ARIC Manuscript Proposal Form

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Publication Committee Review Date: **04/09/24**
ARIC Manuscript Proposal Number: **# 4429**

1.a. Full Title: Investigating the association of traditional and non-traditional tobacco product use with subclinical and clinical cardiovascular disease: The Cross-Cohort Collaboration-Tobacco working group

b. Abbreviated Title (Length 26 characters): Traditional and nontraditional tobacco products and cardiovascular outcomes

2. Writing Group [please provide a middle initial if available; EX: Adam L Williams]:

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __ET___ **[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 (The ARIC author should be involved enough in ARIC to

be able to point the lead author to appropriate ancillary study PIs and to be able to search ARIC manuscript proposals if the lead author doesn't have the access needed to do such a search).

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3. Timeline: 6 months

4. Rationale: We propose to harmonize tobacco use data across the NHLBI cohorts to create a dataset of unprecedented power for the study of the cardiovascular health effects of cigars, pipes, ST, and e-cigarettes. Our harmonized dataset will: 1) be contemporary and widely representative of the US population; 2) allow the study of these products in vulnerable and understudied groups, including women and minorities.

5. Main Hypothesis/Study Aims: Aim 1: Create a harmonized "CCC-Tobacco" dataset leveraging individual participant tobacco use data (cigar, pipe, smokeless tobacco (ST), and combustible cigarette) from each CCC cohort.
Aim 2: Evaluate the impact of the cigar, pipe, ST and combustible cigarette on biomarkers of subclinical cardiovascular injury, and cardiovascular events
Develop e-cigarette use data from the NHLBI cohorts and study the pooled association with candidate markers of cardiovascular toxicity

6. Design and analysis - please address the following aspects:

a) inclusion/exclusion

Inclusion: 1) Age ≥ 18 yrs, 2) presence of measurement of cigarette use. No exclusion.

b) study design

Guideline-driven organizational structure: In 2016, the Maelstrom research team published "Guidelines for Rigorous Retrospective Data Harmonization". The CCC-Tobacco Working Group has prepared Implementation Strategies for each of these essentials, including the formation of several committees (the Harmonization Committee, Data Use Committee, Publications, and Presentation Committee,) and scheduled activities including monthly Working Group teleconferences, and weekly Quality Control reviews. The CCC-Tobacco Working Groups has also planned the creation of a cloud-based, password-protected shareable data documentation archive.

Harmonization Methods: The CCC-Tobacco Working group has endorsed the following 6 step approach to harmonization after adaptation from TOPMed, LRPP, and Maelstrom.

Step 1: Create a relational, searchable database linking tobacco variables and their related documentation. Step 2: Clean data and translate into a consistent format. Step 3: Perform quality control on exposure phenotypes and select biomarkers. Step 4: Create harmonization algorithm for each tobacco exposure type. Step 5: Harmonize data using a fully reproducible, programmable algorithm. Step 6: Produce documentation of a harmonized dataset to allow sharing/merging with other CCC datasets.

c) outcome and other variables of interest with specific reference to the time of their collection

We requested and obtained individual-level de-identified data from all participating studies based on the following variable list. Baseline characteristics included sociodemographic variables such as age, sex, race/ethnicity, study site, education status, and income level. Past medical history, family history, and anthropometric variables including body mass index (BMI) were also requested. Measured cardiometabolic parameters including systolic blood pressure (SBP), diastolic blood pressure (DBP), total cholesterol (TC), high-density lipoprotein (HDL) cholesterol, low density lipoprotein (LDL) cholesterol, lipoprotein a [Lp(a)], and triglycerides data were requested. Data on the use of lipid-lowering therapy, anti-hypertensive therapy, anti-hyperglycemic medications, and anti-platelet medications were also collected.
Participating studies provided baseline and longitudinal data over multiple study visits on the use of cigarettes, cigars, pipes, smokeless tobacco, and e-cigarettes, as well as secondhand smoke exposure. Data on the intensity and duration of exposure including tobacco-product use-years and usage per day were also collected when available. Additionally, data on the patterns and changes in tobacco use over time such as poly-product use, product switching, and quitting were collected.
Biomarkers of subclinical cardiovascular injury based on three domains – subclinical inflammation, thrombosis, and atherosclerosis – were collected. Inflammatory biomarkers included high-sensitivity C-reactive protein (hsCRP) and interleukin-6. Thrombosis biomarkers included fibrinogen and D-dimer. Measures of atherosclerosis included CAC, carotid plaque, cIMT test readings, pulse-wave velocity, and ankle-brachial index. The most recent data on cardiovascular outcomes were requested from each participating study. The outcomes included cardiovascular events (myocardial infarction, stroke, atrial fibrillation, heart failure) and mortality (coronary, cardiovascular, and all-cause). Furthermore, harmonized time-to-event variables will be constructed for the purpose of future survival analysis.

