intervention is deemed acceptable[7]. This is especially critical in the context of osteoporosis diagnosis, as many individuals who could benefit from osteoporosis medications remain untreated. This widespread lack of treatment has been described as an 'osteoporosis crisis[8]. Recent studies related to AI-assisted osteoporosis tools is relative limited. Most studies focused on the performance of prediction and some studies tend to emphasize opportunistic screenings instead of clinical application and the health benefit[9-14].

The primary objective is to evaluate the improvement of bone density between interventional group and control group among patients with high-risk or extreme high-risk osteoporosis. The secondary objectives related to the effectiveness, including assessing the risk of bone fractures, all-cause mortality, and a composite outcome. Additionally, the exploratory objective is to analyze healthcare resource utilization and associated costs.

2.1 Investigational product(s)

VeriOsteo OP (TFDA Approval No. 007973) is a software utilizing a closed deep learning method, designed for individuals aged 20 and older. The software detects whether chest X-ray PA view images include the last thoracic vertebra and the first lumbar vertebra, then performs bone density analysis. It compares chest X-ray PA view images to DXA standards to estimate simulated bone mineral density (BMD) and calculate T-scores or Z-scores. Relevant approval documents are provided in **Appendix 1**.

In the AI model development stage, the combined dataset of 5,122 paired chest x-ray (CXR) PA view images and DXA reports from the patients aged 20 to 98 years at a medical center was collected. The images were enhanced and filtered for hardware retention such as pedicle screws, bone cement, artificial intervertebral discs or severe deformity in target level of T12 and L1. The dataset was then separated into training, vali- dating, and testing datasets for model training and performance validation. In the clinical validation stage, we collected 440 paired CXR PA view images and DXA reports from both the TCVGH and Joy Clinic, including 304 pared data from TCVGH and 136 paired data from Joy Clinic. The pre-clinical test yielded an area under the curve (AUC) of 0.940, while the clinical validation showed an AUC of 0.946. Pearson's correlation coefficient was 0.88. The model demonstrated an overall accuracy, sensitivity, and specificity of 89.0%, 88.7%, and 89.4%, respectively. This study proposes an AI model for opportunistic osteoporosis screening through CXR PA view, demonstrating good performance and suggesting its potential for broad adoption in preliminary screening among populations with high-risk or extreme high-risk of osteoporosis. The overall efficacy indicator (using DXA as golden standard) of VeriOsteo OP is listed in **Table 1**.

Table 1. Efficacy indicators of VeriOsteo OP

Indicator	**Performance**
Sensitivity	91.5%
Specificity	92.8%
Accuracy	92.7%
False negative (FN) rate	7.17%

False positive (FP) rate	8.52%
PPV	65.05%
NPV	98.68%

2.2 Risks / benefits Assessment

VeriOsteo OP is a AI-guided diagnosis which detecting osteoporosis using prior existing chest X-ray (CXR) PA view image. Participants in this study will receive one-time DXA which may expose under the low-radiation but will not cause additional harm to the patients.

2.5 Regulatory

This study will be conducted in compliance with the protocol approved by the Institutional Review Board, and according to Good Clinical Practice standards. No deviation from the protocol will be implemented without the prior review and approval of the IRB of Taichung Veterans General Hospital except where it may be necessary to eliminate an immediate hazard to a research subject. In such case, the deviation will be reported to the IRB of Taichung Veterans General Hospital as soon as possible.

3. Objectives and Endpoints

3.1 Study Objectives

The overall objective of this study is to examine consistency and effectiveness, health care resource use, and cost outcomes associates with the use of AI-guided diagnosis (VeriOsteo OP), compared with regular care among patients with high-risk or extreme high-risk osteoporosis.

3.1.1 Primary objective

The primary objective is to evaluate the clinical effectiveness in terms of the improvement of BMD, of AI-guided diagnosis (VeriOsteo OP)

3.1.2 Secondary objectives

The secondary objectives include assessing the risk of bone fractures and a composite outcome.

