1.a. Full Title: Using Medicare Part D Phase to Identify Effects of Medication Adherence

b. Abbreviated Title (Length 26 characters):

2. Writing Group:
   Writing group members: Carla A. Sueta, Jo Ellen Rodgers, Orly Vardeny, Carlos Rodriguez, Sally Stearns, Alan Brookhart, Patty Chang, others welcome

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

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3. Timeline:

We expect final data file construction to take 2 months. We expect the analysis to be completed within 4 months. The short time is feasible because final construction of the data file is similar to the process used for MS 1951.
4. Rationale:

Nonadherence to medications among heart failure patients is associated with poor outcomes. In Denmark, nonpersistence (break in therapy > 90 days) was linked to increased mortality in 107,092 patients discharged after 1st hospitalization with heart failure.1 In the US, nonadherence has been associated with increased all-cause mortality and cardiovascular hospitalizations.2,3 This association remained significant when all 3 classes of heart failure medications (ACE-I/ARB, BB, aldosterone antagonists) and when the components of the composite end point were considered separately. Increased readmissions,4 more Emergency Departments visits,5 subsequent higher length of stay,6 and higher health care cost4 have also been linked to nonadherence.

Nonadherence to heart failure medications has been reported to be between 11 and 48%.2,4,7 Some studies have reported nonadherence rates for individual classes of medications: 11-65% for ACE-I/ARB, 19-43% for beta blockers, and 58-87% for aldosterone antagonists.2,8,9 Many of these studies have used annual rates of adherence. A recent study of hospitalizations with heart failure in the ARIC cohort that measured medication adherence using Medicare Part D claims showed that despite having Part D coverage, patient-level medication adherence after discharge declined over time for three medication classes studied [angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (ACEI/ARB), beta blockers (BB), or diuretics].10 The largest decline occurred over 2 to 4 months after discharge, followed by a plateau over the subsequent year. Across the three medications, adherence at one month (70% - 76%) declined to 53% - 62% at 12 months.

While the decline in monthly medication adherence following discharge likely results in poor outcomes (high rates of readmission or death) for patients, treatment selection may bias estimates of the potential effect of improvements in adherence on outcomes. For example, the higher rates following discharge and decline in monthly adherence rates may reflect unobserved aspects of prognosis that are associated both with likelihood of adherence and likelihood of bad outcomes. Patients who are inherently sicker in unmeasured ways may be less likely to be adherent and more likely to be readmitted. Observational studies try to control for all observed covariates that may be associated with both adherence and outcomes, but observed measures are often not sufficient.

Instrumental variable (IV) approaches have been proposed as an alternative way to reduce treatment selection bias.11,12 An IV is a factor that is directly related to the choice of treatment, but it is not directly related to the patient outcome (and is also not indirectly related to patient outcome through unmeasured variables).12 The association of the treatment (i.e., adherence to HF medications) with outcomes is estimated in a two-equation process that provides an estimate of the “local average treatment effect,” which is the estimated effect of the treatment (i.e., improved adherence) on outcome for someone whose choice of treatment was affected (changed) by the instrumental variable.

Medicare Part D drug coverage, which was implemented in 2006, provides price variation within a benefit period that arguably could serve as an instrumental variable. Specifically, prices faced by Medicare beneficiaries with Part D but without other
coverage (e.g., without Medicaid or retiree health insurance coverage) vary over the course of a year as follows:

- 100% copay for the first $250 in drug costs (i.e., a deductible);
- 25% copay for drug costs from $250 to $2,250;
- 100% copay for drug costs from $2,250 to $5,100 (the “donut hole”); and
- 5% copay for drug costs in excess of $5,100.

