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9 **Department of Veterans Affairs Cooperative Studies Program**

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16 **CSP#597: Diuretic Comparison Project (DCP)**  
17 **a proposal from the Point of Care Program**

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**Diuretic Comparison Project (DCP)**

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71 **A. Executive Summary**

72 Thiazide-type diuretics have been in use for more than 50 years and are considered in JNC-7 and  
73 VA guidelines to be the first-line treatment for hypertension. Of the more than 1 million  
74 veterans prescribed a thiazide-type diuretic each year, more than 95% receive  
75 hydrochlorothiazide, and fewer than 2.5% receive chlorthalidone. However, indirect evidence  
76 has been accumulating for many years that chlorthalidone may be more effective than  
77 hydrochlorothiazide at preventing cardiovascular events, by about 20% according to a recent  
78 network meta-analysis. Possible mechanisms for such an effect include longer duration of  
79 action, better nighttime blood pressure control, and pleiotropic effects of chlorthalidone. A  
80 randomized trial comparing the effect of the two drugs on cardiovascular outcomes has never  
81 been conducted, primarily for reasons of cost.

82 We are proposing a new type of efficient, less expensive randomized trial (termed a "clinically  
83 integrated" or "point of care" trial) to answer the question of whether chlorthalidone is more  
84 effective than hydrochlorothiazide at preventing cardiovascular outcomes in older patients with  
85 hypertension. Our primary outcome will be a composite consisting of: stroke, myocardial  
86 infarction, non-cancer death, urgent coronary revascularization, and hospitalization for acute  
87 congestive heart failure. We plan to enroll patients over age 65 years currently prescribed  
88 hydrochlorothiazide 25 or 50 mg daily with no recent systolic blood pressure below 120 mm Hg,  
89 and randomize them to either continue on hydrochlorothiazide or receive open-label  
90 chlorthalidone at suggested doses of 12.5 or 25 mg, respectively.

91 To have a 90% power with 2-sided  $\alpha = 0.05$  to detect a 17.5% reduction in the expected 3% per  
92 year primary outcome occurrence rate in the hydrochlorothiazide group, we plan to randomize  
93 13,500 patients (270 patients per center at 50 centers) over 3 years and follow them for a mean  
94 of 3 years, for a total study duration of 4.5 years.

95 The key feature of our design is that, instead of employing local investigators, we substitute  
96 centralized study processes and rely on usual primary care. Specifically, this involves: 1)  
97 identification of eligible patients using the VA electronic medical record system (EMR), 2)  
98 centralized recruitment and enrollment, involving permission from the patient's primary care  
99 provider, an 'opt-out' patient recruitment letter, and informed consent obtained by telephone,  
00 3) centralized placement of notes and orders using the VA EMR, 4) all patient care including  
01 the study drug to be managed by the primary care provider, and 5) centralized passive  
02 collection of outcomes and process variables using the VA EMR, Medicare, and other national  
03 VA and non- VA databases.

**I. Abbreviations and Acronyms**

|    |            |   |
|----|------------|---|
| 04 |            |   |
| 05 | ACCOMPLISH | Avoiding Cardiovascular Events in Combination Therapy in Patients Living  |
| 06 |            | with Systolic Hypertension  |
| 07 | ACCORD     | Action to Control Cardiovascular Risk in Diabetes Trial                   |
| 08 | ACE        | Angiotensin Converting Enzyme   |
| 09 | ACEI       | Angiotensin Converting Enzyme Inhibitors                                  |
| 10 | ACME       | Automated Classification of Medical Entities                              |
| 11 | AHA        | American Heart Association  |
| 12 | ALLHAT     | Antihypertensive and Lipid-Lowering Therapy to Prevent Heart Attack Trial |
| 13 | ANBP2      | Second Australian National Blood Pressure Study                           |
| 14 | ARB        | Angiotensin Receptor Blocker  |
| 15 | ARIC       | Atherosclerosis Risk in Communities                                       |
| 16 | BIRLS      | Beneficiary Identification and Records Locator Subsystem database         |
| 17 | CAC        | Clinical Application Coordinator  |
| 18 | CBOC       | Community Based Outpatient Clinics  |
| 19 | CDW        | Corporate Data Warehouse  |
| 20 | CFR        | Code of Federal Regulations   |
| 21 | CHD        | Coronary Heart Disease  |
| 22 | CHF        | Congestive Heart Failure  |
| 23 | CI         | Confidence Interval   |
| 24 | CPRS       | VA Computerized Patient Record System                                     |
| 25 | CSP        | Cooperative Studies Program   |

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|    |       |   |
|----|-------|---|
| 26 | CSPCC | Cooperative Studies Program Coordinating Center   |
| 27 | CSR   | Clinical Sciences Research and Development        |
| 28 | CSSEC | Clinical Sciences Scientific Evaluation Committee |

|         |  |
|---------|--|
| CVD     | Cardiovascular Disease   |
| DM      | Diabetes Mellitus  |
| DMC     | Data Monitoring Committee  |
| DoD     | US Department of Defense   |
| ECG     | Electrocardiography  |
| EMR     | Electronic Medical Record  |
| EHR     | Electronic Health Record   |
| EXAMINE | EXamination of cArteriovascular outcoMes with alogliptIN versus standard of carE in patients with type 2 diabetes mellitus and acute coronary syndrome |
| FDA     | US Food and Drug Administration  |
| HCTZ    | Hydrochlorothiazide  |
| HDFP    | Hypertension Detection and Follow-up Program   |
| HF      | Heart Failure  |
| HIPAA   | Health Insurance Portability and Accountability Act  |
| HR      | Hazard Ratio   |
| ICD-9   | International Classification of Disease, 9th edition.  |
| ICD     | Internal Cardiac Defibrillator   |
| IRM     | Information Resource Management  |
| ISO     | Information Security Officer   |
| JNC-7   | Seventh Report of the Joint Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure  |
| meq/L   | Milli-equivalents per liter  |
| mg      | Milligram  |
| MI      | Myocardial Infarction  |
| mmHG    | Millimeters of Mercury   |
| MRFIT   | Multiple Risk Factor Intervention Trial  |

|    |                  |  |
|----|------------------|--|
| 30 | NHLBI            | National Heart, Lung, Blood Institute                                  |
| 31 | NIH              | National Institutes of Health  |
| 32 | PACT             | Patient Aligned Care Team  |
| 33 | PBM              | VA Pharmacy Benefits Management  |
| 34 | PCP              | Primary Care Provider  |
| 35 | PEACE Trial      | Prevention of Events with Angiotensin-Converting Enzyme Inhibition PHI |
| 36 |                  | Protected Health Information   |
| 37 | POC-CT           | Point of Care Clinical Trial   |
| 38 | PROBE            | Prospective, Randomized, Open-label, Blinded-Endpoint Trial            |
| 39 | SBP              | Systolic Blood Pressure  |
| 40 | SHEP             | Systolic Hypertension in the Elderly Population Trial                  |
| 41 | SPRINT           | Systolic Blood Pressure Intervention Trial                             |
| 42 | SOP              | Standard Operating Procedure   |
| 43 | TOMHS-T          | Treatment of Mild Hypertension Study                                   |
| 44 | TRACER           | Thrombin-Receptor Antagonist Vorapaxar in Acute Coronary Syndromes     |
| 45 | (TRA2°P)-TIMI 50 | Thrombin Receptor Antagonist in Secondary Prevention of                |
| 46 |                  | Atherothrombotic Ischemic Events Trial                                 |
| 47 | UK NICE          | United Kingdom National Institute for Health and Care Excellence       |
| 48 | VA               | US Department of Veterans Affairs                                      |
| 49 | VAMC             | VA Medical Center  |
| 50 | VIREC            | VA Information Resource Center   |
| 51 | VISN             | Veterans Integrated Service Network                                    |
| 52 | WHO              | World Health Organization  |



## II. Study Question

Does treatment with chlorthalidone reduce cardiovascular outcomes compared with hydrochlorothiazide in older patients with hypertension?

## III. Background and Rationale

### A. Diuretics for hypertension

Hypertension is the most common primary diagnosis in America (1), and 3 of the 10 most commonly prescribed drugs in the US are antihypertensive agents (2). Thiazide-type diuretics are recommended as first line therapy by VA/DoD hypertension guidelines (3) and by the Seventh Report of the Joint Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7). JNC-7 noted that "diuretics have been virtually unsurpassed in preventing complications of hypertension" and as a result "should be used in drug treatment for most patients with uncomplicated hypertension" (4). In a network meta-analysis of 42 trials involving 192,478 patients randomized to active drug treatment for hypertension vs. placebo, low-dose diuretics (usually hydrochlorothiazide or the thiazide-type diuretic chlorthalidone) were "the most effective first-line treatment for preventing the occurrence of cardiovascular disease morbidity and mortality" (5).

### B. Hydrochlorothiazide and chlorthalidone

Nearly all thiazide-type diuretic prescriptions in the U.S. are for hydrochlorothiazide. Hydrochlorothiazide is among the top 10 most commonly prescribed drugs in the US (2), with 135 million prescriptions written annually (6). In the VA national outpatient prescription database, of the more than 1 million veterans prescribed a thiazide-type diuretic each year from 2003-8, more than 95% received hydrochlorothiazide, and fewer than 2.5% received chlorthalidone (7). From our own search of the subsequent 3-year period 2009-11, 1.5 million veterans received hydrochlorothiazide from the VA and 50,000 received chlorthalidone.

The nearly universal use of hydrochlorothiazide has been attributed to a variety of factors, including 1) early aggressive marketing by its manufacturer (Merck) using "the largest pharmaceutical sales force in the world" (8), 2) its use in the early landmark VA hypertension treatment trials, 3) its early and frequent inclusion into combination pills, numbering at least 28 preparations (8), and 4) the ease of abbreviation to "HCTZ", which may influence physician preference (9).

Both drugs have been approved by the FDA and in use for more than 50 years, have long been available as generics, and are included in the VA national formulary in the same drug class: USP code CV 701, thiazide-related diuretics. There is no patient characteristic that influences the choice between these two drugs - it is based solely on physician preference.

87 C. Drug dosages

88 Both drugs were once commonly used at doses of 100 mg per day and higher, but by 1990,  
89 concern over the lack of reduction in coronary events from blood pressure reduction by  
90 thiazides (despite proven efficacy for stroke), and further concern that this might be due to  
91 competing harms (particularly ventricular arrhythmias) from thiazide-induced metabolic  
92 abnormalities, led to recommendations to use lower doses of diuretics, including suggestions  
93 to use 12.5 mg of hydrochlorothiazide (10).

94 In the early 1990's, publications of randomized dosing trials from the VA cooperative study  
95 group concluded that the doses of 25-50 mg of hydrochlorothiazide were nearly as effective as  
96 higher doses at controlling blood pressure with fewer adverse metabolic effects, favoring the  
97 use of 25 mg and a maximum dose of 50 mg (11,12). Several randomized dosing trials of  
98 chlorthalidone found 12.5 mg per day to be effective, and found 25 mg per day to be nearly as  
99 effective as higher doses with fewer adverse metabolic effects (13,14). Since then, doses of  
100 12.5- 25 mg per day have been widely used (15) and rarely exceeded for both drugs, with higher  
101 doses accounting for only 7% of VA prescriptions in 2008 (7). However, several authors have  
102 pointed out that hydrochlorothiazide doses lower than 25 mg have not been shown to reduce  
103 cardiovascular outcomes and have performed poorly in randomized trials (6). As a result, JNC-8  
104 recommends target doses of 25-50 mg per day for hydrochlorothiazide and 12.5-25 mg per day  
105 for chlorthalidone (16).

106 D. MRFIT – the first evidence that chlorthalidone may be more effective

107 Despite the near universal use of hydrochlorothiazide in the U.S., evidence has accumulated over  
108 the past 30 years suggesting that chlorthalidone may be more effective at reducing  
109 cardiovascular outcomes. The first indication was from the Multiple Risk Factor Intervention  
110 Trial (MRFIT), a large randomized trial of a multi-component 'special intervention' to prevent  
111 cardiovascular events in which either hydrochlorothiazide or chlorthalidone could be used as  
112 first-line treatment of hypertension in the special intervention arm. During the study, clinics that  
113 used hydrochlorothiazide were noted to have 44% more coronary heart disease deaths than  
114 those using chlorthalidone. In 1980, the MRFIT Policy Advisory Board changed the protocol,  
115 recommending chlorthalidone over hydrochlorothiazide for initial therapy, and lowered the  
116 maximum dose to 50 mg. Mortality in the former hydrochlorothiazide clinics subsequently  
117 dropped 28% (which could, of course, partially reflect regression to the mean). A recent analysis  
118 of the use of chlorthalidone and hydrochlorothiazide within MRFIT reported significantly fewer  
119 cardiovascular events with chlorthalidone, though the findings of this non-randomized  
120 comparison are confounded by large differences in dosage, randomized group, and lipid lowering  
121 (17). A separate non-randomized analysis of MRFIT data concluded that chlorthalidone was  
122 associated with less left ventricular hypertrophy than hydrochlorothiazide (18).

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225 E. Indirect comparisons of randomized trial data

226 Because of the MRFIT observations, most subsequent NIH-funded blood pressure trials have  
227 used chlorthalidone, including the Hypertension Detection and Follow-up Program (HDFP), the  
228 Systolic Hypertension in the Elderly Program (SHEP), the Treatment of Mild Hypertension Study  
229 (TOMHS), and the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial  
230 (ALLHAT), and in the ongoing Systolic Blood Pressure Intervention Trial (SPRINT), it is  
231 'preferred'. The use of chlorthalidone in these trials and of hydrochlorothiazide in many other  
232 trials has enabled indirect comparisons of the effects of the two drugs against a third drug or  
233 class. Thus, hydrochlorothiazide resulted in worse outcomes than an ACE inhibitor (enalapril) in  
234 men in the Second Australian National Blood Pressure Study (ANBP2) (19), and worse outcomes  
235 than amlodipine (with all patients receiving benazepril) in the Avoiding Cardiovascular Events in  
236 Combination Therapy in Patients Living with Systolic Hypertension (ACCOMPLISH) trial (6),  
237 whereas in ALLHAT, chlorthalidone was found to be superior to an ACE inhibitor (lisinopril) or  
238 amlodipine "in preventing 1 or more major forms of CVD" (though there was no difference in the  
239 primary outcome) (20). These and other indirect comparisons have recently been combined into  
240 a focused network meta-analysis that estimated a 21% risk reduction ( $p < .0001$ ) in  
241 cardiovascular events with chlorthalidone relative to hydrochlorothiazide that persisted (as 18%,  
242  $p = .024$ ) in an analysis adjusted for attained blood pressure (21).