3.1.3 Other exploratory objectives

The exploratory objective is to analyze healthcare resource utilization and associated costs.

3.2 Study endpoints

3.2.1 Primary endpoint

The primary endpoint of this study is the improvement of BMD (i.e., T-score). The diagnosis of osteoporosis identified as T-scores $\leq$-2.5 obtained from the DXA examination followed the definition of the International Osteoporosis Foundation (IOF) and Consensus and Guidelines for the Prevention and Management of Osteoporosis in Adults in Taiwan in 2020.

To avoid inflating the detection rate for osteoporosis based on the protocolized DXA at baseline in the intervention arm, a positive AI screen was required to be present to count the chest X-ray findings for the purpose of the primary end point.

3.2.2 Secondary endpoints

The secondary endpoints of this study are the incidence of bone fracture (including hip fracture, vertebral fracture, wrist fracture, and other fracture) and all-cause death. Participants will be followed every six months by telephone and the bone fracture will be identified from the interview and by International Classification of Diseases codes extracted from electronic medical records (EHRs) of three sites.

3.2.3 Other exploratory endpoints

The exploratory endpoints include osteoporosis-related healthcare resource utilization and costs, which will be collected through a structured questionnaire via telephone interview at the 12^{th} month of follow-up.

4. Study Design

4.1 Overall Design

This study will adopt before-after clinical trial with control design. The modified intention-to-treat (mITT) approach will be used. Participants at high risk for osteoporosis, as defined by OSTAi or MOSTAi, will be enrolled and randomized 2:1 into either the intervention or control group by an independent database programmer from Taichung Veterans General Hospital.

Eligible patients will be stratified based on baseline characteristics, including T-score (>-2.5 vs. ≤ -2.5), age, sex, and history of fragility fractures. Block randomization will be applied, with patients randomized in blocks of three (reflecting the 2:1 ratio of the intervention and control groups). A computer-generated random sequence will be created by the Clinical Trial Center of Taichung Veterans General Hospital, and a centralized web-based randomization system will be implemented to prevent allocation bias.

Both intervention and control group will receive fully reimbursed VeriOsteo OP and DXA examination, simultaneously covering the lumbar spine and hip. Participants randomized to the intervention will be informed that the AI algorithm had identified them as being at high risk for osteoporosis.

All participants will be observed until the occurrence of an event, all-cause death, or the end of the study, whichever comes first. Baseline characteristics, disease history, and anthropometric details of the subjects will be recorded.

4.2 Number of Patients

A total of 1,181 participants will be enrolled and randomized 2:1 into either the intervention or control group.

