ARIC Manuscript Proposal Form

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Publication Committee Review Date: **11/12/24**
ARIC Manuscript Proposal Number: **#4555**

1.a. Full Title: Trial eligibility for medications targeting cardiovascular-kidney-metabolic syndrome in large cohort studies

b. Abbreviated Title (Length 26 characters): Eligibility for CKM Medications

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

Writing group members: Louisa A Mounsey, Juhi Parekh, Chiadi Ndumele, Norrina Allen, Bruce Psaty, Daniel Levy, Rudolf de Boer, Kevin Damman, Sadiya Khan, James Floyd, Michelle Odden, Navin Suthahar, Ron Gansevoort, Dhruv Kazi, Kuni Matsushita, Joseph Coresh, Robert Yeh, Jennifer E Ho

I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. __LAM___ **[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:
Data analyses: 3 months
Manuscript preparation: 3 months

4. Rationale:
A 2024 advisory from the American Heart Association highlighted the significant morbidity and mortality associated with cardiovascular-kidney-metabolic syndrome (CKM) and the need for cohesive efforts to understand the pathophysiology, develop algorithms to predict adverse outcomes, and implement interventions for treatment and prevention.[1] In the past decade, sodium-glucose cotransporter-2 (SLGT-2) inhibitors and glucagon-like peptide-1 (GLP-1) agonists have been shown in multiple trials to improve diabetes control, contribute to weight loss, and improve cardiac outcomes. While these medications have been FDA approved following Phase III clinical trials demonstrating beneficial outcomes, examination of the trial eligibility criteria illustrates the varying populations enrolled in these trials. A prior analysis of four clinical trials of SGLT-2 inhibitors showed that only 26% to 44% of those in a large registry of diabetic patients would qualify for enrollment in one of the trials, depending on the eligibility criteria.[2] A similar analysis of the LEADER trial, examining the GLP-1 agonist liraglutide in patients with type II diabetes and high cardiovascular risk, demonstrated that only 48% of patients in the same registry would qualify for trial enrollment.[3] With the FDA approval of additional SGLT-2 inhibitors and GLP-1 agonists, and the recent publication demonstrating beneficial heart failure outcomes with the non-steroidal mineralocorticoid receptor antagonist (nsMRA) finerenone, it is crucial to understand the population of patients being studied in each of these medication trials.[4] While the primary outcome studied may be similar, there are marked differences in the eligibility criteria and thus the enrolled population that benefitted from use. In this analysis, we will qualitatively describe the patients from pooled cohort studies who meet trial eligibility criteria. By understanding the populations these medications have been studied on, we can determine if future studies on specific groups who also may benefit are indicated.

5. Main Hypothesis/Study Aims:
We hypothesize that application of eligibility criteria from large randomized controlled trials for evolving cardiometabolic therapies (including glucagon-like peptide-1 (GLP-1) agonists, sodium-glucose cotransporter-2 (SLGT-2) inhibitors, and non-steroidal mineralocorticoid receptor antagonists (nsMRAs)) to patients across longitudinal community-based cohort studies will (1) elucidate potential broader therapeutic eligibility across the community and (2) illuminate differences between specific therapies as applied to clinical samples within the context of clinical trials vs community-based samples.

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

1. To elucidate potential therapeutic eligibility of evolving cardiometabolic therapies (GLP-1 agonists, SLGT2 inhibitors, and nsMRAs) among community-based samples by applying key trial eligibility criteria as defined by randomized controlled trials.

2. To compare clinical characteristics and overlap between community-based samples that are found therapy-eligible with RCT trial patients specific to medication class.

3. To examine incident clinical cardiovascular outcomes among those found therapy-eligible among the community, including major adverse cardiovascular disease and all-cause death. We will specifically compare event rates across different trials within each medication class, with secondary comparisons to RCT placebo groups in the respective clinical trials.

Study Sample:
Pooled individual-level clinical data from 5 longitudinal community-based cohorts: (1) Multi-Ethnic Study of Atherosclerosis, (2) Framingham Heart Study (FHS), (3) Atherosclerosis Risk in Communities (ARIC), (4) Cardiovascular Health Study (CHS), and (5) and the Prevention of Renal and Vascular Endstage Disease (PREVEND).

