ARIC Manuscript Proposal #4049

PC Reviewed: 5/17/22 **Status: _____** **Priority: 2**
SC Reviewed: ___/___/___ **Status: _____** **Priority: ____**

1.a. Joint model framework for data with a terminal event, recurrent event, and associated longitudinal measure: A Bayesian approach

b. Abbreviated Title (Length 26 characters): Bayesian 3-way joint model

2. Writing Group:
Writing group members: Emily Damone (PhD Candidate, UNC Biostatistics), Matt Psioda (Co-Dissertation Advisor), Joseph Ibrahim (Co-Dissertation Advisor), David Couper

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _EMD_ **[please confirm with your initials electronically or in writing]**

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ARIC author to be contacted if there are questions about the manuscript and the first author does not respond or cannot be located (this must be an ARIC investigator).
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3. Timeline: Our goal is to have a draft of the manuscript by early Fall 2022 and submit the manuscript by the end of 2022.

4. Rationale: This paper is a statistical methods paper. The goal is to develop a joint model which can incorporate terminal and recurrent event data as well as longitudinal measures believed to be causally linked with the time-to-event processes. **This manuscript will not make any scientific claims about cardiovascular health with regards to ARIC participants**. The purpose of the real data analysis is to serve as a proof-of-concept for the proposed joint model.

5. Main Hypothesis/Study Questions: The joint model uses subject-specific random effects to connect the survival data (terminal and recurrent events) with a longitudinal outcome measure. Bayesian methods will be used for estimation of the model. In addition to the real data application, we will demonstrate via simulation studies that our joint modeling method provides quality point estimates for parameters of interest and we will investigate other operating characteristics (comparing to existing statistical methods). We hope to show this joint modeling approach is a flexible general model that can be utilized in a wide range of health applications and allow for development of further measures involving multiple outcomes while simultaneously accounting for underlying associations.

6. Design and analysis (study design, inclusion/exclusion, outcome and other variables of interest with specific reference to the time of their collection, summary of data analysis, and any anticipated methodologic limitations or challenges if present).

For the purpose of this manuscript, we plan to use data from cohort participants enrolled across all four ARIC Field Centers. We will use a data cut at Visit 7 for all participants in the study to avoid association with the COVID-19 pandemic.

Our terminal event of interest will be CHD death, our recurrent event of interest will be CHD related hospitalizations (MI, stroke, heart failure, or cardiac procedure), and our longitudinal measures of interest will be blood pressure (2^{nd} and 3^{rd} measure average systolic and diastolic) and cholesterol (total, HDL, and LDL).

We will use the following baseline measures as possible covariates as measured at Visit 1: sex, age, race, smoking status, and prior MI. We will explore the following time-varying measures as possible covariates measured across visits: weight, BMI, and diabetes status.

We plan to include participants lost to follow-up to help determine the method's sensitivity to censoring and dropout. Participants who were lost to follow-up but have registry-based date of death will have their deaths excluded from the analysis.

The manuscript will include sensitivity analyses to demonstrate the impact of varying the choice of prior distribution, as well as in comparisons to existing statistical methods. As such, we reiterate that the use of ARIC data will be for illustrative purposes only and acknowledge further conclusions are outside the scope of the method presented.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes __X__ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ___ Yes ____ No
(The file ICTDER 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 current derived consent file ICTDER05 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://www.cscc.unc.edu/aricproposals/dtSearch.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)?

MS1527, MS2275, MS3572

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes __X_ No

11.b. If yes, is the proposal

___ A. primarily the result of an ancillary study (list number* _____)

___ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____ _____ _____)

*ancillary studies are listed by number https://sites.cscc.unc.edu/aric/approved-ancillary-studies

12a. 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.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PubMed Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.