243 F. Relative Potency

244 Several studies have found chlorthalidone to have about twice the potency of  
245 hydrochlorothiazide (22,23,24) and this is reflected in the VA Pharmacy Benefits Management  
246 (PBM) 2009 evidence review (25). Two indirect meta-analyses have reported similar  
247 conclusions. Ernst et al (26) found that at identical doses, chlorthalidone had a greater effect  
248 than hydrochlorothiazide on lowering blood pressure. Pederzan et al (27) considered the 2  
249 drugs to have equivalent effects at equally potent doses, which they considered to be 3 to 1.  
250 Despite these indications of greater potency, in practice chlorthalidone is not used in lower  
251 doses than hydrochlorothiazide (7,28,29). This may reflect greater awareness of appropriate  
252 thiazide dosing by the small proportion of prescribers who use chlorthalidone, rather than  
253 widespread belief that the potencies are equivalent. There is essentially universal agreement  
254 among experts that chlorthalidone at 12.5 or 25 mg is equipotent to hydrochlorothiazide at 25  
255 or 50 mg (respectively).

256 G. Possible differences between the two diuretics

257 No randomized trials have been conducted that directly compare clinical (e.g., cardiovascular)  
258 outcomes of chlorthalidone and hydrochlorothiazide, but several short-term randomized trials

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have examined blood pressure and metabolic effects. Two recent short-term (10 and 12 weeks) randomized double-blind trials of 609 and 1071 patients (respectively) compared blood pressure

control and adverse effects when taking chlorthalidone 25 mg or hydrochlorothiazide 25 mg in patients also taking an angiotensin receptor blocker (ARB) (30,31). In both studies, chlorthalidone resulted in lower systolic blood pressure by at least 5 mmHg in clinic and, in the larger study, by 24 hour ambulatory recording.

Chlorthalidone is known to have a longer duration of action than hydrochlorothiazide. The elimination half-life of chlorthalidone is 50-60 hours compared with 9-10 hours for hydrochlorothiazide (32). Ernst et al (23) randomized 30 patients to either chlorthalidone 12.5mg/day, titrated to 25 mg/day or hydrochlorothiazide 25 mg/day, titrated to 50mg/day. After 8 weeks, there was no significant difference in office systolic blood pressure (SBP), but 24-h ambulatory SBP favored chlorthalidone over hydrochlorothiazide:  $-12.4 (\pm 1.8)$  vs.  $-7.4 (\pm 1.7)$  mmHg, respectively,  $P = 0.054$ , an effect primarily driven by the lower nighttime SBP for chlorthalidone compared with hydrochlorothiazide:  $-13.5 (\pm 1.9)$  and  $-6.4 (\pm 1.8)$  mmHg, respectively,  $P = 0.009$ . Of note in this regard, large observational studies have found nighttime blood pressure to be a better predictor of cardiovascular outcomes than daytime blood pressure (33,34).

A recent in vitro study reported that chlorthalidone reduced epinephrine-induced platelet aggregation and increased angiogenesis more than the thiazide bendroflumethiazide (35). There have been no reports of any related clinical effects (e.g., increased bleeding), but these mechanisms could help to explain differences between thiazides in reducing vascular events (36).

In summary, given the longer duration of action, better nighttime blood pressure control, and possible pleiotropic effects of chlorthalidone, it is possible that chlorthalidone and hydrochlorothiazide could have different long-term effects on cardiovascular outcomes even at doses that result in similar office blood pressures.

#### H. Drug costs

Although both drugs are inexpensive generic products, chlorthalidone costs the VA seven times as much as hydrochlorothiazide. According to VA Pharmacy Benefits Management (PBM), the cost to the VA for hydrochlorothiazide 50 mg is 1.6¢ per tablet and for chlorthalidone 25mg is 11¢ per tablet (with half doses costing half as much). Thus if the approximately 1 million VA patients using hydrochlorothiazide (nearly all on 12.5 or 25 mg) were switched over to chlorthalidone 12.5 mg at an additional cost of 5¢ per day, the total increased cost would be about \$18 million per year.

#### I. Comparative metabolic effects

295 Thiazide diuretics have a variety of metabolic effects. They generally lower serum sodium (36)  
296 and potassium (27,38) levels and increase blood sugar (39,40) and uric acid (27,41) levels. In a  
297 small randomized trial (42), hydrochlorothiazide 50 mg per day lowered potassium by a mean of

0.44 meq/L more than placebo, regardless of whether potassium supplements or triamterene were added. Perhaps the best source of information on the effect of thiazides comes from ALLHAT, which randomized 33,357 patients with hypertension: 15,255 to chlorthalidone and 9000 each to amlodipine and lisinopril. Overall, chlorthalidone was considered superior to the other drugs in preventing cardiovascular events (20). The year-1 incidence of hypokalemia (<3.5 meq/L) was higher with chlorthalidone (12.9%) than with lisinopril (1.0%) or amlodipine (2.1%), but only 3.5% of the chlorthalidone group had a level <3.2 meq/L, and, in the chlorthalidone group, hypokalemia was associated with fewer cardiovascular outcomes than was normokalemia (38).

According to UpToDate (43): "The severity of the manifestations of hypokalemia tends to be proportionate to the degree and duration of the reduction in serum potassium. Symptoms generally do not become manifest until the serum potassium is below 3.0 meq/L, unless the serum potassium falls rapidly or the patient has a potentiating factor, such as a predisposition to arrhythmia due to the use of digitalis. Symptoms usually resolve with correction of the hypokalemia. ... Muscle weakness usually does not occur at serum potassium concentrations above 2.5 meq/L if the hypokalemia develops slowly. ... In addition to causing muscle weakness, severe potassium depletion (serum potassium less than 2.5 meq/L) can lead to muscle cramps, rhabdomyolysis, and myoglobinuria." In one study, occurrence of premature ventricular contractions was twice as common when serum potassium was below 3.0 meq/L (43).

In ALLHAT (39,40), chlorthalidone was also associated with more incident diabetes (defined as any fasting blood sugar >125 mg/dL) than were the other drugs (chlorthalidone: 14%, amlodipine: 11.1%, lisinopril: 9.5%). While overall, those with incident diabetes had more cardiovascular deaths, incident diabetes in the chlorthalidone group had lower cardiovascular deaths than incident diabetes in other groups, leading the ALLHAT investigators to conclude that "there is no conclusive or consistent evidence that this diuretic-associated increase in DM risk increases the risk of clinical events" (39), so "concerns regarding potential adverse diabetic effects associated with thiazide-type diuretic therapy should not inhibit its use" (40). Roush et al (44) recently reviewed this literature and concluded that "Chlorthalidone-induced diabetes mellitus (DM) is "chemical diabetes" rather than DM leading to cardiovascular pathology."

Also in ALLHAT, chlorthalidone did not increase the rate of development of either end-stage renal disease or of a 50% or greater decrease in glomerular filtration rate compared with lisinopril or amlodipine (45,46).

Sodium, uric acid, and gout were not followed in ALLHAT. Thiazides have been associated with hyponatremia in observational studies. In the Rotterdam study, about 50 of 3400 patients treated with thiazides over 6 years developed Na < 130 meq/L, 4.5 times as many as controls (36).

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However, in SHEP, patients randomized to chlorthalidone did not differ from those receiving placebo in sodium levels after 1 year (47).



Similarly, in the observational Atherosclerosis Risk in Communities (ARIC) study, thiazides were associated with an increased risk of incident gout mediated by increased uric acid levels

(41). A recent systematic review concluded "There is a trend toward a higher risk for acute gouty arthritis attacks in patients on loop and thiazide diuretics, but the magnitude and independence is not consistent. Therefore, stopping these useful drugs in patients who develop gouty arthritis is not supported by the results of this review" (48). In HDFP, patients randomized to chlorthalidone had reduced mortality compared with usual care regardless of baseline uric acid level (49). In a matched sample comparison of national pharmacy records, new onset gout episodes occurred with similar frequency in the year following prescription for chlorthalidone or hydrochlorothiazide, despite the 2 drugs being used in equal milligram doses (50).

The above comparisons involving thiazide vs. no thiazide demonstrate effects that are minor and of uncertain clinical importance. In addition, two studies from university (51) and VA (52) settings changed 19 and 40 patients (respectively) on a stable dose of hydrochlorothiazide to an equal milligram dose of chlorthalidone. Both reported reduced blood pressure with no significant metabolic effects except for one instance of hypokalemia in the university study.

Changing from hydrochlorothiazide to a roughly equipotent half dose of chlorthalidone (the intervention proposed in this study) should result in even smaller effects. In the randomized study by Ernst et al (23), hypokalemia < 3.5 meq/L occurred in nearly identical proportions at 2:1 doses: 50% of patients on hydrochlorothiazide 25/50mg and 46% on chlorthalidone

12.5/25mg. Within the commonly used dosing range of 12.5-25 mg per day, potassium reduction was found to be equivalent for the 2 drugs in one meta-analysis (26), whereas the other found it to mirror the potency results, i.e. greater for chlorthalidone at equal milligram doses (27). In a Dutch population-based case-control study, hyponatremia was twice as common with chlorthalidone compared with hydrochlorothiazide at equal doses, but no difference was observed comparing 2:1 dosing (53). In the short-term randomized trials of 609 and 1071 patients that compared equal doses (25 mg) of the 2 drugs in patients also taking an angiotensin receptor blocker, hypokalemia was rare, occurring in 1-2% (30,31). Summarizing the metabolic data available for the 2 drugs, a recent review (54) concluded that "factors such as serum potassium, glucose, lipids, endothelial function, and oxidative status" "are either favorable to chlorthalidone or are neutral in arriving at a decision as to which drug is superior."

More recently, a population-based observational study from Ontario compared effects of starting treatment with chlorthalidone (10,384 patients) vs. hydrochlorothiazide (propensity matched sample of 19489 patients) with a mean follow-up of about one year (29). Patients treated with chlorthalidone received higher doses (despite its greater potency), and were less likely to also be treated with an ACEI or ARB (drugs that raise potassium levels). Chlorthalidone was associated with a small non-significant reduction in the composite cardiovascular outcome,

374 from 3.4 to 3.2 per 100 patient-years (adjusted HR 0.93, CI: 0.81-1.06). However, treatment  
375 with chlorthalidone was associated with significantly more hospitalizations with (not necessarily  
376 "for") hypokalemia (0.69 vs 0.27 events per 100 patient-years, adjusted HR 3.06, CI: 2.04-4.58)  
377 and hyponatremia

0.69 vs 0.49 events per 100 patient-years, adjusted HR 1.68, CI: 1.24-2.28). The authors included hospitalizations that listed electrolyte abnormalities as secondary diagnoses noted during hospitalizations for other reasons. Hypokalemia and hyponatremia were each recorded as a secondary outcome noted during hospitalization less than once per 100 patient-years. In response to a letter suggesting that the analysis should be restricted to hospitalizations "for" hypokalemia (as primary diagnosis), the authors responded that doing so would result in so few hospitalizations that "such an analysis would be severely underpowered" (55). So while it is not known whether chlorthalidone caused more hospitalizations "for" hypokalemia, it is clear that such hospitalizations were rare.

The Ontario study had the advantages of large size and direct comparison of the two drugs in a population. The principal disadvantages were the observational design and the very small (and therefore potentially quite different) proportion taking chlorthalidone. Incomplete adjustment for known confounders (e.g., for dose and co-treatment) or from unrecognized confounders in the treated populations could have influenced the findings, as noted in a letter by the ALLHAT investigators (56). For example, chlorthalidone is likely used more often by hypertension specialists who might have been more attentive to recording electrolyte abnormalities on discharge summaries. Review of US data indicates that chlorthalidone is used in patients with more severe co-morbidities than those given hydrochlorothiazide (57). The Ontario study nevertheless raises questions regarding the possible superiority of chlorthalidone. In the correspondence following its publication, both the ALLHAT investigators and the Ontario authors stress the need for a randomized trial, such as the one we are proposing, to resolve this uncertainty (55,56).

In summary, the metabolic effects of thiazides are minor and have little or no clinical effect. Evidence from a variety of studies indicates that substitution of an equipotent dose of chlorthalidone for hydrochlorothiazide can be expected to have no more metabolic effect than might occur if the patient remained on hydrochlorothiazide without the substitution. **This is the basis for our assertion that this substitution constitutes minimal risk.**

#### J. Expert views on the choice of drugs and the need for a randomized trial

The evidence summarized above is consistent with a substantial benefit from using chlorthalidone rather than hydrochlorothiazide, but is not compelling, as the Ontario study illustrates. Many of the studies describing a possible advantage of chlorthalidone were conducted by Ernst and colleagues at the University of Iowa (7,18,22,23,26,28), but those authors have stated that "we do not believe there is strong evidence to support the use of chlorthalidone over HCTZ" (22). Ernst and Marvin Moser (who pioneered thiazide use in the 1950's) wrote in 2009: "Whether hydrochlorothiazide and chlorthalidone are interchangeable in reducing the risk of cardiovascular events is questionable" (32). On the other hand, Messerli et al reviewed the literature and concluded that "there is no evidence showing that HCTZ in the dose

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of 12.5-25 mg reduces myocardial infarction, stroke, or death" and argue that "if a thiazide-type diuretic is

117 indicated, either chlorthalidone or indapamide should be selected" (6). The 2011 UK National  
118 Institute for Health and Care Excellence (NICE) guidelines for hypertension (58) recommend "a  
119 thiazide like diuretic, such as chlorthalidone..., in preference to a conventional thiazide diuretic  
120 such as bendroflumethiazide or hydrochlorothiazide", whereas the 2013 European Society  
121 guidelines dispute this and conclude that "no recommendation can be given to favor a  
122 particular diuretic agent" (59).

