1.a. Full Title: Antiphospholipid antibodies (APLAs) as a risk factor for premature cardiovascular events in African-Americans

b. Abbreviated title (Length 26 characters): PLAs in African-Americans

2. Writing Group (List the individual with lead responsibility first):
   Robert W. McMurray, M.D. University of Mississippi Medical Center
   Principal Investigator

   Andrew Brown, M.D. University of Mississippi Medical Center

   Daniel Jones, M.D. University of Mississippi Medical Center

   William D. Johnson, Ph.D. University of Mississippi Medical Center,
   Biostatistician

   Coordinating Center Representative

   Additional ARIC Field site investigators as appropriate

   Lead: Division of Rheumatology
   L525 clinical Sciences Building
   UMMC
   2500 North State Street
   Jackson, Mississippi 39216
   Phone: 601-984-5540 Fax:601-984-5535
   E-mail: rupus1@hotmail.com

3. Timeline:

   Proposal prepared 3/1/00
   Publications Committee Review and Recommendations 4/1/00
   Proposal Priority Set 5/1/00
   Dataset Requests/Analysis/Assays 6/1/00
   Writing Group preparation of Draft manuscript 12/1/00
   Distribution of manuscript 2/1/01
   Official Analysis/Data Verification 4/1/01
   Steering Committee/NHBLI approval 6/1/01
   Submission to Journal 7/1/01
4. Rationale:

Racial differences in cardiovascular events (stroke and myocardial infarction) are known to exist, with African Americans having a higher morbidity, mortality, and incidence of stroke and myocardial infarction compared to Caucasians. Young blacks (<65 years of age) lose more years of life compared to whites due to cardiovascular disease among hypertensives. While higher frequencies of hypertension, diabetes, elevated lipoprotein levels, and low socioeconomic class have been identified as risk factors, other potentially treatable factors have not been fully elucidated.

It is known that blacks have higher immunoglobulin concentrations, higher incidences of autoimmune diseases (e.g. SLE, scleroderma, and dermatomyositis), and an increased frequency of autoantibodies compared to whites. Recent evidence has suggested that antiphospholipid antibodies such as lupus anticoagulant (LAC) or anticardiolipin antibodies (ACA) are associated with thrombotic events. Others have shown that the adjusted odds ratio for stroke for any positive (IgG or IgM) anticardiolipin antibody titer was 3.9, perhaps higher than previously suspected. In preliminary studies, African-Americans have been shown to trend towards a higher incidence of lupus anticoagulant or anticardiolipin antibodies compared to whites. However, few studies have directly investigated the hypothesis that the increased incidence, morbidity, or mortality of cardiovascular events in blacks is due to the presence of lupus anticoagulants or anticardiolipin antibodies. Initial regression analysis of ARIC data by Folsom et al. have shown that hemostatic parameters (vWF, FVIIIc, white blood cell count, fibrinogen) correlate with ischemic stroke, supporting the concept that abnormalities of hemostatic and inflammatory markers are associated with increased risk of stroke. Aggressive intervention in patients with this potential risk factor may reduce the excessive cardiovascular morbidity and mortality in African-Americans.

5. Main Objectives:

African-Americans with premature (<60 years of age) stroke or myocardial infarction (MI) have an increased incidence of lupus anticoagulant or anticardiolipin antibodies (IgM, IgG, or IgA) compared to age- and sex-matched Caucasians

6. Data (variables, time window, source, inclusions/exclusions)

In a case-control manner the following variables would be compared:

**Variables – Controlled** – age, sex, hypertension, diabetes, hyperlipidemia, smoking, obesity, stroke, myocardial infarction

**Variables – Measured** – aPTT, platelet count (thrombocytopenia in association with LAC), C-reactive protein, and, if available, IgM/IgG/IgA anticardiolipin antibodies and dilute Russell viper venom time. Measurement of these variables in serum through an ancillary study proposal, if necessary.

**Time window** – ARIC study timeline using the baseline visit (visit 1) as the measured immune parameter source with prospective case ascertainment of stroke, myocardial infarction, and coronary heart disease cases.
Methods – Comparison of lupus anticoagulant and anticardiolipin antibody incidence between African-American and Caucasian cardiovascular cases will be made as well as comparison between race/sex/age matched controls.

<table>
<thead>
<tr>
<th>Cardiovascular Disease</th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Race</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>-</td>
</tr>
<tr>
<td>African-American</td>
<td>Control APLAs</td>
<td>Case APLAs</td>
</tr>
<tr>
<td>Caucasian</td>
<td>Control APLAs</td>
<td>Case APLAs</td>
</tr>
</tbody>
</table>

As a second level of analysis, a comparison of associations between APLAs and cardiovascular events will be made across racial groups (i.e. stratify on race and compare quartiles of APLAs). Ultimately odds ratios (as estimates of relative risk) for cardiovascular events could be made by comparing the upper quartile of measured APLAs with the lower quartile.

Source – ARIC study and nested cohorts with available serum for additional testing if necessary

Expected results – If the hypothesis were true, we would expect that African-Americans with premature stroke or MI would have an increased incidence of LAC or APLAs compared to Caucasians and to race/sex/age matched controls.