1. Full Title: Association of the interleukin-1 gene cluster with incident CHD
   Abbreviated Title (Length 26): IL-1 gene cluster and CHD

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 incident CHD case-cohort sample has been completed for four single-nucleotide variants in the IL-1 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:
   Increasing evidence suggests that inflammatory responses play a critical role in the etiology of coronary artery disease including thromboembolic events. Recently, our collaborators have reported that specific IL-1 gene polymorphisms are associated with increased biological activity of IL-1 proteins, which play a key role in the inflammatory response. Clinical studies by this group have indicated that a variant in the IL-1 receptor antagonist gene (IL-1RN +2016) is associated with single-vessel artery disease with an odds ratio of 2.4 for the heterozygous individuals and 5.4 for the homozygous individuals (chi[squared] = 8.56, p<0.005; Fisher's Exact; CI=6-17.97). This was the first evidence relating IL-1 gene variation to inflammatory responses and coronary clinical events. This significant finding in a relatively small study (n=63 controls, 45 cases) prompted a rapid genotyping effort in the much larger ARIC population. These data will ultimately enable us to characterize the IL-1 genetic contribution and putative gene-environment interactions in the context of known cardiovascular risk factors. This first paper 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 CHD morbidity and mortality. 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 has an independent association with incident coronary heart disease in the presence of known risk factors.
6. Data (variables, time window, source, inclusions/exclusions):
IL-1 genetic variants were measured in the incident CHD cases 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. Analysis will be case-cohort analysis as accomplished through the SAS macro by Barlow, respecting the stratified random sample nature of the "cohort random sample."