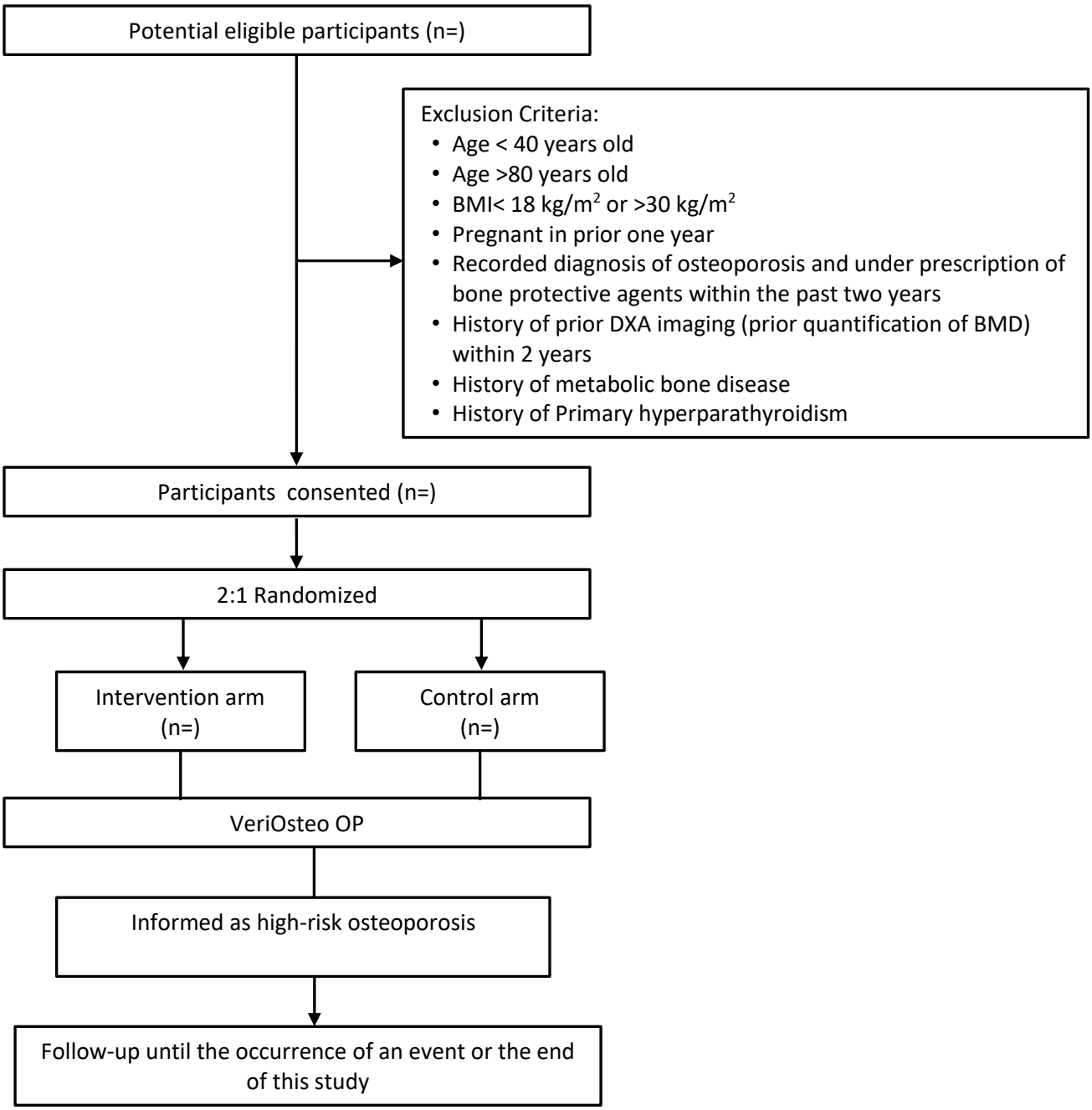


Figure 1. Study Flow Chart

4.3 Schedule of Activities

This study will adopt the **before-after trail** with control design. Potential eligible participants will be identified by the EHRs database of three site hospitals. Participants, starting with those at highest risk, will then be contacted by the site study coordinator until 1,181 have been recruited. They will be invited via a telephone call or at subsequent hospital visit to complete informed consent procedures if they agree to participate. Following informed consent, participants will then be randomly assigned (2:1) to the intervention or control arm and a unique study identifier (ID) will be assigned.

In the first interview at site hospital, a doctor will review the participants and the research nurse will record the baseline characteristics, disease history, and anthropometric details of participants. All participants will have VeriOsteo OP testing to evaluate the risk of osteoporosis for the patient whether they have osteoporosis or not. Baseline characteristics, including age, sex, history of frailty fracture, history of fracture, and FRAX score will be collected.

Participants in the intervention group will receive a report if they had high-risk of osteoporosis which defined by VeriOsteo OP. In the intervention group (AI-guided group), lifestyle intervention and regular care will be provided after identifying high-risk osteoporosis via VeriOsteo OP. In the control group (regular care group), participants will receive standard care throughout the study period and will be informed of their high-risk osteoporosis status via VeriOsteo OP at the end of the study (18^{th} month).

