**ARIC Manuscript Proposal # 1122**

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| **PC Reviewed: _11/22/05** | **Status: __A_** | **Priority: __2__** |
| **SC Reviewed: __11/23/05** | **Status: __A__** | **Priority: __2__** |

**1.a. Full Title**: Correcting the effect of CKD risk factors for measurement error

**b. Abbreviated Title (Length 26 characters)**: Measurement error and CKD

**2. Writing Group (list individual with lead responsibility first)**:

**Lead**: **Ciprian Crainiceanu**
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Writing group members: Ciprian Crainiceanu, Joe Coresh (others to be added)

**3. Timeline**: begin analysis upon approval; publish in the "Measurement Error in Nonlinear Models" book, co-authors R. Carroll, D. Ruppert and L.A. Stefanski
www.stat.tamu.edu/~carroll/eiv.SecondEdition/
A draft will be circulated draft in December 2005.

**4. Rationale**:

Risk factors such as eGFR, blood pressure and total cholesterol have been used extensively to estimate individual CKD risk. However, these risk factors are measured with, sometimes substantial, biological or instrument measurement error. Typically, the effect of measurement error is to bias the estimated effects towards the null and increase their variability. Correcting for measurement error is especially challenging in this context because eGFR has a nonmonotonic (U-shaped) effect on the hazard function.

We propose to study the effect of measurement error on risk factor estimation when some of the covariates have a non-monotonic effect on the probability of primary CKD incidence. We will use a Cox model for time to primary CKD events that, in addition to other risk factors and covariates, incorporates a flexible function (penalized spline) of the baseline eGFR. SIMEX (simulation extrapolation) will be used for inference and software will be developed and disseminated. SIMEX is a statistical methodology that injects increasing amounts of measurement error and calculates risk factor estimates (simulation) and extrapolates them back to the case of no measurement error (extrapolation).

The substantive results from this analysis have already been analyzed as part of previous manuscript proposals. The emphasis here is on the methodology. The intent is to use this

as an example in the "Measurement Error in Nonlinear Models" book, co-authored by Dr. Crainiceanu with R. Carroll, D. Ruppert and L.A. Stefanski.

**5. Main Hypothesis/Study Questions**:
Our main study hypothesis is that after adjustment for measurement error, the traditional CKD risk factors will have larger relative effects.

**6. Data (variables, time window, source, inclusions/exclusions)**:

Individuals without information on risk will be excluded.

Covariates: age, race, gender, eGFR
Outcome: Time to incident primary CKD
Analysis: SIMEX (simulation extrapolation) of Cox regression using a flexible (penalized spline) function of eGFR. Our analysis will use regression calibration and SIMEX techniques implemented in R.

**7.a. Will the data be used for non-CVD analysis in this manuscript? __ Yes __X__ No**

**b. If Yes, is the author aware that the file ICTDER02 must be used to exclude persons with a value RES_OTH = "CVD Research" for non-DNA analysis, and for DNA analysis RES_DNA = "CVD Research" would be used?**
**___ Yes ____ No**
(This file ICTDER02 has been distributed to ARIC PIs, and contains the responses to consent updates related to stored sample use for research.)

**8.a. Will the DNA data be used in this manuscript? ____ Yes _X__ No**

**8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER02 must be used to exclude those with value RES_DNA = "No use/storage DNA"?**
**____ Yes ____ No**

**9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status.** ARIC Investigators have access to the publications lists under the Study Members Area of the web site at:
http://bios.unc.edu/units/cscc/ARIC/stdy/studymem.html

__X___ Yes _____ No

**10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?**

**MP#347 approved paper:**
Marsh-Manzi, J, Crainiceanu CM, Astor BC, Powe NR, Klag MJ, Taylor HA, Coresh J, MD, Increased Risk of CKD Progression and ESRD in African Americans: The Atherosclerosis Risk in Communities (ARIC) Study.

**11. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.**

Reference List

(1) Marsh-Manzi, J, Crainiceanu CM, Astor BC, Powe NR, Klag MJ, Taylor HA, Coresh J, Increased Risk of CKD Progression and ESRD in African Americans: The Atherosclerosis Risk in Communities (ARIC) Study, submitted.

(2) Astor, BC, Jane V. R. Marsh-Manzi, J, Levin, A, Crainiceanu, CM, Josef Coresh, Moderately Decreased Hemoglobin Predicts Incident Chronic Kidney Disease in Diabetic and Non-diabetic Adults with Normal Kidney Function: The Atherosclerosis Risk in Communities (ARIC) Study