123 A recent review from investigators at the New Mexico VA (15) concludes: "The available  
124 evidence therefore supports both HCTZ and chlorthalidone as safe and effective drugs for  
125 treating hypertension. Although there are favorable trends both in terms of antihypertensive  
126 efficacy as well as clinical outcomes data with chlorthalidone compared with HCTZ, the results  
127 are not conclusive, and as such may not be enough to shift the treatment paradigm in favor of  
128 chlorthalidone, given the comfort level that most prescribers have with HCTZ. A head-to-head  
129 study looking at hard clinical outcomes, which may or may not ever be performed, may be the  
130 only way to resolve the ongoing debate as to which is the preferred thiazide for treating  
131 hypertension." Floyd and Psaty noted in 2012 (60) that "In the area of pharmacological drug  
132 treatment for high blood pressure, the current question of primary interest is whether health  
133 outcomes associated with the use of hydrochlorothiazide and chlorthalidone may differ.

134 ...Reliable and valid comparisons between hydrochlorothiazide and chlorthalidone will require a  
135 large, long-term clinical trial."

136 As suggested by the New Mexico authors, it is extremely unlikely that a randomized clinical  
137 outcomes trial of hydrochlorothiazide vs. chlorthalidone will ever be undertaken except by the  
138 inexpensive methodology we are proposing. Neaton and Grimm, University of Minnesota  
139 Professors who participated in MRFIT, SHEP, and subsequent NIH hypertension trials, have  
140 been lobbying for such a trial since the end of SHEP more than 20 years ago. They have  
141 discussed the idea with the NHLBI project office numerous times over conference calls and had  
142 a meeting in Bethesda about this issue. According to Dr. Grimm, NHLBI project officers have  
143 maintained that they will only consider a 5 year proposal capped at \$1.5 million a year. The  
144 Director of the NHLBI Cardiovascular division has recently written that "we can no longer  
145 afford to undertake randomized effectiveness trials that cost tens or hundreds of millions of  
146 dollars" (61). Apart from a trial design such as we are proposing, which may be unique to the  
147 VA system, these investigators found it impossible to design a study for an amount close to this  
148 budget. Richard Grimm concluded a 7/29/13 email to the principal proponent (FAL) with: "It  
149 looks like the last chance of getting a definitive answer for this incredibly important question is  
150 your VA proposal."

151 K. Summary of evidence and potential impact of the proposed trial

152 Direct evidence shows chlorthalidone to be more potent and longer-lasting than  
153 hydrochlorothiazide, and indirect interventional evidence from the Roush network meta-  
154 analysis

155 (21) suggests that chlorthalidone may have a more beneficial effect on cardiovascular events,

156 whereas the large Ontario observational study (29) did not find a significant reduction in adverse  
157 cardiovascular events. In comparing these 2 methodologies, the International Society for  
158 Pharmacoeconomics and Outcomes Research Indirect Treatment Comparisons Good Research  
159 Practices Task Force concluded that "a network meta-analysis must be considered observational  
160 evidence, but is arguably less prone to confounding bias than an observational comparative  
161 (prospective) cohort study" (62).

162 Currently available data thus favor a likely substantial benefit from chlorthalidone compared  
163 with hydrochlorothiazide, but these data have had little effect on prescribing, which continues  
164 to overwhelmingly favor hydrochlorothiazide.

165 If cardiovascular events were reduced by even a small amount by chlorthalidone, the public  
166 health effect would be considerable because of the large number of patients who take  
167 diuretics. For the VA, it would likely justify the effort and cost of implementing a national policy  
168 to change drugs. However, the evidence is not yet persuasive enough to justify active  
169 measures directed at increasing chlorthalidone use. A randomized head-to-head comparison of  
170 the effectiveness of these two drugs at reducing cardiovascular events is clearly necessary to  
171 determine whether chlorthalidone is superior and if so, to justify efforts to change practice.

#### IV. The Point of Care Program within the VA's Office of Research and Development

##### A. Program Background

Medical decision making is informed by clinical trials and observational studies. While clinical trials are the gold standard in clinical research the high cost of conducting these studies combines with issues of generalizability to limit their contribution to changes in medical practice.

Observational studies are far less expensive and thus more numerous, addressing a broader scope of clinical issues. However, their primary failing is that the lack of randomization often leaves open the possibility of bias due to selection by indication, and residual confounding of results due to unobserved prognostic factors that influence treatment decisions.

Point of care (POC) randomization represents an intermediate strategy between these two approaches. The intent is to introduce the opportunity to randomize patients at decision points in clinical care where two or more alternatives are considered equivalent on average by the medical community (that is, clinical equipoise exists). Patients who agree to be randomly assigned to treatment options will become subjects in the clinical experiment.

POC randomization preserves the experimental quality of clinical trials without the cost of the clinical trial apparatus; recruitment and randomization is done at the point of care with minimal perturbation of work flow, and outcomes are assessed by automated extraction of data from the medical record. Reduction of the need for research staff interaction with potential subjects (limited to obtaining informed consent) greatly reduces cost and generates data that reflects the *effectiveness* (rather than efficacy) of experimental interventions in clinical care.

To be effective, the additional burden on patients and health care providers imposed by POC randomization must be minimal. The VA electronic medical record system (VistA) can be customized to identify, enroll and randomize patients and serve as the source of outcomes data and is thus well suited for such a trial design. Subject recruitment and enrollment will be accomplished by embedding processes within the VistA system through a series of dialog boxes.

As noted in a recent editorial (63), "With optimal use of EMRs, the administrative costs of a trial need not increase with the sample size; this decoupling of costs and size facilitates large, simple, and inexpensive trials that have the potential to transform health systems into entities that learn and continuously improve."

As the VA system continues to lead in the development of EMR that support increasingly sophisticated monitoring for outcome-based evaluation of care, we anticipate that the methods we test using POC randomization will have even greater scope for application. The



506 methods are also a natural fit for testing personalized and precision medicine strategies and  
507 for experimental comparative effectiveness research.

508 B. POC Pilot Study

The first implementation of POC randomization is a pilot study that is currently underway at 3 VAMC across 2 VISNs. The goal of the pilot was fivefold:

1. To test the feasibility of the method for modification of VistA/CPRS screens and the ability to randomize within the system;
2. To assess patient and provider acceptance of the new methodology;
3. To assess the regulatory acceptance of:
  - a. Informed consent procedures;
  - b. Safety monitoring;
  - c. Ethical considerations;
4. To test the method for data extraction and passive collection of endpoint data using the EMR;
5. To apply Informatics techniques to refine and improve efficiencies in the identification of endpoints, etc.

The pilot is a comparison of two standard strategies of insulin administration for hospitalized patients and is designed as an open-label, randomized trial comparing sliding scale regular insulin (ssRI) to a weight based regimen for control of hyperglycemia in non-ICU inpatients. The strategy is to enroll patients into the study directly from the point of contact with clinical care within all inpatient facilities. All non-ICU patients who require in-hospital insulin therapy are eligible for this study. Clinicians decide at the time of care (through the VistA order entry screen for insulin) whether or not they will allow their patient to be contacted by POC study staff. If the treating clinician agrees, consenting patients are randomized to treatment arms and treated by their clinicians according to usual practices. All technical modifications necessary are executed within the "Clinical Alert" package. Consenting patients are then followed through VistA from randomization until 30 days post discharge. Comparisons of effectiveness will be formally conducted using length of hospital stay measured in days as our primary outcome measure.

The pilot has demonstrated the feasibility of the POC method as an alternative design to traditional trials. To date, 92% of eligible patients have accepted participation and have been consented into the pilot protocol. Additionally, 71% of all clinicians that are able to order medications have accepted randomization within the clinic and have referred their patients to the protocol. All patient data has been extracted from the EMR and has been validated with chart review by a qualified clinician. There have been no significant safety events and no findings from regulatory audits or the local institutional review boards.

### C. The POC National Program

The goal of POC program is to deliver state of the art treatments to patients simultaneously with enrolling them as subjects to redefine that care. By institutionalizing a process of statistically sound and efficient learning, and by integrating that learning with automatic

548 implementation of best practice, the participating VA health care systems will accelerate  
549 improvements in the effectiveness of care for veterans. With this goal in mind, Point of Care  
550 Research has been designated as one of the Secretary's (SECVA) Transformational Initiatives  
551 within the VA and

552 within the Office of Research and Development (ORD). Accordingly, this initiative has a  
553 national scope and an operating budget of approximately \$10.2Million (exclusive of study  
554 budgets).

555 The MAVERIC CSPCC at the Massachusetts Veterans Epidemiology Research and Information  
556 Center (MAVERIC) has been tasked with leading the effort to implement POC randomization  
557 within the VA. To that end, MAVERIC's mission is to build the infrastructure necessary to  
558 support POC research; to educate providers, veterans and investigators on the initiative; to  
559 build consensus for support of the initiative among the VA community as a whole; and to  
560 explore the ethical, scientific, and regulatory aspects of the POC method itself. In order to fulfill  
561 its mission, MAVERIC collaborates with national leaders in the fields of medical ethics and  
562 pragmatic clinical trials to produce scholarly works and it will conduct focus groups of veterans,  
563 veteran service organizations, and providers in order to develop a national educational  
564 campaign for all VA stakeholders.

## V. **Relevance of our trial design to current needs of VA healthcare**

The most reliable way to learn if medical interventions provide more benefit than harm for our patients is through large randomized trials (64). However, large randomized trials that enroll thousands of patients can cost hundreds of millions of dollars, placing them out of range for most payers, including VA. As a result, many important questions remain unanswered.

We are proposing herein a 'clinically integrated' study design (65,66) that will incorporate and extend previously described VA 'Point of Care' Clinical Trial methodology (67,68). This is an efficient and inexpensive design, that will rely on a centralized processes involving mail, phone, and data extraction from the VA electronic medical records (EMR) , assisted by a designated study champion at each site (the site Liaison) and by local Clinical Application Coordinators (CACs). These methods will allow us to avoid having to employ study personnel at each site to manage patients and collect data. As a result, the infrastructure costs typically dedicated to these activities can be reinvested to answer other questions for the healthcare system. The goal, as Lauer and D'Agostino suggest, is "to design and conduct megatrials with what we have: bigger data and smaller budgets" (61).

The following quotes, excerpted from the 2011 Institute of Medicine report "Learning what works best - the nation's need for evidence on comparative effectiveness in health care"(69), provide support for our study objectives and design:

"A core objective for the nation is achieving the best health outcome for every patient. This objective simply cannot be accomplished until we have better evidence on which to base healthcare decisions"; "the most rapidly growing problem is that of our inability to produce the needed evidence in a timely fashion"; "Estimates of the proportion of medical care in the United States that is based on, or supported by, adequate evidence range widely. However, given concerns about the extent to which this information may be generalized, and the quality of the evidence which is used, some place this figure at well below half."; "Within the overall umbrella of clinical effectiveness research, the most practical need is for studies of comparative effectiveness, the comparison of one diagnostic or treatment option to one or more others."; "issues in need of additional systematic evaluation ... include issues related to the comparative evaluation of different drugs within a single class"; "A learning healthcare system is one in which the clinical research paradigm depends more judiciously on the serial conduct of randomized controlled trials—important, but often too expensive, untimely, and of limited applicability—and draws more heavily on electronic health records (EHRs) to generate evidence as a natural by-product of the clinical experience."

More recently, the FDA has launched a Clinical Trials Transformation Initiative intended to promote and enable the conduct of larger, simpler, less expensive randomized trials using streamlining methodologies such as use of electronic health records (70).

501 In addition to addressing an important clinical question, our proposed trial is responsive to all  
502 these needs. This trial represents a new efficient methodology designed to provide reliable  
503 answers to practical clinical questions at a greatly reduced cost.

## VI. Study Design

The study design is a multicenter clinically integrated (65) [or "point of care" (67,68)] prospective randomized open-label blinded-endpoint (PROBE) trial (71).

## VII. Study Population

### A. Inclusion Criteria

Eligible patients are those (including women and minorities) who:

1. Are over age 65 years
2. Are receiving hydrochlorothiazide from the VA pharmacy at a daily dose of 25 or 50 mg
3. Have a most recent SBP in CPRS  $\geq$  120 mm Hg, with no SBP  $<$  120 mm Hg recorded in CPRS in the previous 90 days

### B. Exclusion Criteria

Patients will be excluded if they are known to have any of the following:

1. Impaired decision-making capacity rendering the patient unable to provide informed consent (i.e., if there is any question during the nurse's CPRS chart review that the individual does not have the ability to make an autonomous decision or the PCP declines permission to randomize)
2. Death expected within 6 months (inferred by PCP permission to randomize)
3.  $K <$  3.1 meq/L (or 3.5 meq/L if on digoxin) in the past 90 days (assessed by CPRS review)
4.  $Na <$  130 meq/L in the past 90 days (assessed by CPRS review)
5. Known to be enrolled in Medicare Part C (assessed through administrative data or on consent phone call). This exclusion will only be employed if we determine that we cannot obtain sufficient information from Part C data (see below under Rationale).

### C. Rationale

We limit to age over 65 years to allow data collection through Medicare (which is only widely available starting at this age) [and will exclude known Part C enrollees (those enrolled in Health Maintenance Organizations), for whom usual encounter data is not available through Medicare if we determine that we cannot obtain sufficient information from Part C data].

533 We limit randomization to patients receiving hydrochlorothiazide because a) 95% of thiazide-  
534 type diuretic prescriptions are for hydrochlorothiazide, b) there is little evidence to suggest  
535 that chlorthalidone is inferior to hydrochlorothiazide, and c) the few PCPs who have  
536 deliberately chosen to use chlorthalidone over the much more commonly used  
537 hydrochlorothiazide are less likely to be willing to change drugs.

