1.a. Full Title: Mortality in Parkinson Disease: The PEACE Consortium

b. Abbreviated Title (Length 26 characters): Mortality in PD

2. Writing Group:
   Writing group members: Alvaro Alonso, Alexa Beiser, Robert Boudreau, Honglei Chen, Samuel Frank, Jayandra Himali, Xuemei Huang, Samay Jain, Margaret Kelly-Hayes, Caterina Rosano and Sudha Seshadri

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

First author: Samuel Frank, MD
Address: 72 East Concord St., C3
         Boston, MA 02118

         Phone: 617-638-8647   Fax: 617-638-5354
         E-mail: samfrank@bu.edu

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: Alvaro Alonso
   Address: 1300 S 2nd St, Suite 300
            University of Minnesota
            Minneapolis, MN 55454
            Phone: 612-626-8597
            E-mail: alonso@umn.edu

3. Timeline: This study began funding in September 2014 and is expected to last one year. A meta-analysis is in planning and we plan to have preliminary data to present in the spring 2015.

4. Rationale: Although mortality associated with Parkinson disease (PD) has been extensively studied, debate continues about its rate and cause. We propose to build upon
previous studies and seek modifiable factors that may impact mortality. Such knowledge may lead to interventions allowing patients with PD to live longer.

Most studies of PD mortality are not community-based in nature, so results are not easily generalizable. Often studies that are population-based in nature lack a reference population or are conducted in international settings where treatment and healthcare systems may substantially differ from those in the US. We will address limitations of previous studies by constructing an inception cohort of incident PD meta-analyzing results from three population-based studies in the US: Framingham Heart Study (FHS), Cardiovascular Health Study (CHS), and the Atherosclerosis Risk in Communities Study (ARIC). All are studies of cardiovascular disease in which PD has been previously identified and in which follow-up extends up to 20 years from baseline. We will also construct a reference group among those without PD matched by age and sex.

5. Main Hypothesis/Study Questions:
Our specific aims are:
1. Assess whether PD is associated with risk of all-cause mortality. We hypothesize that PD is associated with an increased risk of all-cause mortality.
2. Characterize causes of death in those with and without PD, and assess the strength of association between PD and deaths related to cardiovascular disease, infections, and injuries. We hypothesize that PD is associated with increased risk of death from infectious disease and injuries, but a decreased risk of death from cardiovascular disease.
3. Explore whether the association between PD and all-cause mortality is modified by sex, age at onset, uric acid concentration, and smoking status. We hypothesize that the association between PD and all-cause mortality will be stronger among men, people with younger ages of PD onset, with lower uric acid levels, and among non-smokers

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).
Our study is a retrospective cohort design based on secondary data previously obtained as part of ARIC, FHS, and CHS. Within each cohort study, we will construct an inception cohort in which those with incident PD will be matched to five people without PD based on age, sex, and calendar year. Baseline will be defined as the incident date among those with PD, and the matching date for those without PD. All subjects will be followed for time to death. We will also document causes of death, age at PD diagnosis, urate levels, date of urate measurement, and smoking status proximal to index date. Once the analysis is completed in each cohort, the University of Pittsburgh will coordinate the meta-analysis.

Inclusion/exclusion criteria:
In ARIC, we will include all confirmed diagnosed PD cases and a sample of matched individuals without PD. Patients will be excluded if they did not consent for non-CVD analyses or had missing values in any of the relevant covariates.

**PD diagnosis**
Cases of PD have been identified from several sources: ICD9 codes from hospitalizations, self-report, use of PD-related medications. Validation of cases has been conducted through contact with participants, proxies and their physicians as described in submitted manuscripts MS#1176 and MS#1316.

**Covariates**
Age, sex, race, smoking, serum uric acid, body mass index, total serum cholesterol, blood pressure, diabetes, prevalent CVD,

**Outcome**
All-cause and CVD mortality

**Statistical analysis**
Cohort-specific Cox proportional hazards model with time to death as main outcome variable. ARIC analyses will be performed at the University of Minnesota. Results from ARIC will be pooled with CHS and FHS using a random-effect model.

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 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 ICTDER 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 ICTDER03 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:  
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)?
No previous manuscripts in ARIC have looked at outcomes among participants with PD.

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

11b. If yes, is the proposal
   __X__ A. primarily the result of an ancillary study (list number* 2009.19, 2014.17)
   _______ 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/

12a. 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.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is your responsibility to upload manuscripts to PUBMED Central whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in http://www.cscc.unc.edu/aric/index.php, under Publications, Policies & Forms. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to Pubmed central.