1. Full Title: Association of the interleukin-1 gene cluster with carotid intimal-medial wall thickness
   Abbreviated Title (Length 26): IL-1 gene cluster and IMT

2. Writing Group (list individual with lead responsibility first):
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   ** Investigators from Medical Science Systems and the University of Sheffield will be added to the writing
   group if the study results are released into the public domain prior to submission of the full manuscript.

3. Timeline:
   Successful genotyping of the ultrasound case-cohort sample has been completed for four single-nucleotide
   variants in the IL-I gene cluster known to be related to the inflammatory response. Data analyses are expected to
   be completed within 2-3 months of starting, and the start is expected to be around Oct 1, 1998.

4. Rationale:
   Inflammation is a critical component of endothelial cell damage, atheroma formation and calcification, and
   vascular smooth muscle cell proliferation. IL-1 proteins have been implicated as critical mediators of this
   process. Recently, our collaborators have indicated that variation within the IL-1 gene cluster is associated with
   increased production of IL-1 alpha and beta proteins and decreased levels of IL-1 receptor antagonist. The net
   effect is a genetic conformation that confers a hyperinflammatory phenotype. Thus, we hypothesize that these
   IL-1 polymorphisms may be associated with subclinical atherosclerosis. This first manuscript on IMT will
   focus on the independent effects of the four loci as part of a larger effort to characterize the role of the IL-1 gene
   cluster in subclinical atherosclerosis. Subsequent papers will examine multiple-locus (i.e., haplotype) effects as
   well as more complex analyses with other potential mediating factors.

5. Main Hypothesis:
   Variation in the IL-1 gene cluster independently contributes to predictive models of carotid intimal-medial wall
   thickness in the presence of known risk factors.

6. Data (variables, time window, source, inclusions/exclusions):
IL-1 genetic variants were measured in the ultrasound cases, including supplementary African-American ultrasound cases and controls, as well as the cohort random sample. Visit 1 variables in the analyses will include, but are not limited to, the standard AHA risk factors: hypertension status, diabetes status, smoking status, blood lipids, age, and gender. IMT will be analyzed in cross-sectional mode as both a continuous and categorical variable, using methods to account for the stratified random sample nature of the data.