538 We limit to hydrochlorothiazide doses of 25 or 50 mg because lower doses may not be effective  
539 and cannot be easily converted to chlorthalidone (which is available only in 25mg tablets), and  
540 because higher doses are not recommended and are rarely used.

541 We limit to SBP  $\geq$  120 mmHg primarily to minimize risk from hypotension, and also to avoid  
542 enrolling patients whose blood pressure is already low enough that a potentially more effective  
543 drug would not be expected to add benefit (72, 73). The cutoff point of 120 mmHg was  
544 selected, in part, because we are using routine clinic blood pressures recorded in CPRS to  
545 determine study eligibility. These are obtained using a less rigorous measurement protocol than  
546 is normally used in randomized trials and that tends to overestimate blood pressure (74), in  
547 one study by a mean of 8 mmHg (75).

548 We will attempt to exclude patients in Part C as long as it appears that we will not be able to  
549 obtain adequate data. Part C data have not been available for research purposes in the past,  
550 but CMS plans to make the Healthcare Effectiveness Data and Information Set (HEDIS) for the  
551 years 2006-2011 available sometime in 2015. We plan to check with CMS periodically, and if,  
552 before or during enrollment, adequate Part C data appear to be accessible, we will discontinue  
553 the exclusion and attempt to enroll these patients.



### VIII. Study Intervention

Participants will be randomly assigned to remain on their current dose of hydrochlorothiazide (25 or 50 mg), or to replace it with half that dose of chlorthalidone (12.5 or 25 mg, respectively), both changeable by the PCP. Chlorthalidone 12.5 mg will require tablet splitting, and a splitter will be mailed with the prescription. [Tablet splitting is a common procedure in VA pharmacy, sometimes including the splitting of hydrochlorothiazide 50 mg to get 25 mg. A recent review (76) concluded that "Tablet splitting does not seem to significantly affect clinical outcomes related to management of hypertension, cholesterol, or psychiatric disorders, nor influence overall patient adherence."]

Rationale for the default use of 1:2 chlorthalidone dose: Because chlorthalidone is not used at lower doses than hydrochlorothiazide in practice (7,28,29), it could be argued that the most appropriate pragmatic comparison would be a 1:1 substitution. We selected the 1:2 dose default for 3 reasons: 1) as noted above, the use of similar doses in practice probably reflects greater awareness of appropriate thiazide dosing by the small proportion of prescribers who use chlorthalidone, rather than belief that the potencies are equivalent, 2) a 1:1 design would change the study question from assessment of a possible inherent difference between the two diuretics to an assessment whether low doses of hydrochlorothiazide are less effective, whereas our interest is in the former question, and 3) an equal dose of chlorthalidone would represent an intensification of diuretic therapy, resulting in increased effects on blood pressure and blood chemistries (51,52,53), whereas the 1:2 design results in virtually no change in blood pressure or metabolic effects (see Background and Rationale, parts F and I).

## IX. Study Procedures

### A. Procedures prior to patient enrollment

We will identify a "Liaison" at each site, usually a physician in primary care and/or hypertension management whose role will be limited to identifying key personnel at the site and introducing the study by giving presentations to local Primary Care Providers (PCPS), pharmacy, the Information Resource Management service (IRM), Clinical Application Coordinators (CACs), and Information Security Officers (ISOs) and subsequently referring all questions and comments to MAVERIC CSPCC. The Liaison will not be involved in recruitment or have patient interaction related to the study. Because we are introducing a new design and intend to evaluate its success, PCPs are also considered to be research subjects (see XI. Biostatistical Considerations, F. Secondary Data Analysis, 4. Primary Care Provider Metrics of Interest).

Our procedures are summarized in a flow diagram (**Appendix C**). Working through the VA national ISO structure and local CAC's and pharmacy personnel, we will obtain permission for MAVERIC CSPCC to have the necessary access to local CPRS systems to enter notes and post orders as View Alerts to PCPs and to collect the study data on enrolled patients. Research staff at the MAVERIC CSPCC will be responsible for communicating with local PCPs, coordinating and implementing all patient recruitment activities and completing the enrollment process including randomization and placing assigned treatment orders for signature by the PCP in CPRS. The MAVERIC CSPCC will partner with the Canandaigua VA Medical Center to conduct centralized calling and mailing activities, including contacting potential participants and obtaining informed consent by telephone.

We plan to roll out the study in blocks of sites. When a site starts up, the MAVERIC CSPCC will generate a local list of PCPs along with their eligible patients. We will also identify local PCP email groups and obtain the PCPs' VA Outlook email addresses. The MAVERIC CSPCC will send an introductory letter (by mail and email) to local PCPs signed by the co-Chairs providing information about the study (**Appendix A.1**). The site Liaison will present information about the study at primary care staff meetings and other forums (individual PACT meetings, video staff meetings for Community-Based Outpatient Clinics, etc.).

After these activities are completed, a View Alert 'testpatient' order will be sent to each PCP identified by the method above. The testpatient order will accompany a progress note containing the text of the Provider Information Sheet which will contain the elements of informed consent and detail the study procedures. (**Appendix B.3**) By signing the 'testpatient' view alert order, the PCP is agreeing to participate in the study as a research subject and allowing the recruitment letter (**Appendix A.2**) to be sent to eligible patients by the MAVERIC CSPCC. Alternatively, the PCP can "discontinue" the order, in which case that PCP will not be enrolled in the study and his/her patients will not be contacted.

711

B. Enrollment procedures

712 The procedures described below are summarized in a flowchart (**Appendix C**) and relevant  
713 CPRS screen shots are shown in **Appendix D**.

714 Using the VA electronic medical record, the MAVERIC CSPCC will identify eligible patients of  
715 PCPs who signed the testpatient order and will mail the study recruitment letter (**Appendix A.2**)  
716 with the Patient Information Sheet containing the consent transcript (**Appendix B.2**) to these  
717 patients. We will attempt to send the letter 3-4 months before the patient's next planned  
718 appointment with the PCP to make it easier for the PCP to obtain any follow up on blood  
719 pressure and laboratory tests that the PCP might want. However, the VA Advanced Clinical  
720 Access/Recall system may prevent early detection of these appointments. The study  
721 recruitment letter and the Information Sheet with the transcript of the consent phone call that  
722 will be sent with the letter provide information about the study and the opportunity for the  
723 patient to opt out of future contact from the study.

724 If no 'opt out' reply is received by the coordinating center within 2 weeks after mailing the study  
725 recruitment letter, the patient will be contacted to confirm the details of consent. This will be  
726 done through the Canandaigua VAMC Call Center using a telephone line that displays the  
727 calling source as the VA on caller ID. We will make multiple attempts to reach the patient, only  
728 leaving a message on the first and last attempt. The U.S. National Health Interview Survey used  
729 a maximum of 15 call attempts and a 1994 study confirmed this number to be optimal (77). In 2  
730 surveys conducted by Statistics Sweden, nonresponse rates stabilized at 15 and 20 maximum call  
731 attempts (78). In the Consumer Assessment of Health Plans Study, "most hard-to reach non-  
732 respondents were called 10 or more times" (79). A recent study at the University of Minnesota  
733 (80) had an amendment approved by the UMN IRB in 2011 to increase the maximum number of  
734 call attempts from 6 to 12. Regarding left messages, Koepsell (81) "found that leaving a brief  
735 message about the study and promising a call-back improved the response rate by nearly 20  
736 percentage points". On the phone call, the information included in the letter will be reviewed  
737 and the patient's informed consent will be sought using a pre-approved telephone script  
738 (**Appendix B.1**).

739 After telephone consent is obtained, a View Alert order will be sent to the PCP which, if signed  
740 by the PCP, will indicate permission to randomize that particular patient. Alternatively, if the  
741 PCP believes that patient should be excluded for any reason (e.g., incompetence or short life  
742 expectancy), the order can be "discontinued" and the patient will then receive a letter saying  
743 that their PCP declined their participation in the study (**Appendix A.3**).

#### 744 C. Randomization

745 After the PCP signs the order allowing the patient to be randomized, the patient will be  
746 randomized by the MAVERIC CSPCC. Randomization will be to chlorthalidone or  
747 hydrochlorothiazide with equal probability. Randomized group will be open label, but allocation

748  
749

will be concealed before randomization and irrevocable afterwards. All randomized patients will

750 be included in the analysis according to the intent-to-treat principle. Outcome assessment will be  
751 conducted by investigators blinded to treatment assignment.

752 We are thus proposing a "prospective randomized open-label blinded-endpoint" (PROBE) trial  
753 (71). The rationale for our open-label design is several fold: 1) since there is no local  
754 coordinator, it is essential that the PCP manage the diuretic therapy, and we are concerned that  
755 this may not always occur if we use a blinded study drug, 2) there is no local investigator to  
756 assist with emergency unblinding, 3) we believe that keeping patients on open label therapy,  
757 being more familiar and straightforward from the patient's perspective, will enhance  
758 recruitment, thereby improving both feasibility and generalizability, 4) local pharmacy  
759 management of blinded drug would require a level of effort and local engagement in research  
760 incompatible with our streamlined study structure, 5) the expense of producing a study  
761 preparation that is identical for the two drugs, and then labeling and tracking each patient's  
762 therapy, would greatly increase cost, defeating the purpose of our highly efficient clinically  
763 integrated design. A recent meta- analysis found PROBE trials to be comparable to blinded trials  
764 in terms of assessing antihypertensive drug effect on blood pressure measurements, though  
765 clinical outcomes were not examined (71).

766 After randomization, a templated progress note placed by the MAVERIC CSPCC will appear as a  
767 View Alert to the PCP. The note will provide information on relative drug potency and provide  
768 the following reminders: 1) when resolving the view-alert orders, the PCP can accept the order  
769 by signing as is or change the dose, 2) the PCP can discontinue the order to continue their  
770 patient on his/her current diuretic, 3) the PCP may wish to order any desired laboratory tests or  
771 blood pressure checks, and 4) the PCP should manage the diuretic in the future according to the  
772 patient's needs.

773 Patients will be sent a letter informing them of their randomized group (**Appendix A.4**). Patients  
774 assigned to hydrochlorothiazide will simply remain on their current prescription. For patients  
775 randomized to chlorthalidone, the MAVERIC CSPCC will also generate View Alert orders to the PCP  
776 cancelling the hydrochlorothiazide prescription and replacing it with chlorthalidone.

777 Patients randomized to chlorthalidone will be instructed to discard their hydrochlorothiazide  
778 pills, and will be reimbursed for their co-pay on the discarded pills. The change from  
779 hydrochlorothiazide to chlorthalidone is a typical pharmacy action in usual care and will  
780 otherwise be handled with usual pharmacy procedures and information at that medical center.

781 Randomization will generate "health factors" that will serve to identify patients as enrolled in  
782 the study for tracking purposes in the VA EMR. In the unlikely event that the PCP, having very  
783 recently signed the "permission to randomize" view alert order, does not sign (i.e.,  
784 "discontinues") the initial study drug order for chlorthalidone, the patient will still be analyzed

785 in the randomized group according to intent to treat. In these instances, we will contact the PCP  
786 to ask the reason for the discontinuation of the order.

787 We will monitor drug prescribing for study patients throughout the study. If the study drug is  
788 discontinued, a prescription is written for the other diuretic (cross-over), or the prescription is  
789 not refilled for 90 days after expected, a View Alert will be sent to remind the PCP about the  
790 study. If the situation persists after 2 weeks, we will review the chart to determine if the lapse  
791 was intentional and if so, try to determine the reason. If questions remain after the review, we  
792 may query the PCP.



793 **X. Outcome Measures**

794 A. Primary outcome

795 The primary outcome measure will be time to a major cardiovascular event, defined as  
796 a composite outcome comprised of the first occurrence (after randomization) of any of  
797 the following:

- 798 1. Stroke
- 799 2. Myocardial infarction
- 800 3. Urgent coronary revascularization (completed or attempted) because of unstable  
801 angina
- 802 4. Hospitalization for acute congestive heart failure
- 803 5. Non-cancer death

804 B. Secondary outcomes

805 Secondary outcomes will include:

- 806 1. All deaths
- 807 2. The composite outcome substituting all deaths for non-cancer deaths
- 808 3. "Possibly vascular deaths" defined as all deaths caused by vascular diseases, diabetes,  
809 external causes, and unknown causes
- 810 4. The composite outcome substituting "possibly vascular deaths" for non-cancer deaths
- 811 5. Each of the 5 components of the composite primary outcome
- 812 6. Any revascularization of any artery
- 813 7. Erectile dysfunction, defined as first prescription for PDE5 inhibitor or referral for  
814 ED

815 C. Process variables

- 816 1. Mean blood pressure during the study (outpatient clinics only; excludes inpatient,  
817 Emergency Department and Operating Room)
- 818 2. Time to discontinuation of the randomly assigned diuretic (defined as discontinue  
819 order or no prescription for  $\geq 6$  months at last observation during study period)

320 3. Mean compliance with study drug using "Medication Possession Ratio" (82) (used by  
321 VA Pharmacy Benefits Management Services)

322 4. Other antihypertensive drug use

323 D. Tertiary Outcomes

324 1. Hospitalization for primary diagnosis of hypokalemia, hyponatremia, or renal failure

325 2. Renal failure. Defined as dialysis, vascular access for dialysis, or renal transplant.  
326 (Doubling of serum creatinine from baseline will also be recorded and reported in the  
327 final analyses).

328 3. Other recorded hypokalemia (< 3.1 meq/L), or hyponatremia (< 130 meq/L)

329 4. New diabetes, defined as first use of a medication for diabetes

330 5. Acute gout episodes

331 6. New allergic reaction to thiazide-type diuretic, defined as new entry in  
332 Allergies/Adverse reaction (ART) database

333 E. Rationale for elements of composite primary outcome

334 The elements of the composite primary outcome are intended to represent the clinically  
335 important effects of diuretic therapy for hypertension. Myocardial infarction and stroke are  
336 traditional outcomes for cardiovascular clinical trials and will not be further justified here.  
337 Myocardial infarction is defined as the third universal definition (83). Stroke is defined as a  
338 neurological deficit of cerebrovascular cause that persists beyond 24 hours or is interrupted by  
339 death within 24 hours, including ischemic and hemorrhagic strokes (84).