All participants will be followed with a telephone interview at 1^{th} months and 12^{th} months, to collect the bone fracture event. The final DXA examination will be provide in the 18^{th} months to collect the BMD (T-score).

A clinical review will be conducted to exclude participants deemed inappropriate for the trial, such as those nearing the end of life or unable to provide consent. Reasons for exclusion will be documented to enable auditing and assessment for potential selection bias.

to confirm ..... -->

Table 2. Time-Event scheme

	Month 0	Month 1	Month 6	Month 12	Month 18
Inform consent	V				
Baseline information	V				
Disease history interview	V				
Anthropometric details	V				
VeriOsteo OP	V				
DXA examination					V
Receive report of high-risk of osteoporosis by AI algorithm		V			V* (for control group)
Lifestyle intervention and regular care	V		V		
Telephone interview		V		V	
Collecting EHRs			V	V	V
Complete final assessment					V

5. Study Population

Patients between the ages of 40 and 80 identified as high risk osteoporosis (defined by the OSTAi <-1 or MOSTAi ≦11), without a diagnosis of osteoporosis, hyperparathyroidism, or other metabolic bone disease will be enrolled. Participants will be randomized and enrolled between three hospitals (two medical centers and one regional hospital) in Taiwan.

5.1 Inclusion Criteria

- Aged between 40 to 80 years old
- Identified as high-risk by the Osteoporosis Self-Assessment Tool for Taiwan Postmenopausal Women (OSTAi) <-1 or Male Osteoporosis Self-Assessment Tool for Taiwan (MOSTAi) ≦ 11 based on the individual's age and weight (kg)

  * Osteoporosis Self-Assessment Tool for Taiwan Postmenopausal Women (OSTAi) =[weight(kg)-age(year)] x 0.2]
  * Male Osteoporosis Self-Assessment Tool for Taiwan (MOSTAi) = 0.3 x weight(kg) - 0.1 x age(year)

- Had chest X-ray (the resolution of X-ray images ≥ 1,024x1,024 pixels) in the prior one year
- Completed baseline assessment

Intervention group: Participants undergo both VeriOsteo OP and DXA assessments and receive a report indicating high risk of osteoporosis.

Control group: Participants undergo both VeriOsteo OP and DXA assessments but do not receive a report regarding high risk of osteoporosis.

5.2 Exclusion Criteria

- Age < 40 years old
- Age >80 years old
- BMI< 18 kg/m^2 or >30 kg/m^2
- Pregnant in prior one year
- Recorded diagnosis of osteoporosis and under prescription of bone protective agents within the past two years, the bone protective agents included but not limited to listed below :
  bisphosphonate (alendronic acid, risedronate, ibandronate, zoledronic acid)
  denosumab/raloxifene/strontium ranelate/teriparatide/romosozumab
- History of prior DXA imaging (prior quantification of BMD) within 2 years
- History of metabolic bone disease
- History of Primary hyperparathyroidism

5.3 Withdrawal criteria

In accordance with Item 22 of the Declaration of Helsinki, all participants could abstain from participation or withdraw their consent to participate at any time during the study without any repercussions. Withdrawing participants will be asked whether thy wishes to provide continued follow-up and further data collection subsequent to their withdrawal.

6. Treatments

6.1.Treatment Administration

All participants will fully reimbursed the VeriOsteo OP testing (at baseline) and a DXA examination (at baseline and 18th months) to confirm the improvement of BMD and the diagnosis of osteoporosis.

7. Efficacy Assessments

The clinical effectiveness will be defined as the improvement of BMD which is assessed by the T-score and the diagnosis of osteoporosis at 18th via DXA examination. The bone fracture event and all-cause death will be collected at 6th, 12th and 18th months via telephone interview and EHRs.

