1.a. **Full Title:** Estimating SPRINT Post-Trial Cardiovascular Disease Events and Survival Using Pooled Epidemiological Cohort Data (R01HL139837)

b. **Abbreviated Title (Length 26 characters):** Post-Trial Survival in SPRINT

2. **Writing Group:**

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

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**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).

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3. **Timeline:** This study is funded by the U.S. NHLBI (R01HL139837; project period December 1, 2017 to November 30, 2021). Following approval of this manuscript proposal, the analyses will be completed within six months and the full manuscript within one year.

4. **Rationale:**
High blood pressure is a leading cause of death worldwide, and is the largest modifiable cardiovascular disease (CVD) risk factor.\(^1\,\!\!^2\) Intensive blood pressure lowering with antihypertensive medications is safe, reduces morbidity and mortality, and is cost-effective.\(^3\,\!\!^4\) However, only about half of individuals have blood pressure controlled to currently recommended goals and lowering blood pressure even further to the intensive goals in Systolic Blood Pressure Intervention Trial (SPRINT) may be difficult and costly for local healthcare systems.\(^5\,\!\!^6\) Identification of individuals who may have the greatest CVD benefit and smallest risk as well the long-term costs, health consequences, and cost-effectiveness in these individuals will aid local healthcare systems in implementation decisions.

Alongside trials cost-effectiveness analyses use patient-level trial data to estimate the economic and health consequences of interventions in trial participants. However, best practices state that cost-effectiveness estimates should extend beyond the duration of the trial to the full life course, necessitating estimates and assumptions about treatment effects after the end of the trial period.\(^7\) In order to assess the long-term costs and health consequences of intensive blood pressure lowering in our SPRINT ancillary study, appropriate estimates of these outcomes are needed in SPRINT-eligible individuals.\(^4\)

Methods for extrapolating survival from observed trial data, e.g., Gompertz regression and survival tables from national sources, exist and are commonly used in alongside trial cost-effectiveness analyses.\(^8\) While these methods are commonly used, they require many assumptions about the underlying data that do not necessarily represent the trial-eligible populations.\(^9\)

We therefore propose to draw from SPRINT individual participant data and data from the Columbia University National Heart, Lung, and Blood Institute (CU-NHLBI) Pooled Cohorts Study to estimate the long-term CVD event risk and survival of SPRINT-eligible individuals in order to extrapolate beyond the observed trial data and estimate related life expectancy among SPRINT participants.

5. **Main Hypothesis/Study Questions:**
**Specific Aim 1:** Identify a representative cohort of SPRINT-eligible individuals from the CU-NHLBI Pooled Cohorts Study and propensity score match them to SPRINT participants.

**Specific Aim 2:** Describe the lifetime CVD event risk and survival of SPRINT participants when extrapolating beyond the observation period using the SPRINT-matched CU-NHLBI Pooled Cohorts Study as well as other methods (e.g., standard Gompertz regression).
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).

We propose to use harmonized and pooled individual-level data from the main ARIC study with similar data from several other NIH-funded prospective cohort studies (related ancillary study proposals in progress for CARDIA, CHS, MESA, Framingham Offspring, and Health ABC). We will include individuals meeting the SPRINT eligibility criteria from the CU-NHLBI Pooled Cohorts Study (N=41,360). To be included, individuals must have the following characteristics:

(1) age ≥50 years;
(2) systolic blood pressure 130-180 mm Hg; AND
(3) have ≥1 high CVD risk condition (i.e., clinical coronary heart disease, estimated glomerular filtration rate 20-59 mL/min/1.73 m², Framingham 10-year CVD risk score ≥15%, or age ≥75)

Individuals with diabetes, a history of stroke, history of heart failure, an estimated glomerular filtration rate <20 mL/min/1.73 m², or missing data on key covariates will be excluded.

Statistical analyses. SPRINT-eligible individuals in the CU-NHLBI Pooled Cohorts Study will be propensity score matched in a 1:1 ratio to SPRINT participants using a “greedy nearest neighbor” approach with calipers. Propensity score matching will occur at the baseline visit for SPRINT participants and the first SPRINT-eligible visit for individuals in the CU-NHLBI Pooled Cohorts. Covariates in the propensity score will include systolic blood pressure (defined at the time of propensity score matching), as well as the baseline covariates listed above; interactions between covariates will be considered. Covariate balance between groups will be determined using standardized mean differences (SMD), with an SMD >0.1 indicating poor covariate balance.

We will use the lifetime CVD risk and survival of the SPRINT-matched CU-NHLBI Pooled Cohorts to extrapolate the SPRINT observed data. We will plot time-to-event outcomes using Kaplan-Meier curves. We will estimate CVD event risk and survival using multivariable Cox proportional hazards models with time-varying covariates. We will then compare this to other methods of extrapolation, including time-varying multivariable Gompertz survival models, which can be used to extrapolate treatment effects over a lifetime using different treatment effect scenarios. The survival models will use the covariates described above to predict survival and generate survival curves. We will also use a US life table approach to extrapolate survival. We will use the observed mortality in SPRINT, stratified by age group, sex, and race, and US life tables to estimate the number of years of lives lost.

7.a. Will the data be used for non-CVD analysis in this manuscript? ____ Yes    __X__ 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
8.a. Will the DNA data be used in this manuscript?  ____ Yes  __X__ 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:  http://www.cscc.unc.edu/aric/mantrack/maintain/search/dtSearch.html

____X____ 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)?

No prior ARIC manuscript proposals have examined the survival of SPRINT-eligible ARIC participants in order to estimate survival after the end of the observed SPRINT trial period. Other proposals examining long-term patterns of blood pressure and risk of CVD events include:

<table>
<thead>
<tr>
<th>MS#</th>
<th>Title</th>
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<tbody>
<tr>
<td>1852</td>
<td>Systolic blood pressure levels among adults with hypertension and incident cardiovascular events: the atherosclerosis risk in communities study</td>
</tr>
<tr>
<td>2146</td>
<td>Longitudinal Patterns of Change in Systolic Blood Pressure and Incidence of Cardiovascular Disease: The Atherosclerosis Risk in Communities Study</td>
</tr>
<tr>
<td>2823</td>
<td>Stroke, CHD and CVD risk by blood pressure, BMI and anti-hypertensive categories</td>
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</tbody>
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11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data?  ____ Yes  __X__ No

11.b. If yes, is the proposal

____ A. primarily the result of an ancillary study (list number* __________)  
____ 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 https://www2.cscc.unc.edu/aric/approved-ancillary-studies
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.

References: