SOF Analysis Plan Submission Form

Date: July 11, 2011

Investigator’s Name: Mei-Ling Ting Lee, Ph.D.

Clinical Center: University of Maryland, College Park, Maryland, USA

Sponsor (if not a SOF investigator): Dr. Marc Hochberg

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Other investigators who will be working on this analysis: Xin He

Analysis Plan Title: Threshold Analysis of BMD for Risk Assessment of Fractures

Data sets to be used: visit 1 to visit 8

Primary variables to be used in the analysis: Primary predictor variables are: age, BMI, total hip BMD, femoral neck BMD, total hip BMD percent change, femoral neck BMD percent change, falls in previous years, walk for exercise, family history of fractures, smoking status, and alcohol consumption. Primary outcome variables are: hip fractures, non-spine fractures, deaths, and FRAX scores.

Do you plan to submit an abstract based on these results? ☒ YES ☐ NO
If YES, when is the abstract due? June 2012

Who will perform the analyses?
☐ Coordinating Center
☒ Other local analyst, please specify: University of Maryland

Please attach a 1-2 page description of your analysis plan. Please include the following:
1) Short background/rationale for addressing the research question
2) Brief description of statistical methods
3) Mock tables

E-mail this completed form (as an attachment) to Dana Kriesel (dkriesel@sfcc-cpmc.net).
Background:
In the past many years, relative risks of disease outcomes were often assessed by using either logistic regression or proportional hazards regressions. The logistic regression, however, does not take into account the stochastic trajectory of the longitudinal changes in health measurements and the proportional hazards model has a mathematical assumption that may not be realistic. The threshold Regression (TR) model that we developed recently [1, 5, 6] can model the trajectory of health measurements and it does not require the proportional hazards assumption.

The TR model is a relatively new approach to analyzing event-time data but has been gradually applied in a wide range of medical and health studies. The TR model is based on the fact that the onset of event occurs when the health status first crosses a critical level. Current methods of the TR models, however, are limited by the assumption of pre-specified boundary level. On the other hands, not much has been investigated on risk assessment for recurrent events. It is also important to extend the basic TR model to include longitudinal health measurements with missing and censored data. In this project we propose to extend the basic TR model for general use in practical health research.

Statistical Analysis:
Based on the TR model, we will use baseline and follow-up data to visit 8 in SOF to examine the change of BMD as a predictor of hip and non-vertebral fractures over the long term. We will give probabilistic risk assessment for long term risk of hip and non-vertebral fractures in general. Main outcome variables: days to event (fracture and death), incident fracture, death. Main covariates: age, weight and height, total hip BMD percent change, femoral neck BMD percent change. In this project, we propose to
(1) generalize the TR model by estimating the critical threshold level;
(2) provide risk assessment for fractures;
(3) generalize the TR model by considering recurrent fracture events;
(4) generalize the TR model by including censored data;
(5) generalize the TR model by including missing data;
(6) comparing the proposed fracture predictions with the FRAX model [7].

We will use BMD data from visit 2 to visit 8 data to predict fractures. Receiver operating characteristics (ROC) curve and area under the ROC curve (AUC) will be used to compare the prediction of non-vertebral fracture and mortality using our models.

References:


**Mock Table**: baseline Characteristics of women with fractures

<table>
<thead>
<tr>
<th># of subjects</th>
<th>Age, mean years (SD)</th>
<th>Date of birth</th>
<th>Weight</th>
<th>Height</th>
<th>Race</th>
<th>Current smoking</th>
<th>Alcohol use</th>
<th>Drank alcohol past 12 months</th>
<th>Mean physical activity (SD), kcal/wk</th>
<th>History of previous fracture</th>
<th>Health status</th>
<th>Grip strength</th>
<th>Diabetes</th>
<th>Oral glucocorticoid use</th>
<th>Glitazone use</th>
<th>Total hip BMD (g/cm2)</th>
<th>Femoral neck BMD (g/cm2)</th>
<th>Total hip BMD percent change</th>
<th>Femoral neck BMD percent change</th>
<th>Number of falls past 12 months</th>
<th>BMI categories</th>
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**Who will do the analysis?**
Drs. Mei-Ling T. Lee and Xin He will conduct the proposed analysis. We will discuss with Dr. Marc Hochberg on a regular basis on the progress and results of the proposed study.

**Mock Figure 1**
Risk of fractures by quartiles of spine, total hip and femoral neck BMD

**Mock Figure 2 (estimated survival curves)**
Risk of hip and non-vertebral fracture by history of hip and non-vertebral fracture

**Mock Figure 3 (estimated hazard curves)**
Risk of wrist, femur, (other types of fracture) by history of specific fracture type

**Mock Table 2:**
Relative risk for fractures for spine, femoral and total hip BMD

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<th>5 years</th>
<th>10 years</th>
<th>20 years</th>
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