d) summary of data analysis

The association between smoking and CVD will be analyzed using survival analysis (COX proportional hazard model). In terms of studying the association of tobacco use transitions and CVD outcomes, our team has pioneered an approach that divides each participant's experience into 'person-trials' reflecting tobacco use exposures accruing between each study visit. We have used this approach in one of our peer-reviewed publications. This technique uses a variation of latent class mixed models (LCMM).

For the non-cigarette tobacco products, the primary approach to analysis was pooled individual-level data modeling. Secondary analysis was conducted using weighted cohort-level meta-analysis. Adjusted Cox proportional hazard models were used to evaluate the association between tobacco use and the cardiovascular and mortality study outcomes.

The distribution of subclinical markers was calculated across current cigarette, cigar, pipe, and smokeless tobacco use groups as well as for the never tobacco use group, to facilitate comparison. Continuous variables were presented with means (standard deviation (SD)), or medians (interquartile range (IQR)). Categorized variables were expressed as counts (percentage).
We used multivariate linear and logistic regression to study the relationship of tobacco product use with individual markers of subclinical cardiovascular disease. For continuous markers including hs-CRP, IL-6, fibrinogen, d-dimer, CAC, and cPS we used linear regression model after natural log translation of the individual markers, as all were right-skewed. A logistic regression model was used to study the association between tobacco product use with prevalent CAC, CP, and abnormal ABI≤0.9.

All regression models were adjusted for potential confounders including sex, age, race, and cohort. Models for current non-cigarette tobacco use were additionally adjusted with smoking status.

e) Any anticipated methodologic limitations or challenges if present

Heterogeneity in cohorts' demographical population
Inconsistencies in health behavioral surveys (i.e., Tobacco use
Harmonization of outcomes considering the difference in definitions among cohorts

f) Will the author need Limited data to complete the proposed manuscript? ☐ Yes, Limited data is needed (Provide a brief (2-3 sentences) justification for requesting PHI data) [.] ☒ No, De-identified data will be sufficient.

*Please note, Limited dataset access is strict and rarely provided. Limited data includes identifiable information such as dates (birthdays, visit dates, etc.). CMS, Genomic, Geocoded, Proteomics/Somalogic, and other -omic data all fall under the limited data category. De-identified data does not include dates. All dates are date adjusted to "Days since Visit 1".

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? (Non-ARIC analysis means that the authors are not regarded as ARIC investigators and the "ARIC author" is essentially just a facilitator rather than an integral part of the writing group.) ☒ Yes ☐ 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 is distributed to ARIC PIs annually, 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 ☒ 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 or the "sponsoring" ARIC 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 website at: https://aric.cscc.unc.edu/aric9/proposalsearch [ARIC Website□Publications□Proposal Search]

☒ 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)?
NA

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or does it use current [or ongoing] ancillary study data (this includes ACHIEVE)? ☒ Yes ☐ No → Skip to question 12

11.b. If yes to 11.a., is the proposal

☒ **A. primarily the result of an ancillary study**

☐ **B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables)**

11.c. If yes to 11.a., list number* 2021.20 __

*ancillary studies are listed by number https://aric.cscc.unc.edu/aric9/researchers/ancillary_studies/approved_ancillary_studies [ARIC Website Ancillary Studies 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 https://aric.cscc.unc.edu/aric9/publications/policies_forms_and_guidelines [ARIC Website Publications Publication Policies, Forms, and Guidelines]. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

References: ____

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