8. Safety Assessments

Several safety assessments will be conducted during the study. To minimize false positives, which could lead to unnecessary examinations or treatments, and false negatives, which could result in misdiagnosis or delayed interventions caused by AI-guided diagnosis (VeriOsteo OP), a cross-validation review will be performed by a physician. A confidence level threshold for the AI-guided diagnosis (VeriOsteo OP) will be established to determine when clinician intervention is required. Additionally, regular safety audits of the AI-guided diagnosis (VeriOsteo OP) will be conducted quarterly to ensure its reliability and effectiveness.

9. Adverse event reporting

Principal Investigator (PI) of each site will report SAEs to the IRB of Taichung Veterans General Hospital according to the Serious Adverse Event Reporting Procedures and Guidelines as posted in the Clinical Trials Resource on the website of Taichung Veterans General Hospital IRB. SAE reports to the IRB should include the following information when calling the Medical Monitor:

- Date and time of the SAE
- Date and time of the SAE report
- Name of reporter
- Call back phone number
- Affiliation/Institution conducting the study
- Protocol number
- Title of protocol
- Description of the SAE

9.1 Definitions and reports of Adverse Events

Adverse events related to the use of VeriOsteo OP include false positive (FP) diagnoses, which may lead to overdiagnosis and psychological distress caused by the misdiagnosed condition. Additionally, serious adverse events (SAEs) such as hospitalization, disability, or death will be closely monitored and reported during the study to ensure patient safety and address potential risks.

All adverse events that occur after the informed consent is signed (including run-in) will be recorded on the adverse event CRF (paper and/or electronic) whether or not related to study agent. AE Data Elements including:

- AE reported date
- AE Verbatim Term
- CTCAE Term (v 5.0)
- Event onset date and event ended date

- Severity grade
- Attribution to AI-guided diagnosis (VeriOsteo OP) (relatedness)
- Whether or not the event was reported as a Serious Adverse Event (SAE)
- Action taken with the study agent
- Outcome of the event
- Comments

Identify the adverse event using the NCI Common Terminology Criteria for Adverse Events (CTCAE) version 5.0. The CTCAE provides descriptive terminology and a grading scale for each adverse event listed. AEs will be assessed according to the CTCAE grade associated with the AE term.

DEFINITION of Serious Adverse Events: ICH Guideline E2A and GCP of Taiwan define serious adverse events as those events, occurring at any dose, which meet any of the following criteria:

- Results in death
- Is life threatening (Note: the term life-threatening refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe).
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital abnormality/birth defect
- Events that may not meet these criteria, but which the investigator finds very unusual and/or potentially serious, will also be reported in the same manner.

9.2 Adverse event follow-up

All AEs, including lab abnormalities that in the opinion of the investigator are clinically significant, will be followed according to good medical practices and documented as such. Site staff should send follow-up reports as requested when additional information is available. Additional information should be entered on the IRB of Taichung Veterans General Hospital in the appropriate format. Follow-up information should be sent to IRB as soon as possible according to IRB's Serious Adverse Event Reporting Procedures and Guidelines.

10. Criteria for the termination of the trial

In this study, data may be excluded due to poor image quality. If the data meet the exclusion criteria, they will be removed during the screening process. Exclusion will be based on image quality being poor enough to affect interpretation. Excluded data will be stored in an exclusion database, with the reason and time of exclusion recorded for documentation.