340 Urgent coronary revascularization. Urgent coronary revascularization is an important outcome  
341 because these events accurately reflect both the progression of underlying atherosclerotic  
342 vascular disease and represent an important contributor to cardiovascular morbidity and  
343 healthcare costs. Disease progression that formerly resulted in myocardial infarction now  
344 frequently results in revascularization that aborts the infarction. Furthermore, because of  
345 increasingly sensitive troponin assays, many patients having urgent coronary revascularization  
346 attributed to unstable angina actually have mild troponin positivity and would be classified as  
347 myocardial infarctions in a classic trial design with in-depth outcome review (Christopher P.  
348 Cannon, MD, personal communication, Aug 2013). Including urgent coronary revascularization  
349 in our study will prevent us from missing these infarctions. Urgent coronary revascularization is  
350 more restrictive than the revascularization outcome usually reported in previous trials and  
351 selects for the most clinically relevant events. For example, in the PEACE trial of patients with  
352 stable coronary artery disease and normal ejection fraction (85), "all coronary

353 revascularizations" were more frequent than all the other events combined that make up our  
354 composite. On the other hand,

355 in the (TRA2°P)-TIMI 50 trial of an antiplatelet agent in patients with vascular disease (86),  
356 urgent coronary revascularization because of unstable angina was less frequent than myocardial  
357 infarction and similar in frequency to cardiovascular death or stroke, and increased the  
358 composite rate in the placebo group from 10.5% for those 3 outcomes to 12.4% for those 3  
359 outcomes plus urgent revascularization.

360 Reductions in urgent coronary revascularization represent an important contribution to the  
361 overall effectiveness of therapy. The observed reductions in urgent revascularizations in  
362 randomized trials are concordant with changes in other major outcomes. In (TRA2°P)-TIMI 50  
363 (87), the hazard ratio for the primary composite outcome of cardiovascular death, myocardial  
364 infarction, or stroke was 0.87, and for urgent coronary revascularization was 0.88. Urgent  
365 coronary revascularization has also been used in TRACER (82) and is being used in EXAMINE  
366 (88). CSSEC recently approved a broader revascularization outcome for VA CSP #593, the VA  
367 Fenofibrate Intervention Trial (VA-FIT) (for which the indications included stable angina with a  
368 >50% target lesion).

369 In summary, urgent coronary revascularization is a significant contributor to cardiovascular  
370 morbidity and health care costs, its inclusion will allow assessment of the full impact of therapy,  
371 and its relative contribution to overall endpoints is not anticipated to be disproportionate to  
372 that of other study outcomes. Evaluation of urgent coronary revascularization by review of  
373 EMR is straightforward, as discussed below.

374 Hospitalization for acute congestive heart failure. Hospitalization for acute congestive heart  
375 failure is another important component of our primary outcome. It will, in most instances,  
376 represent a new diagnosis of heart failure because most patients with established heart failure  
377 are maintained on a loop diuretic such as furosemide and are not treated with  
378 hydrochlorothiazide and thus would not be enrolled in our study. We will seek to identify  
379 clinical exacerbations of symptoms (e.g., not hospitalization for ICD placement), which should  
380 be associated with intensification of treatment, which we will assess in our algorithm.

381 Heart failure is a major public health problem with a profound impact on prognosis and also on  
382 costs, and is the most frequent cause of hospitalization among people older than 65 years (89).  
383 Its impact is summarized in the AHA 2013 update (90): "HF incidence approaches 10 per 1000  
384 population after 65 years of age", ... "approximately 50% of people diagnosed with HF will die  
385 within 5 years", ... "One in 9 deaths has HF mentioned on the death certificate", ... "In 2009, HF  
386 any-mention mortality was 274 601" and "HF was the underlying cause in 56 410 of those  
387 deaths".

388 Heart failure and stroke are the two major cardiovascular outcomes most related to  
389 hypertension and most benefited by treatment of hypertension. Seventy-five percent of heart

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failure cases have antecedent hypertension (90). The Framingham Heart Study (91) found the highest risk ratio from hypertension to be for heart failure in men (Figure 1).

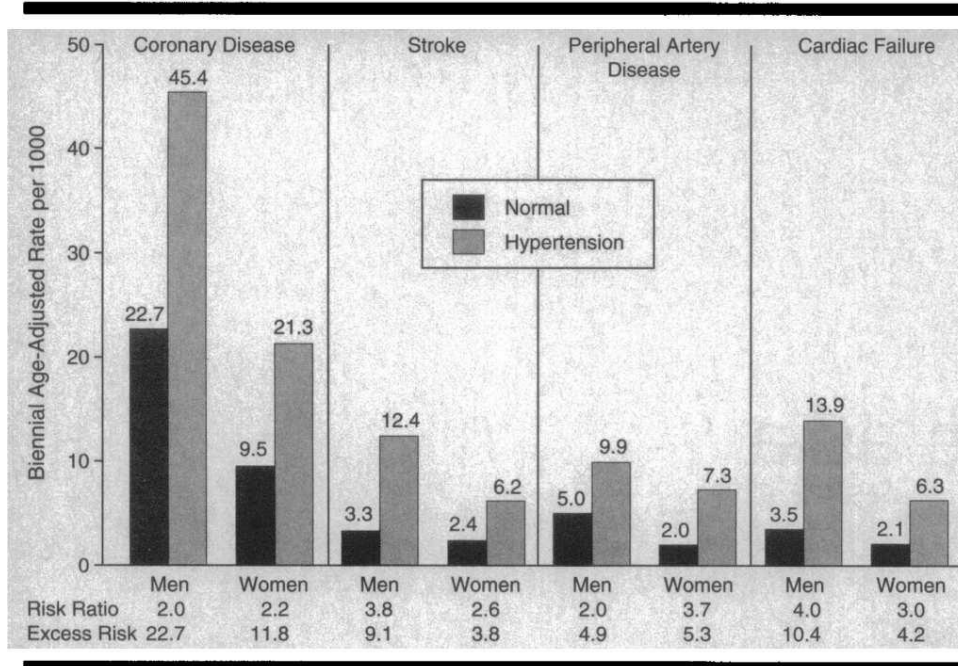


Figure 1. A prospective analysis of the 36-year follow-up data from the Framingham Heart Study (91) demonstrates that hypertension (blood pressure  $\geq 140/90$  mmHg) predisposes to all major atherosclerotic cardiovascular disease outcomes, but the largest risk ratios are for cardiac failure and stroke in men.

Diuretic-based treatment arms in outcome trials have reduced HF by an average of 50% over placebo (compared with 30-40% reduction for stroke), and more effectively than calcium channel blockers and ACE inhibitors in comparative trials (Figure 2) (5). In ALLHAT (89), the alpha blocker doxazosin, the calcium channel blocker amlodipine, and the ACE inhibitor lisinopril were associated with 80%, 38% and 19% higher risk of heart failure compared with chlorthalidone. Therefore, heart failure is likely to be one of the most sensitive outcomes for detecting a true difference in reducing cardiovascular disease between the two diuretics in our study.

**Figure 2.** Network Meta-analysis of First-Line Treatment Strategies in Randomized Controlled Clinical Trials in Hypertension

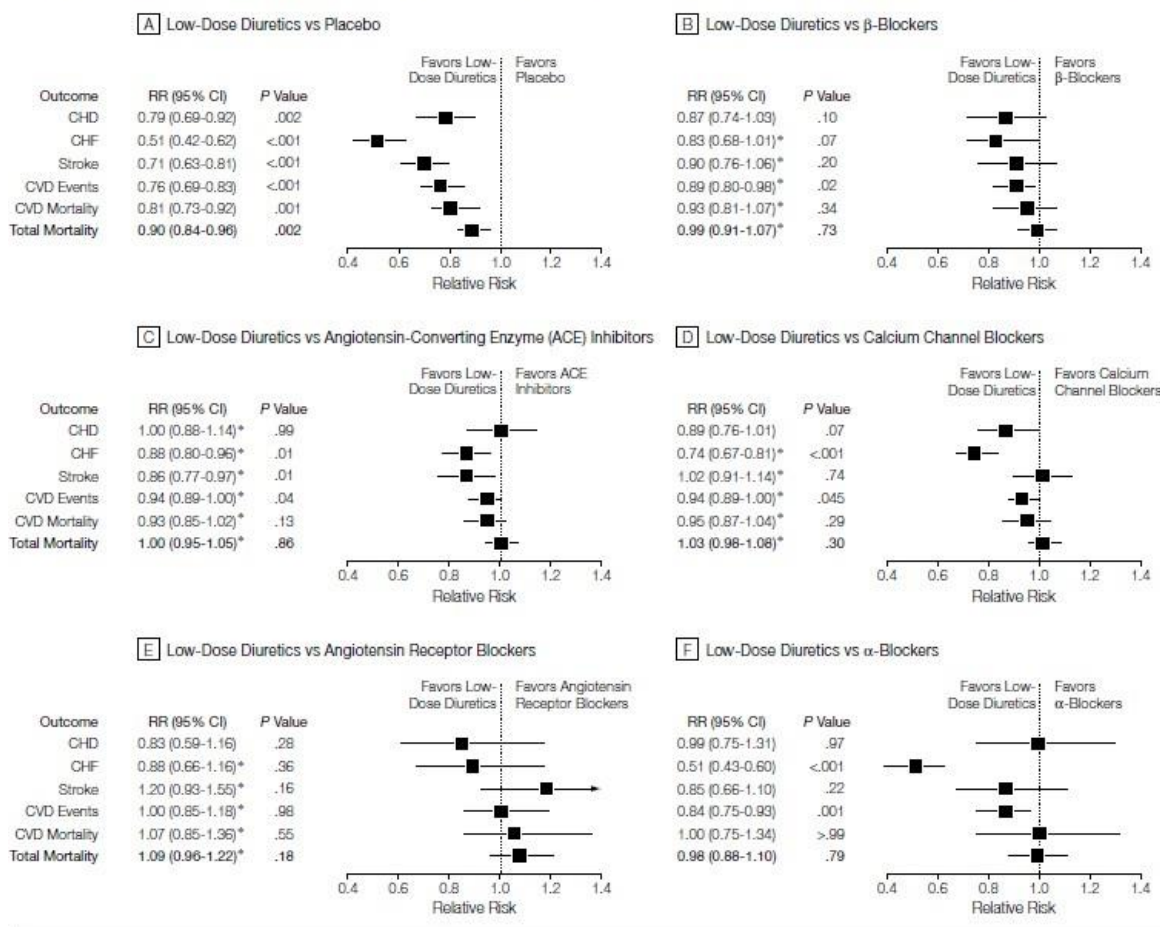


Figure 2. From a network meta-analysis of hypertension trials (5). Heart failure (CHF) can be seen to be a particularly effective outcome for discriminating between diuretics and other drugs. "CVD Events" include CHD, CHF, stroke and CVD deaths.

Hospitalized heart failure is not disproportionately common compared with our other outcomes. In the principal ALLHAT report (20), there were 885 non-fatal MIs, 724 hospitalized or fatal heart failure events, and 675 strokes. Hospitalized heart failure events in ALLHAT attracted close scrutiny because they were reported by site investigators and not adjudicated. The authors undertook a separate study in which they successfully validated these events (89), and from which they concluded "Heart failure proved to be a common outcome in ALLHAT and one that was affected differentially by the randomized treatment assignments. In addition, patients who developed HF had significantly poorer survival than those who did not. Whether this poor prognosis can be altered presents an important clinical and public health question.

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Thus, *in planning future hypertension treatment trials* (and perhaps also treatment trials in other



025 populations at high risk of HF, such as diabetics and survivors of acute coronary syndromes)  
026 *serious consideration should be given to including HF in the primary end point, along with*  
027 *death, MI, and stroke” (italics added).*

028 Heart failure is reasonably well identified using discharge diagnoses. In a population-based  
029 study of 4537 cases of heart failure from Olmsted County MN, ICD-9 code 428 constituted 80%  
030 of heart failure codes, and 82% of the cases coded as 428 met Framingham criteria for heart  
031 failure when records were reviewed by experienced abstractors (92).

032 Identification of clinically important episodes can be improved by looking for evidence of  
033 treatment intensification. The draft report of the FDA expert panel on Cardiovascular Endpoints  
034 in Clinical Trials (93) recommends inclusion of the following criteria for determining a heart  
035 failure hospitalization event: “The patient receives initiation or intensification of treatment  
036 specifically for HF, including at least one of the following: a. augmentation in oral diuretic  
037 therapy, b. intravenous diuretic, inotrope, or vasodilator therapy, or c. Mechanical or surgical  
038 intervention, such as i. mechanical circulatory support (e.g., intra-aortic balloon pump,  
039 ventricular assist device) or ii. mechanical fluid removal (e.g., ultrafiltration, hemofiltration,  
040 dialysis).” We will employ these criteria and others, such as exclusion of admissions for ICD  
041 placement, in our algorithms to maximize the likelihood that the events we capture are  
042 clinically relevant.

043 Non-cancer deaths. We include non-cancer deaths in our primary composite outcome as a  
044 compromise between total mortality, which includes many irrelevant events that dilute the  
045 effect of the intervention, and cardiovascular mortality, which is less accurately distinguished on  
046 death certificates and may miss relevant deaths. We exclude cancer deaths because they are  
047 numerous, relatively accurately identified on death certificates (94,95,96), and believed to be  
048 unrelated to diuretic use, so excluding them reduces “noise” relative to expected effects of the  
049 intervention. In the Physicians’ Health Study (95), cancer deaths in patients older than 65 years  
050 were identified from death certificates using standard nosology protocols and the Automated  
051 Classification of Medical Entities (ACME) Decision Tables with specificity well over 99% compared  
052 with an adjudication committee, meaning that the deaths excluded from our primary outcome  
053 will almost certainly be due to cancer.

