Medical Record No.： Subject Name： Birthday：

National Taiwan University Hospital

Clinical Trial Informed Consent Form

IRB number：201909060RINA

Protocol title The effect of multi-faceted intervention on osteoporosis and CKD-MBD	
Trial Institution: Department of Geriatrics and Gerontology, Department of Internal Medicine, National Taiwan University Hospital and Chu-Tung Branch	Sponsor/Pharmaceutical Company for this trial: nil Source of Research Finding: National Taiwan University Hospital Chu-Tung Branch
Principal Investigator: Dr. Chirn-Bin Chang Title: Attending Physician Sub-Investigator: Dr. Yung-Ming Chen Title: Attending Physician	
24-hour emergency contact person: Dr. Chirn-Bin Chang Telephone No.: 0972654906	
Subject name: Medical Record No. :	

You are being invited to participate in this clinical trial. This form provides information related to this trial. The principal investigator or his/her authorized staff will explain the content of this trial to you and answer any questions you may have. Please do not sign this consent form until all of your questions have been answered satisfactorily. You do not have to decide whether you will take part in this trial right away. Please consider carefully before you sign your name. You must sign the consent form to participate in this trial. If you are willing to participate in this trial, this document will be considered as the record of your consent. You can withdraw from the trial at any time without any reason, even after you have given consent.

I. Trial objective:

Older adults having chronic kidney disease (CKD) have higher rate of fracture than those without CKD. To prevent fracture among older adults having CKD is an important issue because those having fracture will be with higher mortality rate, health resource utilizations, and poor life quality. In addition to osteoporosis, chronic kidney disease mineral-bone disorder which was caused by deterioration of renal function would cause fractures. To prevent fracture, it is important to evaluate chronic kidney disease-mineral and bone disorder (CKD-MBD) and primary osteoporosis among older adults with CKD. For participants with CKD-MBD or primary osteoporosis, we will demonstrate the diet modification, exercise for bone and cardiovascular health for you in order to control the biochemistry abnormalities in MBD and osteoporosis. Osteoporosis medications will be initiated according to the reimbursed criteria of National Health Insurance; otherwise medications are used with non-insurance payment.

II. Background and current status of the treatment:

Previous studies among CKD patients found the fracture incidence to progressively increase by 15.0, 20.5, 24.2, 31.2, and 46.3 per 1000 person-years for CKD stages 1 to 2, 3a, 3b, and 4, respectively. The risk of fracture increases to 5 times higher in patients with an estimated glomerular filtration rate (eGFR) <15 versus >60 ml/min per 1.73 m^2). Patients with CKD and older than 65 years of age have a higher rate of fractures during 3-years of follow-up. It would be an important issue to prevent skeletal fracture among older adults with CKD since fracture can cause higher mortality and health resource utilization and loss of quality of life.

The KDIGO CKD-MBD guideline suggested application of dual-energy x-ray absorptiometry (DXA) in evaluation the fracture risk among CKD patients. In order to prevent fragility fracture, it would be reasonable to target abnormalities of mineral metabolism and primary osteoporosis.

Taiwan is one of the regions having a high annual incidence of hip fractures. Estimated based on the world standard population in 2010, the incidence were about 392 per 100,000 for women and 196 per 100,000 for men. The death rate after one year of hip fracture is 15% for women and 22% for men. The studies to provide fracture liaison services for high-risk groups of osteoporosis has been proven to improve the clinical prognosis of patients. National Taiwan University Hospital and Chu-Tung Branch were approved by the Research Ethics Committee of National Taiwan University Hospital to implement a fracture liaison service at National Taiwan University Hospital and Chu-Tung Branch. This project will use a case management approach similar to fracture liaison services to establish a platform and database for health education and tracking, and introduce information on diet and exercise for bone and kidney health. It is expected to reduce the incidence of fractures and mineral bone diseases in patients with chronic kidney diseases.

