ARIC Manuscript Proposal #3896

PC Reviewed: 7/13/21	**Status: _____**	**Priority: 2**
SC Reviewed: _____	**Status: _____**	**Priority: ____**

1.a. Full Title: Multi-stage optimal dynamic treatment regimes for survival outcomes with dependent censoring

b. Abbreviated Title (Length 26 characters): **DTR for survival outcomes**

2. Writing Group:

Writing group members: Hunyong Cho, Shannon Holloway, Ph.D., David Couper, Ph.D., Michael Kosorok, Ph.D.

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _HC_ **[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:

We plan to analyze the ARIC data during 2021 (by October) and resubmit the manuscript to a journal by February 2022.

4. Rationale:

We have developed a dynamic treatment regime estimator for a multi-stage treatment setting that optimizes patient survival time. The ARIC study with observational data on multi-stage treatments, patient history information at each stage, and time-to-event outcomes (time to cardiovascular disease events and time to all-cause mortality) would provide an excellent

example of how the new method works. Through this data analysis component, we want to illustrate the performance of the method in comparison with the other existing methods.

5. Main Hypothesis/Study Questions:
We will investigate whether applying the aforementioned precision medicine framework would provide benefit to the risk group in terms of postponing their failure time. The method finds the optimal policy that gives physicians or patients a treatment recommendation based on the available patient information at each visit so that the time to cardiovascular disease events (and all-cause mortality time as the second question) is maximized, where treatment is to be defined in #6 below. The main aim of this ARIC data analysis is to compare our new method with existing methods in terms of their policy values, defined as the mean outcome assuming everyone follows the policy.

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).
The new method is flexible in terms of the study design—this method allows randomized trial and observational data with sufficient covariates to minimize the effects of potential confounders—although multiple clinic visits are required for each person to have the best manifestation of the method. We realize that the ARIC study is observational, and plan to use information on medications that was collected at each study visit.

The outcomes of interest include 1) time to cardiovascular disease events and 2) time to all-cause mortality. The conditions for which treatments will be considered are risk factors for cardiovascular disease, such as hypertension, hypercholesterolemia, and diabetes. Participants with and without these conditions are needed. Censoring and missing covariate information are allowed. We will consider either single risk factor that is being treated or a combination of multiple factors.

In addition to information on medication use collected at ARIC study visits, auxiliary data may include baseline information on demographics (e.g., age, race, sex, education), behavioral factors (e.g., smoking habits)., and measurements such as weight, BMI, blood glucose level, blood pressure (systolic and diastolic), and serum cholesterol level (LDL, HDL) obtained at each clinic visit.

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ____ Yes _v__ 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 __v_ 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/aric/mantrack/maintain/search/dtSearch.html

___v_ 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)?
MS2744C: Gao F, Zeng D, Couper DJ, Lin DY. "Semiparametric Regression Analysis of Multiple Right- and Interval-Censored Events." J Am Stat Assoc. 2019;114(527):1232-1240.PubMed: 31588157 : PMC6777710

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? ____ Yes __v_ 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.