054 Prieto-Merino and colleagues (97) note: “If outcomes that are causally related to the trial  
055 treatment are combined with those that are not, the estimate of the treatment effect is  
056 diluted towards the null and we may fail to identify potentially important benefits or harms....  
057 Because few treatments will be causally related to all causes of death, all-cause mortality is a  
058 composite outcome that combines causally related causes of death with those unrelated to  
059 the treatment.” We did not restrict to cardiovascular deaths because some other deaths may  
060 be relevant, such as accidents due to syncope from hypotension and deaths from unknown

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causes (which could have been cardiovascular), and other deaths (e.g., pneumonia, COPD) that are not accurately

distinguished from cardiovascular deaths by death certificate diagnoses. Competing risk from cancer deaths will be considered in a secondary analysis.

#### F. Ascertainment of Outcome Data

Data collection will be via electronic medical records and administrative data. We will use both VA and CMS data. Assessment of outcomes and relevant data elements as well as adverse event is by passive collection of data in electronic health records; the study will not attempt to generate any additional tests or procedures. All outcome processing will be conducted by investigators at the MAVERIC CSPCC unaware of treatment group. Using a 150 chart review confined to VA data we have determined that we can identify the data elements we need to assess each of the components of the primary outcome. In this section we describe our approach to ascertainment and assessment of these outcomes.

The Boston MAVERIC Center has 15 years of experience in ascertainment and assessment of cardiovascular outcomes using the VA electronic health record (EHR) and CMS data. We will build on this extensive experience to refine a specific procedure for doing the same in this trial in order to accurately identify and assess outcomes. The process involves several clearly defined steps. First, we develop a method to screen the electronic medical records of all participants on a periodic basis (every 2 weeks) for potential cases. Second, algorithms are developed to collect and analyze data elements that are used to confirm or refute the potential cases. The algorithms are based on standard criteria used in clinical trials, and are applied to potential cases to determine if the case is confirmed, disconfirmed or deemed indeterminate. Third, indeterminate cases will undergo manual adjudication review. We expect to be left with a relatively small number of events that cannot be resolved by the algorithm, but all of these will be referred for adjudication to an outcomes committee unaware of treatment group. This will greatly lessen the workload for manual adjudication. All patients will be followed until death or the end of the study (even if the primary outcome is determined to have occurred) to collect secondary outcomes including death.

The development of the screening process and the algorithms for confirming cases follows a systematic approach that we have used at MAVERIC for a number of years. The screening approach is used to identify all potential cases using key elements in the EHR. The screening tool varies for each outcome. Algorithms for cases are constructed using "gold standard" cases identified by manual review and data elements used in criteria for confirmation obtained from the medical record, such as cardiac enzymes for MI. Once the algorithm for a specific case is defined, the algorithms accuracy is checked by manual review of cases identified by the algorithm and adjudicated in this way.

A pilot study using VA EHR was conducted to determine the availability of potential cases and core data elements that would be needed to develop algorithms to assess the primary

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outcomes. A total of 150 medical records were reviewed, 30 in each category for stroke, myocardial

001 infarction and urgent coronary revascularization and 60 records of patients with a diagnosis of  
002 acute congestive heart failure. A medical record abstraction form for each outcome was  
003 developed based on standard diagnostic definitions that included information on symptom  
004 presentation, physical findings, critical laboratory values, radiographic or imaging findings,  
005 electrocardiographic results, hemodynamic data and administration of medications and  
006 therapeutic interventions (84, 98) During this study these data will be augmented with CMS  
007 data for all participants. Below we describe the approach to ascertainment of potential cases  
008 and the assessment of each.

009 Deaths: Death ascertainment from combined VA databases and Social Security has been shown  
010 to have comparable accuracy to the National Death Index and is more timely (99). We will  
011 collect data on deaths from combined VA databases (e.g., BIRLS, Medical SAS Inpatient),  
012 Medicare Vital Status, Social Security Administration Death Master File and the National Death  
013 Index.

014 The assigned cause of death will be determined by nosology protocols based on death  
015 certificate information obtained from the National and Social Security Death Indices using the  
016 International Classification of Diseases (ICD) in conjunction with the Automated Classification of  
017 Medical Entities (ACME) Decision Tables. ACME automates the underlying cause-of-death  
018 coding rules. The input to ACME is the multiple cause-of-death codes (ICD) assigned to each  
019 entity (e.g., disease condition, accident, or injury) listed on cause-of-death certifications,  
020 preserving the location and order as reported by the certifier. ACME then applies the World  
021 Health Organization (WHO) rules to the ICD codes and selects an underlying cause of death. This  
022 method has been shown to be accurate for general categories like cancer or vascular death (95).

023 Myocardial Infarction: For myocardial infarction, hospitalization ICD codes (410) as well as  
024 procedure and medications codes, such as lytic therapy, will be used to search for potential  
025 cases. MI codes labeled as "length of stay" diagnoses or labeled as "admitting" or "other"  
026 diagnoses will be considered as potential cases. While the admitting diagnoses can be  
027 overturned after admission [e.g., rule-out-MI scenarios] or may just indicate a previous history  
028 of an event that required consideration during the current admission but was not a current  
029 event, we still include these as potential cases. Cardiac enzyme laboratory values and ECG  
030 results can be extracted.

031 The definition of definite myocardial infarctions is based on third universal definition criteria. In  
032 our experience cardiac biomarker data are generally available. In a small review of 30 charts of  
033 potential MI, we found this to be the case. Based on this manual review of data extracted from  
034 30 charts we are confident that these cases can be identified and adjudicated accurately and  
035 only a small fraction will require manual adjudication.

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Stroke: For stroke using codes 430, 431, 432.x, 434.01, 434.11, 434.91, we were able to identify potential cases. Our review of 30 charts also provided confidence that the data elements for adjudication are available in the electronic records of potential cases. Based on the review of 30

charts, it appears that there will be a slightly higher number of indeterminate cases that will need manual adjudication than for MI but the proportion is still modest.

Unstable Angina with revascularization: The potential cases are easy to identify using a diagnostic code for coronary revascularization (e.g., ICD9 36.x or CPT 33510-45 or 92920-44 or 92997-8). Additional data on the reason for hospitalization such as a code for unstable angina (e.g., ICD9 411.1-.89, and we will explore 413 and 786.5) on the same admission as or up to 15 days before an inpatient procedure code can also be easily obtained. Additional data such as use of an appropriate platelet inhibitor can also be extracted. As there was greater heterogeneity among potential cases, further work will be required to create an acceptable algorithm. As expected we found a number of patients in this preliminary review that underwent coronary revascularization, but did not meet the unstable angina criteria. Further work will be needed to refine how to improve our identification of these cases and adjudication of these potential cases to reduce the number that will be needed to be manually adjudicated.

Acute hospitalization for congestive heart failure: This outcome is more complex than the previous three because it relies more heavily on unstructured data. We will construct an algorithm using such features as: a hospitalization ICD code for heart failure (398.91,402.01, 402.11, 402.91, 404.01, 404.03, 404.11, 404.13, 404.91, 404.93, 425.4x-425.9x, 428.x, 429.3, 514) whether this code is labeled as "length of stay" diagnosis or not. Because of the broad range of ICD-9 codes (15 unique codes) listed for acute congestive heart failure we uncovered considerable heterogeneity in the cluster of potential cases with these codes. We did find that certain ICD-9 codes resulted in a low yield for the primary outcome category. For example, none of the patients reviewed with an ICD-9 code 425.4 "Other primary cardiomyopathies", met the definition criteria for acute congestive heart failure. Additional features such as absence of a code for implantable cardioverter defibrillator placement (generally associated with a chronic rather than acute case of CHF in our review), and evidence of intensification of treatment (as defined above by the FDA expert panel and which can be extracted successfully from the medical record) will be used to construct the screening tools and the algorithms that will minimize the need for manual adjudication.

#### G. Adjudication of events

In cases where the outcome diagnosis is not clear based on the electronic adjudication, we will resort to manual adjudication to determine the validity of the diagnosis. Based on our 150 chart review, it is expected that fewer than 300 to 400 cases will require this form of adjudication. The adjudication will consist of a chart review by a physician of medical records pertaining to the hospital admission for VA admissions and a chart review of VA inpatient and outpatient records as well as CMS data following the discharge date for non-VA hospitalizations. In some cases, we may query the PCP as to whether a possible event occurred.

075 We will also manually adjudicate 10% of outcomes confirmed or refuted by our algorithms to  
076 serve as a quality check on the algorithms. We will develop near-final algorithms during the first  
077 year of the study, but will continue to refine the algorithms and retrospectively apply these  
078 refinements to all data.

079 H. Ascertainment of potential cases, adverse events and other case data

080 Investigators at the MAVERIC CSPCC unaware of treatment group will process potential cases  
081 and adverse events by collecting relevant codes, laboratory values, and prescription data from  
082 CPRS, the VA electronic medical record system (e.g., acute gout episode = ICD9 274.01). Blood  
083 pressures will be collected from routine clinic visits, and not from emergency room visits or  
084 inpatient stays, and only the reading with the lowest SBP of the day will be retained (99).

085 Section XIII details the data sources and the data collection (i.e., data extraction) procedures  
086 that will be used. When the study drug is discontinued, we may query the PCP as to the reason if  
087 not clear from the chart.



## XI. Biostatistical Considerations

### A. Overview of the Study Design

The proposed study is a prospective randomized open-label blinded-endpoint, multicenter, two arm intervention trial testing the effectiveness of chlorthalidone for prevention of cardiovascular events and non-cancer death among patients currently receiving hydrochlorothiazide. The primary hypothesis is that chlorthalidone is superior to hydrochlorothiazide for the prevention of cardiovascular events and non-cancer death over time.

The primary outcome measure is time from enrollment in the study to the first occurrence of a cardiovascular event or non-cancer death. Cardiovascular (CVD) events are defined as stroke, myocardial infarction, urgent coronary revascularization, and hospitalization for acute congestive heart failure. The results for CVD and non-cancer death event-free survival will be analyzed by means of a two-sided log-rank test.

The study will have one interim analysis and one final analysis.

#### 1. Estimated Incidence of the Primary Endpoint

This study will enroll a total of 13,500 patients, 6,750 of whom will receive chlorthalidone and 6,750 of whom will receive hydrochlorothiazide. We expect to enroll, on average, 90 patients per year for three years to accrue approximately 270 patients per site at 50 VA medical centers. All subjects will be followed through the end of the four and one-half (4.5) year study period yielding an average follow-up time of three (3) years. We posit a four and one-half year rate of 13.5% of the composite outcome in the hydrochlorothiazide group and 11.1% in the chlorthalidone group. We utilized the VA National data from fiscal years 2010 to 2012 to identify a subgroup of subjects who would be potentially eligible for the proposed study. Details of the analysis can be found in **Section XII. Feasibility and Recruitment Plan.**

The cardiovascular event rate, using a composite similar to that proposed here, was 2% per year in ALLHAT (20) and ACCORD (101), and is projected as 2% for the ongoing SPRINT. Unlike those studies, we are limiting enrollment to patients over age 65 years and are not excluding very old or seriously ill patients (unless life expectancy is known to be less than 6 months), and we are including all non-cancer deaths rather than only cardiovascular deaths, all of which would be expected to increase the event rate. For patients 65-79 years old with no serious illness (and creatinine <1.5 mg/dL) in ACCORD, the composite event rate (stroke, myocardial infarction, and cardiovascular death) was 2.8% per year (96). Our event rate should be higher because we include urgent revascularization, acute heart failure, and non-cancer deaths. ANBP2 enrolled patients over 65 years but included all deaths in the composite, and observed an event rate of

.23 >4% per year (19).

We believe that the most relevant event rates for our study come from the Ontario observational study (29) comparing chlorthalidone with hydrochlorothiazide, discussed above. The Ontario study is both recent, published in 2013 and reporting data from 1993 to 2010, large (nearly 30,000 patients), and shares important features with our proposed trial, including: 1) study patients are aged 66 and older and taking diuretics for hypertension, 2) outcome data were collected passively from administrative databases, and 3) the primary outcome was a composite similar to the one we are proposing, with two differences: a) they did not include urgent revascularization, and b) they included all deaths whereas we do not include cancer deaths.

We expect these 2 differences to very nearly cancel each other's effect. The rate for the Ontario composite outcome was 3.4% per year in the hydrochlorothiazide group. The rate for all deaths was 1.8% per year, or 45% of the total number of individual outcomes (some patients had more than one of the composite outcome elements). Many studies, such as the Physicians Health Study

(95) have found that all deaths in this age group are comprised of roughly 1/3 each of deaths due to cardiovascular disease, cancer and other causes, suggesting that our exclusion of cancer deaths would reduce the composite rate by 15%. In the (TRA2°P)-TIMI 50 trial (86), urgent coronary revascularization was less frequent than myocardial infarction (0.82% in the Ontario study, or 20% of the total number of individual outcomes) and similar in frequency to stroke (0.46% in the Ontario study, or 11% of the total number of individual outcomes), suggesting that our inclusion of this outcome will raise the composite by 10-15%.

These adjustments result in a best estimate for the expected composite rate of about 3.2% per year. For the proposed study, because event rates tend to decrease over time, we conservatively project a 3% per year event rate in the hydrochlorothiazide group.

## 2. Effects of the Intervention

Of 125,000 VA patients started on drug in routine practice in 2004, 72% of hydrochlorothiazide users and 62% of chlorthalidone users remained on the drug 1 year later (28). Onsite coordinators in standard trials may be able to maintain better drug adherence than occurs in usual practice. ACCORD (101) and SPRINT (84) considered a 20% relative reduction to be an appropriate minimum important difference for power calculations. Because the difference in outcomes in our study could be reduced by patients coming off drug more often than in previously published trials, we reduce the minimum important difference value to **17.5%**. A reduction in CVD events or non-cancer death of this magnitude or greater would be considered clinically significant.

## B. The Primary Analysis

.59 We posit a four and one-half event rate of 13.5% in the hydrochlorothiazide group and a 17.5%  
.60 reduction of CVD events in the chlorthalidone group to inform our primary hypothesis.