III. Main inclusion and exclusion criteria of the trial:

The physicians or relevant researchers of National Taiwan University Hospital who perform this research study will discuss with you the necessary conditions for participation in this research. Please cooperate with us and be honest with us about your past health condition. If you do not meet the requirements of this research, you may not be allowed to participate in this research study.

1. Requirements for participation in the research study:

(1) You must be over 50 years old.

(2) You must have chronic kidney disease stage 3 or 4 and the estimated glomerular filtration rate is over 20 mL/min/1.73m^2.

(3) The FRAX® screening: risk of hip fracture: man with risk over 6%, women with risk over 7% or risk of major: men with risk over 15%, women with risk over 12.5%.

2. You will not be allowed to participate in this research study if you fulfill any of the following conditions:

(1) You have active cancer and are receiving therapy.

(2) You had acute coronary artery syndrome or acute stroke in recent 3 months.

(3) You will not attend clinics for evaluation and therapy.

(4) You have cognitive or functional impairment that prohibit your behavioral intervention.

IV. Methods and related procedures of this trial:

The duration of the trial was January, 1, 2020 to December 31, 2020 and we will enrolled 60 participants. If you have decided to participate in this research trial and signed the consent form, you will undergo physical examination, including blood and urine tests, height and body weight measurement, questionnaire, as well as bone density test and thoracolumbar x-ray film.

The bone density test and thoracolumbar spine lateral view x-ray film are non-invasive with the radiation amount 0.10mSv and 1.48mSv, respectively. The radiation amount was lower than 5mSv.

During the visit period, you should undergo blood and urine test and questionnaire obtaining by the trial staff in 3rd month, 6th month, 9th month and 12th month after enrollment.

If you meet the requirements, medications for osteoporosis and CKD-MBD will be initiated according to the reimbursed criteria of National Health Insurance.

Blood and urine sample collection were needed to evaluate CKD-MBD and performed by our Department of laboratory medicine.

V. Possible risks and their incidence and countermeasures:

1. Risks associated with the investigational drug (side effects of the drug used in this trial: this

trial did not use investigational drugs.

2. Risk associated with the trial process:

- This trial did not use investigational drugs. We aim to investigate the effect of behavioral intervention. The drugs using for chronic kidney disease and osteoporosis in this trial were all proven in Taiwan. If you experience any side effects, please inform your trial physician and other trial staff so that the trial physician can decide on the appropriate treatment for your case.
- Blood sample collection: Blood sample collection from the arm may cause pain, bruising, dizziness, and very rarely, even infection. Countermeasures include: pressure at blood draw site for at least 5 minutes after blood collection; bruising can be eased by hot compress; for dizziness, you should sit or lay down for rest. The bone density test and thoracolumbar spine lateral view x-ray film are non-invasive with the radiation amount 0.10mSv and 1.48mSv, respectively. The radiation amount was lower than the background ration amount (1.6mSv/year) of the Taiwanese.

VI. Alternative treatments and explanations:

This trial did not use investigational drugs. Your diseases will be treated as clinical guideline of osteoporosis and CKD-MBD. Behavioral intervention including diet modification and exercise for bone and kidney health will be given to you. If you do not participate in this trial, there are other treatment options for you, including approved or commercial drugs. Your trial physician can discuss the risks and benefits of these alternative treatment options with you. In addition, you can discuss your options with your primary care physician.

VII. Anticipated trial benefits:

Participating in this trial does not guarantee any improvement of your disease or bring you any other direct benefits. However, you will get the evaluation, treatment, information for life style modification to help you knowing these disease and modifying life styles to improve the bone and kidney health.

VIII. Contraindications, restrictions and rules that must be abided by during the trial:

During the trial period, for your safety, we need your cooperation in the following matters:

-Provide correct information on your past medical history, medical records, and current medical condition.

-During the examination for osteoporosis, you will receive a thoracolumbar spine lateral view x-ray film (1.48mSv) and bone density test for bone mineral density (0.10mSv).

