1.a. Full Title:
Individual participant data meta-analysis of risk factors of atherosclerosis in Africans, Asians, Europeans and North-Americans: a USE-IMT & H3Africa AWI-Gen Collaborative study

b. Abbreviated Title (Length 26 characters):
USE-IMT & H3Africa AWI-Gen Collaborative study

2. Writing Group:
Writing group members:
AWI-Gen: Engelbert A. Nonterah, Nigel J. Crowther, Alisha N. Wade and Lisa K. Mcklesfield
USE-IMT/UMCU: Michiel L. Bots, Kerstin Klipstein-Grobusch, Maryam Kavousi, and Hester M. de Ruijter

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

First author: Michiel L. Bots
Address: Julius Center for Health Sciences and Primary Care
         University Medical Center Utrecht
         Heidelberglaan 100, 3584 CX Utrecht, The Netherlands
         Phone: +31 8 755 9352
         E-mail: m.l.bots@umcutrecht.nl

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).

Name: Gregory Evans
Address: Department of Neurology
         Ward A. Riley Ultrasound Center
         Piedmont Plaza II, Suite 504, 2000 W. First St. \ Winston-Salem, NC 27104
         Phone: 336.716.5814 \ Fax: 336.716.5813
         E-mail: gevans@wakehealth.edu<mailto:gevans@wakehealth.edu>
3. **Timeline:**
   - Request approved: August 2019
   - ARIC data already available: ARIC was part of USE-IMT in 2011 onwards
   - Analyses: October 2019
   - Writing: October – November 2019
   - Manuscript for sharing: December 2019

4. **Rationale:**
   **Introduction**
   Cardiovascular diseases (CVDs) are the leading cause of deaths globally with a quarter of these deaths occurs in low-middle income countries (LMIC) and is projected to increase further (1). CVDs can be prevented by addressing key risk factors. Identification of at risk population through early screening is therefore important in management resource. Associations of risk factors may or may not be the same across populations and the relative strength/magnitude of effect may also differ. This therefore means a differential priority in control the risk factors across different population is required. To determine this, it is imperative to understand the prevailing risk factors across populations. In this collaborative study, we propose to conduct a meta-analysis of individual participant data (IPD) from the Use intima-media thickness (USE-IMT) (2) and African-Wits-INDEPTH partnership for Genomic study (AWI-Gen) (3, 4) to test this hypothesis has previously not been tested. We envisage an IPD as a good approach that will be clinically and statically sound analyses over aggregate level analyses as used in conventional systemic reviews and meta-analysis.

   ARIC can contribute to this project in several important ways. ARIC has unique data to address racial differences, in particular information for African-Americans is an important contribution to the project hypothesis. Also ARIC has detailed information established cardiovascular risk factors and on carotid intima media thickness. As we have already used this information in the USE-IMT initiative, we recognize its importance.

5. **Main Hypothesis/Study Questions:**
   The main aim is to examine the difference in risk to atherosclerosis across different populations and to examine the strength of these risks. Specifically we hypothesize that:
   1. Risk factors associated with atherosclerosis may differ between Caucasians, Asian, diasporan Africans and Africans living in SSA.
   2. The magnitude of effect of these relationships across the study populations any also differ highlighting need for differential targets for the control of CVDs

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).**
   Cross-sectional study design. The Inclusion criteria will be participants 35 years and older with **baseline** CIMT measurements and selected risk factors of interest. These variables of interest include
classical cardiovascular risk factors such as age, sex, smoking, body mass index, blood pressure, alcohol consumption, glucose and serum lipids (cholesterol, LDL, HDL). Additional information of interest includes history of and treatment for hypertension, diabetes, dyslipidemia and CVD.

For the ARIC study, we already have this information as we used the ARIC data in the USE-IMT initiative.[den Ruijter HM, et al JAMA 2012]

Data
USE-IMT has data for Europeans, North-Americans and Asians (2) while the AWI-Gen study has data on Africans living in sub-Saharan Africa (SSA) (3, 4). We envisage both studies to be useful resources for studying the differential effects of CVDs risk factors and atherosclerosis in these populations which represent a larger global community.

The proposed study population shall comprise a total of potentially 19 cohorts, 18 cohorts from the USE-IMT and the AWI-Gen cohort. The Inclusion criteria will be participants 35 years and older with baseline CIMT measurements and selected risk factors of interest. These variables of interest include classical cardiovascular risk factors such as age, sex, smoking, body mass index, blood pressure, alcohol consumption, glucose and serum lipids (cholesterol, LDL, HDL). Additional information of interest includes history of and treatment for hypertension, diabetes, dyslipidemia and CVD.

For the ARIC study, we already have this information as we used the ARIC data in the USE-IMT initiative.[den Ruijter HM, et al JAMA 2012]

Brief analysis plan and methods
We shall summarise descriptive characteristics of the populations using counts and frequencies for categorical data and means (±SD) for normally distributed categorical variables or median (IQR) for skewed continuous data. Population will be stratified into major ethnic groups (e.g. Africans, diasporan Africans, Asians, North Americans and Europeans or Africans, diasporan African, Asians and Caucasians). Differences in risk factors and mean CIMT distribution will be reported along those lines. To determine the factors associated with CIM we adopt a multilevel modeling approach to account for the clusters of studies involved in each ethnic groupings. This will enable as account for across and within ethnic group differences conferred by the different studies will preserving the original design and composition of the study. The outcome variable shall be computed as a mean of right and left CCA IMT and of all available angles measured. Model building shall be in the sequence of age and sex as model 1, age, sex and behavioural factors as model 2 and age, sex, behavioral factors plus metabolic risk as model 3. Model 4 shall include model 3 + history of CVD and history of medication use. To enable comparison of the magnitude of effect we seek to standardize the measures of CIMT by calculating sex and site specific z-scores. Standardized beta estimates will be used to determine the change in CIMT () per SD of the risk factors across the populations. A 2-sided p<0.05 will be considered statistically significant.
Summary/conclusion
The study will be able to demonstrate in a single paper a direct comparison of the different factors associated with CIMT among four major ethnic groupings in the continent. We would also be able to determine the magnitude of effect of relations across the various populations. This will be of great public health importance because it will enable us to identify priority interventions to reduce ASCVDs. The use of IPD will also confer on this study additional advantages including but not limited to: standardized statistical analyses methods across sites, specific subgroup (e.g. ethnicity) analyses can be performed across the various studies and statistical power is improved allowing for adjustment for confounding factors (5).

7.a. Will the data be used for non-CVD analysis in this manuscript? _____ Yes   _xxx No

b. If Yes, is the author aware that the file ICTDER03 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 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   _xxx No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the file ICTDER03 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

_____ Yes   _xxxx_____ No
Not possible since I am not an ARIC investigator. But very unlikely that this initiative is already ongoing.

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)?

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? _____ Yes   _xxxx___ 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 at https://www2.csc.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.csc.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.