11. Statistical Considerations

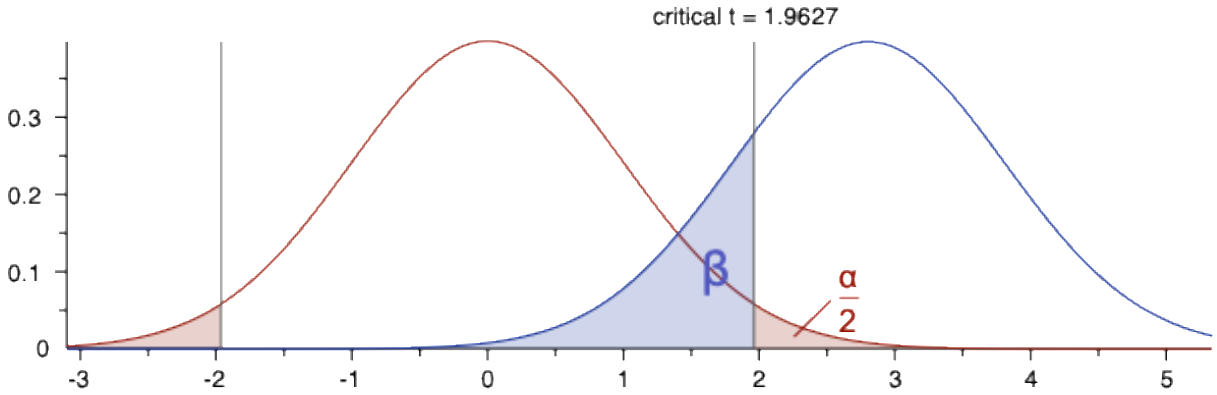
11.1 Sample size Determination

Depending on the primary endpoint of the study, the improvement of BMD (i.e., T-score) and the assumptions listed below, the sample size computed by the. G*Power version 3.1 will be:

- Effect size (d) = 0.2
- α error (two-tailed) = 0.05
- Power (1-β error) = 0.8
- Allocation ratio = 2: 1 (Intervention vs Regular Care)

- Noncentrality parameter δ = 2.8055492
- Critical t = 1.9626512
- Df = 884
- Sample size for intervention group = 886
- Sample size for control group = 591
- Total sample size = 886
- Actual power = 0.8002570

Considering the withdraw and lost to follow-up which assumed 25%, the total samples required will be 1,181.



11.2 Planned Statistical methods of analysis

Description analysis of baseline characteristics, mean and standard division (SD) for continuous variables and counts and percents for categorical variables will be used.

When comparing the mean T-score improvement, the independent t-test will be used and the ANCOVA analysis adjusting for baseline T-score, age, sex and other covariates will use to examine the improvement between two groups.

For the secondary endpoint, incident of bone fracture and all-cause death, the Kaplan-Meier survival analysis and log-rank test will be used to compared the risk of bone fracture and all-cause death between two groups. Cox proportional hazard model, reported as hazard ratio (HR) and 95% confident interval (CI), adjusting for baseline confounders will be used to compare the risk of bone fracture and all-cause death.

11.3 Analysis Population

11.3.1 Main analysis

The primary endpoint is the improvement in BMD (T-score). The modified intention-to-treat (mITT) analysis will be conducted including all randomized patents. Sensitivity analysis using per-protocol (PP) analysis will be conducted for those who completed follow-up.

11.3.2 Subgroup analysis

In addition to the full population analysis of all images interpreted by DXA and VeriOsteo OP, this trial will also conduct follow-up analyses by gender, age group, and hospital, and calculate primary, secondary, and exploratory evaluation indicators for each stratum, to explore the ability of

software to interpret test results under different sub-population stratification.

Patient will be stratified based on age, sex, baseline osteoporosis severity to compare the clinical effectiveness between AI-guided toll and regular care group.

11.4 Procedure for accounting for missing, unused and spurious data

When the physicians participating in the trial screen and assess the reference standards, they will enter their interpretation results into the information system. The physician must complete the interpretation of all data, which means that no form fields can be left blank. If no data is entered, the system will remind you and cannot be closed.

11.5 Procedures for reporting any deviation(s) from the original statistical plan

The Principal Investigator (PI) is responsible for continuous monitoring and identifying any deviations from the trial protocol. All trial deviations must be documented in the relevant records and reported to the Ethics Committee (Institutional Review Board, IRB). Any deviation from the protocol must be submitted to the IRB for review. The PI must be familiar with and comply with the requirements of the IRB.

12. Direct access to source data/documents

Investigators permit IRB to access to the source data of experiment for trial-related monitoring, audits and regulatory inspection.