-For CKD-MBD evaluation, blood and urine sampling will be done in our Department of Laboratory Medicine.

IX. Confidentiality of subject's personal information:

National Taiwan University Hospital will abide by the law to keep the confidentiality of any record containing your identification and your personal private information, and will not disclose it. The research staff will assign you with a research code, and this code will not show any identifiable information such as your name, identification number or address. In the event that trial results are published, your identification will continue to be kept confidential. You also understand that by signing this consent form, you are approving direct use of your original medical records by the monitors, auditors, (the Research Ethics Committee Office) and the competent authorities, in order to ensure that the clinical trial is conducted and data are collected in accordance with applicable laws and regulations. The aforementioned personnel guarantee the confidentiality of your identity

will not be violated.

X. Withdrawal and termination of the trial:

You are free to decide whether to take part in this trial. During the trial, you can withdraw your consent and leave the trial at any time, without giving any reason, and no unpleasantness will be caused, nor will your medical care from your physician be affected.

During the course of the trial, you will be informed of important new information (i.e. information relating to your rights/benefits or that will affect your willingness to continue taking part in this trial/research), and provided you with further explanation. Please consider whether to continue taking part in the trial. You are free to make a decision and this decision will not cause any unpleasantness or affect your future medical care.

It is also possible that the Principal Investigator or the Trial Sponsor will terminate the clinical trial or your participation in the trial whenever necessary.

If you decide to withdraw from the trial, or if the Principal Investigator decides to terminate your participation in this trial, the data collected before your withdrawal will be preserved, and will not be deleted.。

After withdrawal, you may decide the handling method of the samples you previously provided, and decide whether to give consent to allow the Principal Investigator or Trial Sponsor to continue collecting your data, e.g. accessing my medical records to obtain the follow-up medical procedures and lab test results for 1 year. During the period of continuous data collection, your privacy and personal information will remain confidential.

☐I consent to collection.

☐I do not consent to continuous collection or inspection of my data.

XI. Compensation and insurance:

All clinical trials have risks. To ensure the protection you may receive for damages resulting from the adverse events of participating in this trial, please be sure to read the content of this section:

1. National Taiwan University Hospital will bear liabilities for compensation of damages caused by the adverse events resulting from following the protocol designed for this clinical trial。The hospital will provide professional medical care and consultations for adverse events or damages resulting from following the protocol designed for this clinical trial.
2. This trial does not provide compensation in any form other than the compensation and the medical care set forth in above. If you do not accept this level of risk, please do not participate in the trial.
3. You will not lose any legal rights pursuant to your signing of this Informed Consent Form.。
4. This trial is not insured against human research liability.

XII. Storage, use and reuse of subject's samples (including their derivatives) and personal information:

1. Storage and Use of Samples and Residual Samples

(1) Storage and use of samples (including their derivatives)

For the research, your samples collected by us will be used as indicated in the trial protocol and be stored for 3 days in the Department of Laboratory Medicine, National Taiwan University and Chu-Tung Branch. We will destroy the samples in accordance with laws and regulations when the expiration date is due. To protect your privacy, we will replace your name and relevant personal information with a trial code in order to ensure your samples and relevant information are

completely confidential. If you have any concerns about the use of the samples or you have any need to destroy the samples, please contact us immediately (Contact person: Chirn-Bin Chang, Tel: 0972654906), and we will destroy your samples. You can also contact the Research Ethics Committee Office of the hospital) (Tel: (02)2312-3456 ext. 63155) to help you resolve any disputes over the use of samples for research.

(2) Reuse of residual samples (including their derivatives)

This trial did not reuse your biological samples，your residual samples will be destroyed after 3 days.