.61 Formal statement of the primary hypothesis

.62 Under the null hypothesis:

The 4.5 year event rate will be 13.5% (or 578 primary events)

Under the alternative hypothesis for study participants treated with chlorthalidone:

The 4.5 year event rate will be 11.1% (or 477 primary events)

The reductions attributed to chlorthalidone may be viewed in several ways. The absolute reduction from 13.5% to 11.1% is 2.4%, the relative reduction is  $(13.5 - 11.1)/13.5 = 17.5\%$ , and the hazard ratio (chlorthalidone hazard rate/hydrochlorothiazide hazard rate) of 0.81 is approximately midway between the simple odds ratio,  $11.1(100-13.5)/13.5(100-11.1) = 0.80$  and the risk ratio  $11.1/13.5 = 0.82$ .

Formally, the null hypothesis is that the two treatment groups do not differ in their time-to-event hazard rates. The alternative hypothesis is that chlorthalidone has a lower or higher hazard rate than hydrochlorothiazide therapy with a hazard ratio for chlorthalidone compared to hydrochlorothiazide less than 0.82 or greater than 1.22. We will test this hypothesis with a two-sided log-rank test.

### **C. Sample Size and Statistical Power Considerations for the Primary Hypothesis**

The formal hypothesis test is two-sided allowing for chlorthalidone to be either more or less effective than hydrochlorothiazide. A significant difference showing that the intervention chlorthalidone compared to the control hydrochlorothiazide decreases (or increases) the hazard of a major cardiovascular event will be regarded a positive result. The results for the primary outcome measure will be analyzed by means of the two-sided log-rank test to detect either a hazard ratio that exceeds 1.22 or is less than 0.82. The test will have a two-sided 5.9% type I error. The test has 90% power to detect a hazard ratio of 1.22 or larger or 0.82 or less with a total of 13,500 study participants, 6,750 per arm. The remaining Type I error of 0.1% is used for the interim analysis.

If the annual event rate is 2.5% (rather than the posited 3%), then the study has 84% power; if 2%, it has 75% power.

### **D. Primary Data Analysis**

The primary outcome hypothesis will be a time-to-event analysis with the use of a two-sided log-rank test based on intention-to-treat principles. The model will not include any covariates.

Analytic reports will include hazard rates, their ratio, and the 95% confidence interval about the ratio.

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This will be followed by further refined covariate-adjusted exploratory analyses, using Cox proportional hazards regression modeling, controlling for baseline factors. Covariates will include demographic factors (e.g., age, sex, smoking status, education) and clinical factors (e.g.,

blood pressure, medications, comorbidities, history of disease, and BMI). We will test the proportional hazards assumption by including a time-treatment interaction term in the model.

### **E. Interim Analysis**

We will perform one interim analysis when the 500<sup>th</sup> event occurs, approximately 3.5 years after initiation of enrollment. Assuming a uniform rate of enrollment over time, the first patient entered will potentially have 3.5 years of follow-up and the last patient entered will potentially have 0.5 years of follow-up. Thus, we will have an average follow-up time of approximately 2 years on 13,500 subjects.

Using the O'Brien Fleming procedure, this interim analysis will have a type I error of 0.1%, which negligibly decreases the overall type I error and has virtually no effect on the power to show that chlorthalidone is different from hydrochlorothiazide. The sample size of 13,500 accounts for the interim analysis with a corresponding inflation factor, for increase in sample size of 1.001, resulting in 14 more subjects per arm (102). We will confer with the Data Monitoring Committee (DMC) members and the program leadership for potential stopping guidelines based on findings from the interim analysis.

### **F. Secondary Data Analysis**

#### **1. Treatment Effect in Subgroups**

The Cox regression modeling will explore the possibilities of treatment variation across pre-specified subgroups based on status at time of enrollment including:

- a) gender,
- b) age (dichotomized at median),
- c) baseline SBP (dichotomized at median),
- d) history of MI or stroke,
- e) black race vs. not,
- f) diabetes vs. not,
- g) eGFR < 60, and
- h) good compliance (medication possession ratio  $\geq$  80%) with hydrochlorothiazide over the year before randomization.

#### **2. Individual Components of Primary Outcome**

In addition to the subgroup analyses listed above, each component of the composite primary outcome measure (stroke, myocardial infarction, urgent coronary revascularization, hospitalization for acute congestive heart failure, and non-cancer death) will be separately analyzed using log-rank and Cox proportional hazards models to compare chlorthalidone and hydrochlorothiazide. The Cox analyses will include the covariates considered in the primary data analysis.

3. Additional Outcomes of Interest (Analysis of Secondary and Tertiary Objectives)



In addition we will run time-to-event analyses comparing the treatment effect on:

- a) all-cause mortality,
- b) the composite outcome substituting all deaths for non-cancer deaths,
- c) vascular deaths defined as all deaths caused by diabetes, vascular diseases, external causes, and unknown causes,
- d) the composite outcome substituting vascular deaths for non-cancer deaths,
- e) any revascularization of an artery,
- f) hospitalization for primary diagnosis of hypokalemia, hyponatremia, or renal failure,
- g) other hypokalemia (< 3.5 meq/L), hyponatremia (< 130 meq/L), or renal failure,
- h) new diabetes, requiring medications, defined as first use of medication for diabetes,
- i) acute gout episode,
- j) erectile dysfunction (ED), defined as first prescription for PDE5 inhibitor or referral for ED, and
- k) new allergic reaction to thiazide-like diuretic, defined as new flag warning in CPRS

#### 4. Primary Care Provider Metrics of Interest.

- a) percent of patients approved
- b) percent of approved patients for whom order signed
- c) reasons order not signed
- d) rate of discontinuation of both drugs
- e) reasons for discontinuation of both drugs

#### 5. Medication Compliance

We will compare treatments with respect to overall compliance (adherence) to the randomly assigned medication, indirectly measured by the medication possession ratio (MPR) and average daily dose (ADD). The comparison will be made using a GEE analysis to account for varying periods of follow-up. The potential period ends if the subject dies, has an outcome event, or changes medication. Subjects categorized as medication compliant will make up the per-protocol subgroup of the study cohort.

#### 6. Non-acute Outcomes

The repeated measures of systolic blood pressure during the disease-free intervals (free of component events) will be compared by treatment. We will use a mixed effects repeated measures model allowing for irregular time intervals, the spatial power law extension of AR(1) covariance option where  $r(t_1, t_2) = \exp(-\lambda |t_1 - t_2|)$ . In each model we will assume linear growth over time. A random effect will be included for both intercept and linear time. The hypotheses will test if SBP increases/decreases over time for subjects receiving chlorthalidone, if SBP increases/decreases over time for subjects

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receiving hydrochlorothiazide, and if both have non-zero slopes, a test of whether they differ or are equal.

We will conduct a time-to-event analysis comparing treatments for the outcome of time to first discontinuation of assigned diuretic (defined as no prescription for  $\geq 3$  months at last observation during study period) and time to first protocol deviation from assigned diuretic.

## G. Exploratory Objectives

The primary intent to treat analyses of randomly assigned treatments takes no account of post-baseline changes such as protocol deviations and treatment switches from chlorthalidone to hydrochlorothiazide (and vice versa). Thus, exploratory analyses will model such changes to assess robustness of conclusions.

The per-protocol analysis will determine if chlorthalidone and hydrochlorothiazide differ among the subset of protocol compliant subjects. We will run other analyses that include all subjects and attempt to model the time-dependent effects of protocol deviations such as medication changes and levels of compliance. Frailty analyses will assess center effects. We will explore censoring patterns such as models that assume not missing-at-random censoring (103).

A change in medication may alter the subsequent risk of a cardiovascular event. First, we will add time-dependent covariates to a Cox model, such as binary indicators of a switch from chlorthalidone to hydrochlorothiazide, switch from hydrochlorothiazide to chlorthalidone, and the start of new medication that interacts with chlorthalidone or hydrochlorothiazide. To directly estimate subsequent risk, we will use a multistage model (MSM) to assess the hazard rate of a major cardiovascular event after a switch (104). MSM models extend the time-to-first-event models to second, third, and more events. This extension of the Cox model allows direct estimation of the hazard rate associated with any transition adjusted for previous history and baseline characteristics. Within MSM we will carry out a competing risks analysis to assess the effect of cancer deaths.

## H. Randomization

To control for potential imbalance in randomization, both stratification and blocking will be employed. The randomization scheme will be stratified by participating site to account for possible regional differences in clinical practice. Participants will be randomized to either hydrochlorothiazide or chlorthalidone within blocks of size 6.

Enrollment and randomization of subjects will occur in accordance with **Section IX. Study Procedures** and **Appendix C. Recruitment Flowchart**.

## XII. Feasibility and Recruitment Plan

### A. Feasibility

In 2012, 69 VA medical centers prescribed single-agent hydrochlorothiazide 25 mg or 50 mg to at least 2000 patients over age 65 (**Appendix E.1**). In VISN1, 80% of these had SBP  $\geq$ 120 mm Hg at last measurement with no SBP measurement below 120 mm Hg in the previous 90 days (**Appendix E.2**). Applying these regional SBP data to the national medical center data, in 2012 there would have been 76 VA medical centers with  $\geq$ 1500 eligible patients and 104 centers with

$\geq$ 1000 eligible patients.

Based on experience with the CONFIRM study (CSP #577) and the Million Veteran Program and other sources, we estimate that: 15% of PCPs will opt out; PCPs who don't opt out will exclude 5% of their patients; 5% of patients mailed the initial letter will opt out; we will reach 65% of patients we attempt to call; 60% of those we reach by phone will agree to be randomized; 2% of those who agree by phone will opt out or be removed by their PCP before randomization. Combining these rates:  $(.85)(.95)(.95)(.65)(.6)(.98) = .29$ , suggesting we should expect to enroll about 30% of eligible patients identified.

Based on these considerations, randomization of 13,500 patients (270 per site at 50 sites) should be feasible. We anticipate that this process will take 3 years, a duration that could be adjusted by the level of staffing of the central call center. If recruitment falls short of our expectations, our primary strategy will be to add additional sites as needed.

### B. Recruitment Plans

As previously described the primary recruitment plan will be to enroll patients who have been identified through the corporate data warehouse as being eligible and cleared by their PCP through the direct mailing of an opt-out letter followed by telephone based consent. Enrollment will be initiated in 3 VISNs at the start of the study. This will allow the DCP team to learn about the feasibility of recruitment, to identify issues with provider participation and CPRS use, and to refine the primary recruitment plans based on the experience from the vanguard sites. Patients will also be allowed to self-refer to the study call center as well. In this regard, the DCP will allow all patients fitting the eligibility criteria to be enrolled regardless of how they were identified.

In addition, we will initiate 20% more sites (i.e., 10 additional sites) than what is needed for successful enrollment into the study. As sites fail at recruitment or as the potential patient pool decreases at the vanguard sites, enrollment into the DCP will be started at the 10 additional sites. Should this occur, the financial support for the failing sites will be transferred to the new sites.

### **XIII.Data Collection and Data Sources**

Data for this study will be obtained from the medical and administrative data that are collected and maintained by the United States Department of Veterans Affairs (VA) Corporate Data Warehouse (CDW). This database covers the entire veteran population that utilizes the VA and contains individual information on demographic factors, medical history, key laboratory values, procedure codes, and diagnoses (inpatient and outpatient) coded with the ICD-9-CM classification system. Healthcare encounters outside of the VA system will be captured using Medicare data that will be obtained from VIREC for this project. Data from the various VA databases will be linked together using a unique veteran identification number that is assigned to each veteran at entry into the system.

Deaths will be ascertained from the VA Vital Status File. This file allows for complete ascertainment of death as it pulls data from multiple sources, including: the Beneficiary Identification and Records Locator Subsystem database; the Death Master File from the Social Security Administration; and the National Patient Care Database. Ascertainment of death with this method has demonstrated 98% sensitivity and 98% agreement with the National Death Index.

We will monitor for discontinuation or expiration of the assigned diuretic, detection of which will prompt queries to the PCP asking the reason. No effort will be made by the study to influence blood pressure goals or the prescribing of other drugs.

#### **XIV.Data Management and Data Security Plans**

The MAVERIC CSPCC will create and maintain an electronic study database to manage the trial data. All study data will be collected electronically from CPRS by the Coordinating Center throughout the duration of the study. There will be no paper-based study documents.

Study data is housed on secure VA servers, encrypted and protected in accordance with VA policies compliant with FDA requirements, Federal Information Security Management Act and the HIPAA Privacy and Security rules. MAVERIC CSPCC personnel manage the data access request process for the electronic systems to ensure that data access is appropriate for each individual and the level of the individual access. VA's Office of Information & Technology (OI&T) is responsible for managing other VA system access and ensuring the security and integrity of VA information systems, including the databases and servers housing study data. In accordance with VA Handbooks and Directives, OI&T is responsible for ensuring that appropriate firewalls and data security is implemented and maintained, that data backups are performed and that data may be restored in the event of a system malfunction.

Data security incidents will be classified into two main categories for reporting: local incidents (i.e., those occurring at MAVERIC CSPCC), and field-based incidents (i.e., those occurring at the clinical sites managed by the center). Incidents will be reported according to 1058.01. All MAVERIC CSPCC staff will be expected to report data security incidents to the responsible authority as they become aware of the breach. Whenever possible, the reporting of data security incidents will be handled by the MAVERIC CSPCC Associate Center Director for Quality Assurance (ACDQA). This will be done to facilitate communication between the center and the oversight bodies. In the event that an incident must be reported by a staff member other than the ACDQA, all communication after the initial report will be handled by the MAVERIC CSPCC Center Director or the MAVERIC CSPCC ACDQA. [Note: all new and current MAVERIC CSPCC personnel will be trained on reporting data security incidents on a yearly basis.]