Specific cohorts to be included:
- **MESA**: Participants who attended the baseline exam (2000–2002)
- **FHS**: Participants who attended Offspring examination 6 (1995–1998)
- **ARIC**: Participants who attended visit 2 (1990-1992)
- **CHS**: Participants who attended the baseline examination (1989–1990; 1992–1993 for supplemental African-American cohort)
- **PREVEND**: Participants who attended baseline exam (1997–1998).

Exclusion Criteria: missing key clinical covariates.

Analysis Plan for Aim 1: To elucidate potential therapeutic eligibility of evolving cardiometabolic therapies (GLP-1 agonists, SLGT2 inhibitors, and nsMRAs) among community-based samples by applying key trial eligibility criteria as defined by randomized controlled trials.

- We will create a table comparing eligibility criteria for each major clinical trial with cardiovascular outcomes for GLP-1 agonists, SLGT2 inhibitors, and nsMRAs to highlight the different criteria both between and within medication classes.
- In a pooled cohort of patients from MESA, FHS, ARIC, CHS, and PREVEND, sequentially apply inclusion criteria from the major clinical trials for GLP-1 agonists (i.e. LEADER, SUSTAIN-6, PIONEER-6, FLOW), SGLT-2 inhibitors (i.e. CANVAS-R, DELIVER, DAPA-HF, DAPA-CKD, EMPA-KIDNEY), and nsMRAs (i.e. FINEARTS-HF, FIDELIO- DKD, FIGARO-DKD) followed by exclusion criteria to determine the proportion of patients included/excluded at each step and the final trial-eligible population.

- We will examine summary statistics including proportion of individuals eligible for a cardiometabolic therapy based on each trial.

Analysis Plan for Aim 2: To compare clinical characteristics and overlap between community-based samples that are found therapy-eligible with RCT trial patients specific to medication class.

- We will examine overlap in therapy-eligible samples (1) between trials within the same medication class; (2) between medication classes.
- We will examine summary statistics of these overlapping samples, and further compare demographics and clinical characteristics between therapy-eligible samples. We will also examine differences in clinical characteristics between community-based and summary statistics from clinical trial participants.

Analysis Plan for Aim 3: To examine incident clinical cardiovascular outcomes among those found therapy-eligible among the community, including major adverse cardiovascular disease and all-cause death. We will specifically compare event rates across different trials within each medication class, with secondary comparisons to RCT placebo groups in the respective clinical trials.

- We will examine incident cardiovascular outcomes among therapy-eligible samples. Our primary outcome will be MACE (major adverse CV events, defined as cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) and secondary outcomes will be cardiovascular death, nonfatal myocardial infection, heart failure hospitalization, and all cause mortality.
- Specifically, we will examine 1- and 5-year event rates, as well as age- and sex-adjusted incidence rates for each therapy-eligible sample

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)?

The greatest overlap is with prior work led by Chiadi Ndumele, the sponsoring ARIC author and active collaborator for this project.

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* __

*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:

1. Ndumele CE, Rangaswami J, Chow SL, et al. Cardiovascular-Kidney-Metabolic Health: A Presidential Advisory From the American Heart Association. *Circulation*. 2023;148(20):1606-1635. doi:10.1161/CIR.0000000000001184
2. Wittbrodt E, Chamberlain D, Arnold SV, Tang F, Kosiborod M. Eligibility of patients with type 2 diabetes for sodium-glucose co-transporter-2 inhibitor cardiovascular outcomes trials: An assessment using the Diabetes Collaborative Registry. *Diabetes Obes Metab*. 2019;21(8):1985-1989. doi:10.1111/dom.13738
3. Arnold SV, Inzucchi SE, Tang F, et al. Real-world use and modeled impact of glucose-lowering therapies evaluated in recent cardiovascular outcomes trials: An NCDR® Research to Practice project. *Eur J Prev Cardiol*. 2017;24(15):1637-1645. doi:10.1177/2047487317729252
4. Finerenone in Heart Failure with Mildly Reduced or Preserved Ejection Fraction | New England Journal of Medicine. Accessed September 6, 2024. https://www.nejm.org/doi/full/10.1056/NEJMoa2407107

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