2. Personal Information

During the trial period, we will collect related data and information about you from your medical charts, medical records, scales, and questionnaires; and provide a study code to replace your name and relevant personal information, depending on the nature of the trial and content of your authorization. If the above-mentioned data and information are in hard copy, they will be kept in a locked cabinet at the trial institution, separated from the Informed Consent Form. Electronic copies or archives for statistics and analysis purposes will be kept in dedicated computers protected by passwords and appropriate anti-virus software (details about storage and management of paper-based and electronic data in this paragraph are only examples, and may be supplemented and corrected to reflect the actual circumstances of respective studies.) If research is terminated, the data will be stored for five years after the discontinuation of the trial.

XIII. Rights and interests of the subject:

1. During the trial, if you have any questions about the nature of the trial or any concerns about your rights as a patient, or suspect that you have suffered injury as a result of participating in this research, please contact the Research Ethics Committee Office to request for consultation. The telephone number is (02)2312-3456 ext. 63155.
2. During the trial, any significant findings that are related to your health or the disease and may affect your willingness to continue participating in the clinical trial will be provided to you in a timely manner. If you decide to withdraw, the physician will make arrangements for you so that you will continue to receive medical care. If you decide to continue participating in the trial, you may need to sign an updated version of the Consent Form.。
3. You will receive care by Dr. Chirn-Bin Chang during the course of the clinical trial. If you have any questions or conditions now, or during the clinical trial, please do not hesitate to contact Dr. Chirn-Bin Chang at the Department of Internal Medicine (24-hr contact number: 0972654906).
4. This consent form is made in duplicate. The Principal Investigator or authorized staff has given you 1 copy of the signed consent form and has fully explained the nature and purpose of this research. The physician has answered all your questions about the drug and research.
5. If any unintended events occur 2 years after the end of this trial which can directly affect your safety concern, you will be notified.

XIV. Anticipated commercial benefit(s) derived from the trial:

The data obtained from this trial may lead to the discovery, invention or development of commercial products, and all the rights belong to the investigators and National Taiwan University Hospital. You and your family will not receive any financial benefits or monetary compensation for the research results, discovery or other findings derived from the data, or be granted with the ownership of the aforementioned invention.

XV. Signature:

1. The Principal Investigator/Sub-investigator or his/her authorized personnel has explained in detail the nature and objectives of the above research method in this protocol, as well as the possible risks and benefits.

   Signature of Principal Investigator/Sub-investigator:_____

   Date: _____(Month) _____(Day), _____(Year)

   Other research staff participating in the consenting process, including discussion and explanation:

   Date: _____(Month) _____(Day), _____(Year)

2. I fully understand the research method mentioned above and the possible risks and benefits after the explanation, and my questions about the clinical trial have been answered in full detail. I agree to participate in this research voluntarily and will hold a duplicate of the Informed Consent Form.

   Signature of the Subject: Date: ____(Month)_____(Day), _____ (Year)

   Date of Birth: ____(Month)_____(Day), _____ (Year) Telephone No.:

   National ID Number: Gender:

   Correspondence Address:

   Signature of the Legal Representative, Person who Has Right to Give Consent:
   Date: ____(Month)_____(Day), ____ (Year)

   Relationship with the Subject:

   Date: ____(Month)_____(Day), ____ (Year)

   Telephone No.:

   National ID Number:

   Correspondence Address:

   *For those that the proviso of paragraph 1 of Article 79 of the Medical Care Act or the proviso of paragraph 1 of Article 12 of the Human Subjects Research Act applies to, exercising their right to give consent should be in accordance with paragraph 2 of Article 79 of the Medical Care Act, Article 5 of the Regulations on Human Trials, or paragraphs 3 and 4 of Article12 of the Human Subjects Research Act.

   Signature of the Witness:_____ Date: ____(Month)_____(Day), ____ (Year)

* In the event that none of the subject, legal representative or the person who has right to give consent can read, a witness shall be present during every discussion of subject's consent. The witness shall confirm that the consent given by the subject, legal representative or person who has right to give consent is of voluntary nature before signing and dating the Informed Consent Form. The trial staff shall not be a witness.