13. Ethical considerations

This study will be conducted according to Taiwan and international standards of Good Clinical Practice for all studies. Applicable government regulations and Taichung Veterans General Hospital research policies and procedures will also be followed.

This protocol and any amendments will be submitted to the Taichung Veterans General Hospital Institutional Review Board (IRB) for formal approval to conduct the study. The decision of the IRB concerning the conduct of the study will be made in writing to the investigator.

All subjects for this study will be provided a consent form describing this study and providing sufficient information for subjects to make an informed decision about their participation in this study. This consent form will be submitted with the protocol for review and approval by the IRB. The formal consent of a subject, using the IRB-approved consent form, will be obtained before that subject is submitted to any study procedure. This consent form must be signed by the subject or legally acceptable surrogate, and the investigator-designated research professional obtaining the consent.

14. Data handling and keeping

14.1 Data Handling

The imaging data will be processed by the research staff, who are responsible for sampling, anonymizing the data, and assigning serial numbers. The serial numbers will be stored securely. The serial number format consists of a letter prefix followed by a four-digit number. The letter prefix represents different institutions, and the four-digit number corresponds to the participant's serial number. For example, the serial number for the 312th patient at Hospital A would be: A0312.

After the images are interpreted by physicians and analyzed by software, the results will be

entered into the clinical trial system (REDCap) provided by Taichung Veterans General Hospital Clinical Trial Center. The interpretation results from the software will also be uploaded by the research staff to the system. All data handling processes will be carried out on computers with secure user passwords. The collection of trial data, including reference standards for image interpretation and results from the trial software, will be uniformly collected and organized by the research staff on a secured computer.

14.2 Data Analysis

Trial data (including the physician's reference standard for image interpretation and results from the trial software) will be processed and statistically analyzed using SAS or R software, and a report will be generated. A two-tail p-value less than 0.05 was considered significant.

14.3 Data Storage

Clinical trial data will be stored according to the regulatory requirements for Good Clinical Practice (GCP) for pharmaceuticals and medical devices, for a period of two years after the product is marketed. Data exceeding the retention period will be securely deleted. All trial records from the Principal Investigator and the Smart Medical Center of Taichung Veterans General Hospital will be archived in accordance with ICH GCP E6 guidelines and the quality system and SOPs of Taichung Veterans General Hospital.

The Principal Investigator will retain all research records, reports, and medical records for two years following the approval of the competent authority. If no application is made or if the application is not approved, the records must be retained for two years after the completion or termination of the trial and after notifying the competent authority. However, if required by applicable regulations or at the request of Taichung Veterans General Hospital or its authorized representative, these documents may be retained for a longer period. After trial completion, detailed information on the storage process of records must be provided to the Smart Medical Center of Taichung Veterans General Hospital. All research records must be available for inspection by the competent authority at any time.

The Investigator will retain records including, but not limited to:

- Case Report Forms (CRFs), source data, and primary records (e.g., test results and any other diagnostic procedures required for assessing trial progress)
- Signed trial protocol and protocol amendments
- Signed documentation for trial personnel
- Correspondence between Taichung Veterans General Hospital Smart Medical Center, contracted design and manufacturing companies, designated personnel, and the IRB
- CVs of the Principal Investigator and Coordinating Investigators
- Ethics Committee approval letter and re-approval letter (if applicable)
- Other documents related to the conduct of the trial

These documents must be maintained and archived by the Principal Investigator for detailed recording and monitoring of trial conduct. The research records may not be transferred or destroyed without prior written consent from Taichung Veterans General Hospital and the contracted design and manufacturing companies and the Principal Investigator. All research records must be available for inspection by the competent authority at any time.

15. Financing and Insurance

The study was funded by the Ministry of Health and Welfare (grand no. MOHW-113- IM-I-212-000013-18). All PIs have no conflict of interest.

