1.a. Full Title: Genome-wide association study of pulmonary function: joint meta-analysis of two consortia – CHARGE and SpiroMeta.

b. Abbreviated Title (Length 26 characters): GWAS of PFTS:CHARGE/SpiroMeta Meta-Analysis

2. Writing Group:
   Writing group members: Stephanie London, Dana Hancock, Laura Loehr, Kari North, Nora Franceschini, Alanna Morrison, David Couper, and other interested ARIC investigators.

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

First author: Stephanie London
Address: NIEHS, PO Box 12233, MD A3-05, RTP NC 27709

Phone: 919-541-5772 Fax: 919-541-2511 Email: london2@niehs.nih.gov

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: Kari North
Address: UNC
137 E. Franklin St., Suite 306
Campus Box 7435
Chapel Hill, NC

Phone: 966-2148 Fax: 966-9800 Email: kari_north@unc.edu

   Draft manuscript to MS committee by June 2009
   Submit to journal by September 2009
4. **Rationale:**

This manuscript is a direct follow-up ARIC MP# 1357r which Genome-Wide Association Study (GWAS) of Pulmonary Function and Chronic Obstructive Pulmonary Disease (COPD). In this manuscript, we analyzed GWAS data from the CHARGE consortium in relation to FEV1 and FEV1/FVC, two major pulmonary function measures. We replicated 30 SNPs that represented our genome-wide and nearly genome-wide loci in a second consortium from the UK called SpiroMeta. CHARGE and SpiroMeta submitted paired manuscripts to Nature Genetics and these are both in press. The CHARGE manuscript is being published as “Meta-analyses of genome-wide association studies identify multiple loci associated with pulmonary function”. In our meta-analysis, the Q-Q plots suggest a substantial deviation from expectation below the genome-wide significance level suggesting that there are other SNPs that merit follow-up. SpiroMeta has proposed that they take the lead on a complete joint meta-analysis of the data from the CHARGE cohorts and SpiroMeta along with several new cohorts that are joining with CHARGE or SpiroMeta. SpiroMeta has funding for follow-up genotyping of top hits.

5. **Main Hypothesis/Study Questions:**

To identify additional novel genes/loci associated with pulmonary function (FEV1 and FEV1/FVC) by doing a joint meta-analysis of cohorts in CHARGE and SpiroMeta for a combined GWAS sample size of more than 42,000.

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).**

GWAS output that was already generated from ARIC for the Nature Genetics paper in press will be combined with GWAS output from other CHARGE cohorts as well as the cohorts in SpiroMeta. The meta-analysis will be done by Martin Tobin and his group at SpiroMeta and it will be checked by a CHARGE analyst. The same software (METAL) and analytic techniques and annotation pipeline will be used as were used in the Nature Genetics paper. We will be looking for SNPs that reach genome wide significance that did not rise to this level in the CHARGE only analysis. Some number of top hits will be genotyped in a number of cohorts that are affiliated with SpiroMeta. SpiroMeta will do and fund this replication genotyping. SpiroMeta is anxious to do this analysis and manuscript quickly and this should be feasible because all of the cohorts have already done the necessary GWAS.

No individual data needs to be shared with SpiroMeta in order to do this manuscript – only the GWAS result files for FEV1 and FEV1/FVC. The GWAS was run using Probabel. A data sharing agreement will be signed by all co-authors to protect
confidentiality of the findings through the analysis and submission process. The agreement also contains language regarding authorship.

7.a. Will the data be used for non-CVD analysis in this manuscript?  ____x__ Yes  ____ 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 ICTDER03 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?  ____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. ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: http://www.cscc.unc.edu/ARIC/search.php

    ____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)?

    1360- discontinued and folded into 1357
    1384 Genome-Wide Association Study (GWAS) of Pulmonary Function and Chronic Obstructive Pulmonary Disease (COPD) – interaction with traffic exposure in ARIC
    1357 and 1357r Genome-Wide Association Study (GWAS) of Pulmonary Function and Chronic Obstructive Pulmonary Disease (COPD)
    1562 Genome Wide Association Study of interaction with smoking in relation to pulmonary function and COPD

11. a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  ____ Yes  ____x__ 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 http://www.cscc.unc.edu/aric/forms/

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.