Researchers have demonstrated a demand response to changes in price experienced by consumers over the course of a year, though the response may include anticipatory behavior (i.e., a person who thinks they will spend out of the donut hole may be more likely to buy drugs even with a 100% copay than someone who thinks they may not spend out of the donut hole).\textsuperscript{13} The Part D copay would be best as an instrument if the price changes occurred randomly throughout the year; instead, this anticipatory behavior could compromise the validity of the Part D copay as an IV. Regardless, HF patients often have high levels of comorbidity and are taking drugs for other conditions. Therefore, the changes in copay that beneficiaries hospitalized with HF experience over the course of the year following discharge arguably could be a good instrument to identify the effect of medication adherence on outcomes for HF patients during the year following discharge.

5. Main Hypothesis/Study Questions:

The main research question to be addressed is:

- Using the Part D copay as an instrumental variable, is higher adherence to HF medications during months 2-12 following discharge from hospitalization for HF associated with reduced monthly likelihood of poor outcomes (hospital readmission, observation stays/ED use, or death).

Tentatively, we will assess three classes of medication (ACEI/ARB, beta blockers, and diuretics) in either separate or combined models.

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).

The treatment (adherence) and outcomes will be measured on a person-month basis for months 2-12 among patients who do not have death or readmission within 30 days of discharge. We much limit our analysis and the research question to months 2-12 following discharge for two reasons:

1. First and most important, to avoid confounding treatment and outcome, we need to observe the treatment during a period (month) prior to the month in which
outcome is observed. We will therefore model outcomes each month as a function of adherence in the prior month.

2. For the first 30 days following discharge, we don’t have a measure of adherence prior to that month. (Furthermore, 30 day outcomes are being addressed in a second analysis for MS 1951, though not as a function of adherence.)

We will use data on all ARIC cohort HF hospitalizations from the cohort community surveillance from 2006-2012 for cohort members enrolled in Medicare Part D. The sample, which will be derived from the sample used for MS 1951, has 5,349 person months of data for 952 hospital HF discharges for 541 cohort members. Although the sample is defined by hospital discharge for acute decompensated or chronic HF, we will use information from all hospitalizations as well as observation stays and ED visits to identify outcomes. A unique feature of this analysis is the inclusion of observation stays and emergency room visits as outcomes. Since Medicare has imposed financial penalties for hospitals with high risk-adjusted 30 day readmission rates, observation stays have significantly increased as readmission rates have declined.\textsuperscript{14}

The estimation model will consist of two equations:

- The first equation will have a dependent variable of adherence [measured as a dichotomous indicator of whether the person had \textgreater 80\% proportion ambulatory days covered (PADC) during a 30-day period “month”] as a function of a number of patient measures (demographics and case mix measures from the hospital record abstraction) and dummies indicating the Part D copay/phase during the month. The dummies will be interacted with Medicaid status to control for the fact that Medicaid covers most of the copay amount.

- The second equation will model outcome as a function of the same patient measures and medication adherence.

Two estimation approaches will be considered. The first and main estimation approach will be bivariate probit, which provides joint estimation of the two equations and accounts for the recursive adherence measure (which is a dependent variable in the first equation and an explanatory variable in the second equation). The second method will explore the use of “two stage residual inclusion” (2SRI) given recent work by methodologists (Anirban Basu and Norma Coe) showing that this methods provides improved estimates when dealing with rare outcomes and does not have some of the parametric assumptions of the bivariate probit model. All models will adjust the standard errors for multiple observations per person and will control for whether the person had at least one hospitalization in the prior year. We will conduct statistical tests of the instrumental variable including assessments of the strength of the instrument, the first stage estimation results, the distribution of patient risk factors across levels of the IV and treatment, and other tests as appropriate to the statistical methods.
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
(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 __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/search.php

__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)?

MS 1951 (prior MS with Carla Sueta as lead)

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 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.cscn.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.

13. Per Data Use Agreement Addendum for the Use of Linked ARIC CMS Data, approved manuscripts using linked ARIC CMS data shall be submitted by the Coordinating Center to CMS for informational purposes prior to publication. Approved manuscripts should be sent to Pingping Wu at CC, at pingping_wu@unc.edu. I will be using CMS data in my manuscript __X__ Yes ____ No.

REFERENCES