The cost of DXA examinations will be fully covered by this study, and the intervention with VeriOsteo OP will include only the notification and examination costs. Pharmaceutical treatments and other medical expenses will be determined through discussions between participants and their clinical physicians and will not be covered in this study.

16. References

1. Consensus development conference: diagnosis, prophylaxis, and treatment of osteoporosis. *Am J Med* 1993;94(6):646-50. doi: 10.1016/0002-9343(93)90218-e
2. Harvey NC, McCloskey EV, Mitchell PJ, et al. Mind the (treatment) gap: a global perspective on current and future strategies for prevention of fragility fractures. *Osteoporos Int* 2017;28(5):1507-29. doi: 10.1007/s00198-016-3894-y [published Online First: 20170207]
3. Morin SN, Feldman S, Funnell L, et al. Clinical practice guideline for management of osteoporosis and fracture prevention in Canada: 2023 update. *Canadian Medical Association Journal* 2023;195(39):E1333-E48. doi: 10.1503/cmaj.221647
4. Leslie WD, Morin SN, Lix LM, et al. Comparison of treatment strategies and thresholds for optimizing fracture prevention in Canada: a simulation analysis. *Archives of Osteoporosis* 2020;15:1-10.
5. Paccou J, Zeboulon N, Combescure C, et al. The Prevalence of Osteoporosis, Osteopenia, and Fractures Among Adults with Cystic Fibrosis: A Systematic Literature Review with Meta-Analysis. *Calcified Tissue International* 2010;86(1):1-7. doi: 10.1007/s00223-009-9316-9
6. National Institute for Health and Care Excellence: Guidelines. Osteoporosis: assessing the risk of fragility fracture. London: National Institute for Health and Care Excellence (NICE), Copyright © NICE 2019. 2017.
7. Van der Velde RY, Wyers CE, Teesselink E, et al. Trends in oral anti-osteoporosis drug prescription in the United Kingdom between 1990 and 2012: Variation by age, sex, geographic location and ethnicity. *Bone* 2017;94:50-55. doi: https://doi.org/10.1016/j.bone.2016.10.013
8. Khosla S, Shane E. A Crisis in the Treatment of Osteoporosis. *Journal of Bone and Mineral Research* 2016;31(8):1485-87. doi: 10.1002/jbmr.2888
9. Gao L, Jiao T, Feng Q, et al. Application of artificial intelligence in diagnosis of osteoporosis using medical images: a systematic review and meta-analysis. *Osteoporosis International* 2021;32(7):1279-86. doi: 10.1007/s00198-021-05887-6
10. Lin C, Tsai DJ, Wang CC, et al. Osteoporotic Precise Screening Using Chest Radiography and Artificial Neural Network: The OPSCAN Randomized Controlled Trial. *Radiology* 2024;311(3):e231937. doi: 10.1148/radiol.231937
11. Welsner M, Navel H, Hosch R, et al. Opportunistic Screening for Low Bone Mineral Density in Adults with Cystic Fibrosis Using Low-Dose Computed Tomography of the Chest with Artificial Intelligence. *J Clin Med* 2024;13(19) doi: 10.3390/jcm13195961 [published Online First: 20241007]
12. Pan Y, Shi D, Wang H, et al. Automatic opportunistic osteoporosis screening using low-dose chest computed tomography scans obtained for lung cancer screening. *European Radiology* 2020;30(7):4107-16. doi: 10.1007/s00330-020-06679-y
13. Areeckal AS, Jayasheelan N, Kamath J, et al. Early diagnosis of osteoporosis using radiogrammetry and texture analysis from hand and wrist radiographs in Indian population. *Osteoporosis International* 2018;29(3):665-73. doi: 10.1007/s00198-017-4328-1
14. Lee J-S, Adhikari S, Liu L, et al. Osteoporosis detection in panoramic radiographs using a

deep convolutional neural network-based computer-assisted diagnosis system: a preliminary study. *Dentomaxillofacial Radiology* 2019;48(1) doi: 10.1259/dmfr.20170344