1.a. **Full Title**: A Genome-Wide Association Study for HDL-Cholesterol, LDL-Cholesterol and Triglycerides in ~11,000 African Americans

b. **Abbreviated Title (Length 26 characters)**: CARe African American Lipid GWAS

2. **Writing Group**: Includes members from the CARe Project
   - ARIC: Eric Boerwinkle, Christie Ballantyne, Kelly Volcik
   - JHS: Jim Wilson, Ervin Fox
   - CARDIA: Myriam Fornage, Kiang Liu
   - MESA: Stephen Rich, Bruce Psaty, Jerry Rotter
   - Broad: Sekar Kathiresan, Stacey Gabriel
   - Cleveland Family Study: Susan Redline
   - Penn: Dan Rader
   - Others are welcome…

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

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3. **Timeline**:
   - Genotyping for all African Americans of the ARIC cohort for the Affy 6.0 is complete.
   - Genotyping for all African Americans of the participating CARe cohorts (JHS, CARDIA, MESA, CFS) is either complete or near completion. Analyses will begin immediately in the ARIC cohort; all other cohort analyses will begin as their genotyping is completed.

4. **Rationale**:
   - Elevated levels of high-density lipoprotein cholesterol (HDL-C), low-density lipoprotein cholesterol (LDL-C) and triglycerides (TG) are heritable causal risk factors for cardiovascular disease, particularly with regards to certain population subgroups (e.g. African Americans)\(^1\)\(^3\).
Recently, association mapping using common variants and genetic resequencing efforts have proven useful in identifying novel and established genetic contributors to HDL-C, LDL-C and TG measures\textsuperscript{4-7}. If successful, the proposed research should identify new genes related to blood HDL-C, LDL-C and TG in African Americans. Knowledge of such genetic determinants could have substantial preventive and treatment implications.

5. Main Hypothesis/Study Questions:
We hypothesize that common DNA sequence variants at additional novel loci are associated with HDL-C, LDL-C and TG in non-European populations. Specifically, we propose to evaluate this hypothesis by testing a genome-wide set of polymorphisms for association with blood HDL-C, LDL-C and TG in African Americans from the CARe project. CARe represents a compelling resource, comprised of ~11,000 African American participants from multiple studies with measured lipid phenotypes.

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).
We will construct sex- and cohort-specific residual HDL-C/LDL-C/TG values after two adjustment schemes: a) age and sex; and b) a full set of clinical variables shown to affect HDL-C/LDL-C/TG values (e.g. BMI, lipid lowering medications). All analyses will be restricted to African Americans. Additionally, analyses will be repeated after excluding those persons taking lipid lowering medications. We will conduct genotype-phenotype association using linear regression assuming an additive model (additional genetic models will be tested for top hits). To summarize the statistical evidence across cohorts, we will conduct a variance-weighted meta-analysis. We will also compare results obtained from the current proposal to previously published results from studies in whites.

Each cohort will have performed standard quality control checks for their datasets. We will verify that each dataset we receive meets these standard criteria (i.e. excess missingness, low MAF, excess homozygosity, HWE, etc.). These quality control checks will be implemented using PLINK. Analyses will be done in PLINK, which performs linear regression and allows for the adjustment of covariates, as well as taking into account imputation and including permutation tests to adjust for multiple comparisons.

7.a. Will the data be used for non-CVD analysis in this manuscript? ___Yes _X_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

8.a. Will the DNA data be used in this manuscript? _X__ Yes ____ 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”? _X_ 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. ___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)?

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

11.b. If yes, is the proposal
   _X_ A. primarily the result of an ancillary study (list number* _2007.02_)
   ____ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* ______________________)

12. 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.  **Agree**

References