1.a. **Full Title**: Epidemiologic Implications of the Cardiac Arrest Case Definition

b. **Abbreviated Title (Length 26 characters)**: Epidemiology of Cardiac Arrest

2. **Writing Group**:
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3. **Timeline**:
   Final physician case adjudication by July 1, 2005  
   Data analysis and preliminary tables by October 1, 2005  
   Revised tables by December 1, 2005  
   Draft manuscript by March 1, 2006  
   Revised manuscript by May 1, 2006  
   Final manuscript for ARIC review July 1, 2006
4. **Rationale:**

Sudden cardiac arrest (SCA) represents a considerable health burden. However, the exact magnitude of the burden varies substantially with estimates ranging from 200,000 to nearly 500,000 persons suffering SCA annually in the U.S. The magnitude of uncertainty is likely due in part to the method of SCA case definition. Moreover, how these different case definitions influence SCA - risk factor associations is uncertain.

Studies reporting estimates of incidence have typically used a single case definition. In some instances, cases of SCA have been derived either solely from death certificate or emergency medical services records. In death certificate studies of SCA, “sudden cardiac arrest” is identified using death codes indicative of heart disease and a location of death (outside the hospital or in the emergency room) that is a surrogate for an unexpected or “sudden” event. Evidence suggests that incidence based on death certificate methods may overestimate SCA risk. Estimates based on emergency medical services records constitute potentially “treatable” cases but do not consider instances where emergency medical services are not involved; circumstances that may preclude treatment but not preclude SCA prevention. Neither method typically incorporates a rigorous review of medical records to assure that the arrest was due to underlying heart disease rather than a noncardiac cause.

Still another approach incorporates multiple data resources (death certificate, medical records) and uses a physician review panel to identify SCA. This method typically requires that the SCA event occur within a finite time window after the onset of symptoms (i.e. 1 hour), a requirement that often necessitates knowledge of the precise circumstances of the event and consequently may exclude some cases of SCA. Finally, none of these studies include in-hospital SCA events. “Sudden and unexpected” arrests due to heart disease occur in hospitalized patients but the magnitude and composition of this group relative to out-of-hospital SCA is unknown.

No single study has evaluated how different case definitions influence SCA incidence or SCA-risk factor associations. Using the data resources of the Cardiovascular Health Study (CHS) and the Atherosclerosis Risk In the Community (ARIC) Study, this investigation will assess the epidemiologic implications of different SCA case definitions. Specifically, the investigation will assess how SCA incidence, the clinical profile (gender, age, clinical composition of SCA case), and risk factor associations vary across SCA case definitions that use death certificate identification and physician adjudication.

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

We hypothesize that the SCA case definition will influence SCA incidence, the clinical profile, and in some instances the risk factor associations.

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

**Methods Overview**

To accomplish the study aims, the investigators will systematically review all deaths due to heart disease from ARIC and CHS to classify SCA events. An SCA adjudication form has been
developed and piloted (attached). After classifying SCA status, we will assess how incidence, demographic and clinical profile of SCA, and risk factor association vary across the different SCA case definitions. The project will be undertaken as part of the Reynolds Project (PI Burke) to create a common ARIC and CHS data set to study SCA.

**Study Population:**
The study population will include all participants from CHS and ARIC.

**Outcomes**

*SCA case definition*
The primary outcome of interest is SCA. The SCA outcome will be assessed using different case definitions that relate to previously published methodologies. Sudden cardiac arrest will be defined as:

1. death certificate codes indicating death due to underlying heart disease that occurs outside the hospital or in the emergency department. This method adopts the approach used by the Center for Disease Control in some of their publications.
2. death adjudicated by a physician panel to be a sudden pulseless condition without a known non-cardiac cause. The case definition does not necessarily exclude unwitnessed events or events with long-duration prodromal symptoms.

Sensitivity analyses will evaluate the influence of exclusion or inclusion of SCA cases depending on witness status, duration of prodromal symptoms, clinical comorbidity (i.e. renal disease), or in-hospital versus out-of-hospital location.

**Variables of interest**
Variables of interest will include demographic, clinical, exam, medication, and diagnostic characteristics. Demographic characteristics include age, gender, race, and geographical region. Clinical characteristics include common cardiac risk factors such as diabetes, smoking, diet, lipids, and hypertension, and clinical heart disease (congestive heart failure, myocardial infarction) status. Exam information includes resting heart rate and blood pressure. Diagnostic information include echo and electrocardiogram variables as well as subclinical markers of atherosclerosis such as results of carotid ultrasound, C-reactive protein, and measures of renal function. Medication exposures include antihypertensive, digoxin, and antiarrhythmic medications.

**Analytical approach**
In the first stage of the project, we will classify SCA events using a standardized classification form (attached). This approach has been piloted in CHS using definition #2 above with ~85% inter-reviewer agreement. Discordant cases will be adjudicated by a third reviewer.

Using the different case definitions, we will estimate incidence of SCA (events per 1000 person-years), the profile of SCA victim, and the association of particular risk factors with the different SCA outcomes. Additional analyses are planned for groups defined by age, gender, race, and clinical group status. For the association analyses, we will use Cox proportional hazards regression. Persons will enter the analysis at study onset and be followed until an SCA event or censoring event (end of follow-up, death from other cause).
Tentative tables and figures
1. Case definitions
2. Number of SCA cases and concurrence of case identification across the different definitions.
3. Incidence estimates overall and for subgroups according to SCA definitions
4. Comparison of demographic and clinical characteristics of SCA cases across the different definitions including the discordant cases
5. Risk factor associations for the different SCA definitions

Summary
The investigation will provide new information about the epidemiological implications of using different SCA case definitions and help distinguish specific risk factors for SCA.

References
7.a. Will the data be used for non-CVD analysis in this manuscript?  ____ Yes  ____ No

b. If Yes, is the author aware that the file ICTDER02 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 ICTDER02 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?  ____ 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 ICTDER02 must be used to exclude those with value RES_DNA = “No use/storage DNA”?  ____ 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.csecc.unc.edu/ARIC/search.php

____ 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)?

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

11.b. If yes, is the proposal

____ A. primarily the result of an ancillary study (list number* Reynolds)

____ B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* __________ __________ __________)

The proposed analysis is supported in part by the Reynolds Foundation (PI Greg Burke). The effort will combine data sources from ARIC and the Cardiovascular Health Study to better study determinants of sudden cardiac arrest in the community.

*ancillary studies are listed by number at http://www.csecc.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.