All local data security incidents will be reported in accordance with VA policy within one hour of discovering the incident to:

1. The Boston Information Security Officer (ISO)
2. The Boston Privacy Officer (PO)
3. The Boston ACOS for Research
4. The MAVERIC CSPCC Quality Assurance department

The MAVERIC CSPCC will ensure that all field-based data security incidents are reported in accordance with VA policy within one hour of discovering the incident to:

1. The District (local) Information Security Officer (ISO)
2. The District (local) Privacy Officer (PO)
3. The District (local) ACOS for Research

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4. The MAVERIC CSPCC Quality Assurance department

In addition, field-based data security incidents will be treated as unanticipated problems by the MAVERIC CSPCC and reported to the VA Central IRB according to the procedure detailed below for unanticipated problems (Section XVII.C.3).

Study data will be coded and stored using a unique study identifier for each participant. Identifiable information will be collected for patient tracking and safety purposes, and kept in an encrypted, password protected file to which a small number of people will have access. Access to the cross-walk file linking the participant's identifiers and their study data will be restricted to the approved personnel at the CSP coordinating center. This file will be destroyed according to CSP policy well after the close of the study.

Access to the study data is restricted to individuals with CSP approval. Individuals must be properly credentialed research staff and must be compliant with VA security trainings (e.g. HIPAA, Rules of Behavior, and Good Clinical Practices). Once formal training is completed, user accounts utilizing a URL specific to the study to access and use the system and enter patient data will be activated. Accounts will be password protected and unique to the each user. The account permissions will correspond with the users' functional study group (i.e., those for a study chair would differ from those of the coordinating center). Furthermore, the permissions of the electronic systems are heavily restricted. The site Liaisons will not have access to study data.

Research data will be stored on VA secure servers with restricted permissions for copying and exporting data. Only properly approved Coordinating Center personnel will have the ability to copy and export data. These individuals have received training on the local standard operating procedure (SOP) governing their permissions. Access to protected health information (PHI) will be restricted to individuals approved by CSP to have access to the data.

At the MAVERIC CSPCC the following staff will have access to all forms of PHI:

1. Center Director
2. Study Director
3. Project Management
4. Nurse Coordinator
5. Data Management
6. Biostatisticians
7. Quality Assurance Officer



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8. SAS/Database Programmer

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9. Research Assistant

10. Clinical Applications Coordinator

11. Informatics Team

Periodic access control assessments will be made by Coordinating Center Quality Assurance personnel to verify that access is controlled and appropriate for personnel. In addition, the CSPCC QA group will provide continuing education on good clinical practices compliance and will evaluate clinical site operations for violations of VA policies including VA data security policies and GCP.

At the end of the study, the data for DCP will remain property of the Cooperative Studies Program and be stored and shared according to CSP guidelines and procedures. Retention and destruction of data will be conducted according to CSP operating procedures and federal and local VA regulations. This will include electronic data stored at the MAVERIC CSPCC, and at the VA facility housing our servers. Identifiable data will be kept according to CSP policy as outlined in the "CSP Guidelines for the Planning and Conduct of Cooperative Studies".

## **XV. Human Subjects**

### **A. Waiver of HIPAA authorization**

A waiver of HIPAA authorization to use VA data to determine eligibility will be requested because the research could not practicably be conducted without access to and use of this information. In order to conduct the study, it is necessary to first be able to identify eligible patients so that the recruitment letter can be mailed to them.

We will also request IRB approval for a waiver of HIPAA authorization to collect data prospectively. Unlike traditional randomized clinical trials, a feature of the POC methodology is that data collection is performed by passive data capture. All data elements will be collected electronically from CPRS/VISTA using both the Veteran's Information and Computing Infrastructure (VINCI), a collaborative effort between the VA Office of Information Technology and the VA Office of Research and Development, and the Office of Information Technology's Corporate Data Warehouse (CDW). Healthcare encounters outside of the VA will be captured using Medicare data. Data from the various VA databases will be linked together and maintained using a unique veteran identification number (not SSN). Access to the cross-walk file linking the participant's identifiers and their study data will be restricted to approved personnel at the CSP coordinating center.

Because data abstraction is done electronically and not by staff perusing the electronic medical record we believe that a waiver of HIPAA authorization is justified and involves no more than minimal risk to the privacy of individuals, particularly since the protected health information of the patients will remain within the VA. Moreover, it would be impractical to obtain a signed authorization from patients in this study for use of their health information. The PCP's cannot obtain a written HIPAA authorization for research purposes from patients who are subjects in this study because they will not see the patient until weeks or months after the patient has been on the randomized treatment. The PCPs are not study team members. We plan to identify and disclose to participants in our information statement the health information to be collected and the specific databases from which it will be obtained.

In both instances, the patient eligibility screening and the prospective collection of patient data, the use of the requested information involves no more than minimal risk to the privacy of individuals based on the security measures used by the MAVERIC CSPCC to protect the identifiers from improper use and disclosure, and to destroy the identifiers at the earliest opportunity consistent with conduct of the research. The requested information will not be reused or disclosed to any other person or entity, except as required by law, for authorized oversight of the research study, or for other research for which the use or disclosure of the requested information would be permitted by the Privacy Rule.

182 B. Basis for waiver of Documentation of Informed Consent

183 Though we are not planning to obtain written informed consent, multiple measures are in  
184 place to ensure that all subjects are given all of the information they need in a manner that is  
185 understandable before they consent and throughout the study. Primary care providers will  
186 receive information through site liaisons as well as an introductory letter that is both mailed and  
187 emailed to their VA addresses prior to receiving the initial testpatient order in CPRS. The initial  
188 testpatient order will be sent together with a progress note containing the Provider Information  
189 Sheet and by signing the testpatient order, the providers are consenting to participate. Provider  
190 participation is completely voluntary and minimal risk, facts that will be reiterated throughout  
191 this process.

192 Patients are sent a transcript of the consent and an explanatory letter with study contact  
193 information before the first phone call, full consent is obtained on the call, and they are  
194 informed of the randomized group after the call.

195 In this study, the relevant risks involved are those of changing therapy of half of the patients  
196 from hydrochlorothiazide to the equivalent dose of chlorthalidone, a very similar drug with the  
197 same indications and metabolic effects, plus the theoretical risk to confidentiality from  
198 compiling individual data.

199 Regarding the former, both drugs have been in use for more than 50 years, have long been  
200 available as generics, and are included in the VA national formulary in the same drug class: USP  
201 code CV 701, thiazide-type diuretics. The VA frequently selects one member of such a class to  
202 make available "on formulary" based on cost or other considerations, and VA Pharmacy and  
203 Therapeutics Committees will direct VA pharmacies to substitute drugs within a class when one  
204 drug becomes unavailable, so it is not uncommon that VA physicians and patients have limited  
205 choice within a class.

206 While thiazide-type diuretics affect some blood chemical levels as discussed above, these  
207 effects have not demonstrated adverse clinical impact that would affect their being the  
208 preferred treatment for hypertension. Furthermore, our plan to substitute an equivalent dose  
209 of chlorthalidone for the current dose of hydrochlorothiazide, i.e. half the number of milligrams,  
210 would be expected to have an effect on blood pressure and on blood chemical levels, small  
211 enough to be virtually indistinguishable from the variation in these parameters that would  
212 ensue with remaining on the prescribed hydrochlorothiazide (see Background and Rationale,  
213 parts F and I). We therefore propose that the study intervention qualifies as minimal risk.  
214 Because the two drugs are used interchangeably, and the choice between them is not  
215 influenced by any patient factors, but only by physician preference, randomization does not  
216 reduce individualization of patient care. Care remains personalized after randomization because  
217 the PCP manages the diuretic as usual. The patient's needs are thus not subordinated to the  
218 needs of the

trial. Furthermore, because hypertension is a chronic condition, randomized patients will themselves be among those expected to benefit from the information gained from this study.

In their article "Randomized, controlled trials as minimal risk: an ethical analysis", Morris and Nelson (106) conclude that "A randomized, controlled trial poses no more than minimal risk only when all of the following five criteria are met: 1) genuine clinical equipoise exists; 2) all of the treatment options included in the research study fall within the current standard of care; 3) there is no currently available treatment with a more favorable risk-benefit profile than the treatments included in the research study; 4) the nontherapeutic components of the research are safely under the minimal risk threshold; and 5) the research protocol provides sufficient latitude for treating physicians to individualize care when appropriate." We have designed this study to meet all of these criteria.

We believe that the waiver of Documentation of Informed Consent that we are requesting is necessary to the successful completion of our study because obtaining the required sample size within the VA is only feasible if recruitment is maximally efficient, as described in the Feasibility section (XII.A). Published evidence demonstrates that requiring that written consent be returned by mail is likely to result in the loss of the great majority of patients who intend to consent (107-111). If requirement of returned written consent caused loss of most willing patients from our study, it is unlikely that it could be completed within the VA system.

Based on these considerations, we will request IRB approval of a Waiver of Documentation of Informed Consent. Under the terms we are requesting for the Waiver, patients would be recruited by mail, and the elements of consent obtained over the phone, a written summary of the consent will be sent to the patient, but a signed returned document would not be required.

Enrolled patients will be given study contact information for questions or withdrawal.

### C. Engagement in Research

For this study, we consider the site Liaison and the PCP's to be not engaged in research. The site Liaison (sometimes called a "Champion" in other studies) serves to provide information to local site personnel about the study and relays information and questions back to the coordinating center, but in our view takes no action that qualifies as research. The PCPs facilitate implementation of the intervention (after patients provide consent and are randomized by study personnel) by signing an order sent to them by study personnel. The PCPs are themselves research subjects in whom we are studying the implementation of the protocol.

## **XVI. Quality Control Procedures**

Data that is extracted for the DCP will be cleaned and managed according to a rigorous data management plan that will be written in conjunction with the statistical analysis operations plan and the study operations manual (for chairs office and CSPCC personnel). However, the data will also be subject to quality control procedures. As a first line effort to ensure the validity of the data, 100% of the data elements collected from the first 10 individuals from each medical center will be subject to source verification and validation through chart review that will be done by an experienced clinician and clinical applications coordinator. In addition, chart review done through the creation of the algorithms to identify outcomes for the DCP will also be used to perform QC procedures on the data.

In addition, the quality management system (QMS) in place at the CSPCC will ensure further quality control for the DCP. The Quality Assurance Department of the CSPCC will subject the data to risk based audits that will verify and validate data elements according to internal SOPs for conducting risk based monitoring and auditing. In brief, a sample of the data will be verified at routine intervals. If errors are identified they will be referred to the data management teams at the MAVERIC CSPCC or at VINCI for resolution. If the error level rises to a predefined threshold, then the entire record or data element type will be subjected to verification and validation. Further, the CSPCC will conduct internal audits to ensure the quality of the clinical trial processes and procedures. If deviations or non-conformances are identified they will be remedied through the internal corrective action/preventive action system of the QMS.

## **XVII. Study Monitoring Plan**

### **A. Introduction**

The safety issues related to hydrochlorothiazide and chlorthalidone are well established in the medical literature and both diuretics are accepted first-line treatments for hypertension. Based on this information the study poses minimal risks to participants beyond the expected adverse events (AE) associated with the administration of either drug as part of "usual" care.

Monitoring side effects and adverse events in the traditional manner of usual clinical trials is not feasible for Point of Care studies since there are no site personnel and all data is captured passively through the EMR. In addition, real-time monitoring will neither provide new information regarding the safety of these two treatments nor assure adequate (or timely) safety of human subjects beyond that already done by the medical staff as part of routine medical care. Accordingly, we propose an alternative safety reporting plan for the DCP study that ensures protection of the participants and that complies with VHA Policy (i.e., VHA Handbooks 1200.05 and 1058.01). In brief, health providers will identify, monitor, and treat (as necessary) adverse events that occur during the course of the study. The CSPCC will identify the events through the EMR and report them to the monitoring committees for the trial. The sections that follow describe in more detail the proposed safety monitoring and reporting plan for this trial.

### **B. Safety Monitoring Plan**

The participant's physicians, nurses, and other health providers will continue their usual monitoring of the subject throughout the course of his/her treatment. If any treatments are indicated, they will be provided by health providers as a part of the participant's routine medical care. The CSPCC staff will collect safety data from the medical record from the time of consent through the end of the study period. The safety data will then be aggregated and classified according to ICD-9 codes.

Aggregated safety data will be reported to the Data Monitoring Committee, the study Executive Committee, and the VA Central IRB using the processes described in Section C. Please refer to Section XVIII Study Organization and Administration for a more detailed description of the oversight committees for the trial.

In addition to data culled from the EMR, the trial will allow for spontaneous reporting of events by study participants. The informed consent script and information sheet will include the contact information for the study coordinating center personnel should the participant wish to communicate safety concerns with the study team.

### **C. Safety Reporting**

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1. Adverse Events



Adverse events will be collected using the 21 CFR 312.32, International Conference on Harmonisation (ICH) for Clinical Safety Data Management (ICH-E2A), and CSP Global SOP

3.6 definitions. Adverse events (AEs) are defined by the 21 CFR 312.32 as "any untoward medical occurrence associated with the use of a drug in humans, whether or not considered drug related."

According to ICH-E2A,"an AE, therefore, can be any unfavorable or unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the study interventions."

Expected adverse events of interest related to diuretics will be culled from the EMR as part of the outcome ascertainment activities of this protocol. The expected AEs of interest will be:

1. Hospitalization for primary diagnosis of hypokalemia, hyponatremia, or renal failure
2. Renal failure (dialysis, vascular access for dialysis, renal transplant)
3. Other recorded hypokalemia (< 3.1 mEq/L), or hyponatremia (< 130 mEq/L)
4. New diabetes, defined as first use of an outpatient medication for diabetes
5. Acute gout episodes
6. New allergic reaction to thiazide-type diuretic, defined as new entry in Allergies/Adverse reaction (ART) database

These safety events are monitored and treated as part of routine medical care. These events will be identified by the CSPCC through the electronic medical record (EMR). Informatics staff at the MAVERIC CSPCC will extract medical record data on all subjects monthly and identify adverse events through ICD-9 codes, laboratory values, and medication files. Expected adverse events will be reported to the DMC as secondary and tertiary outcomes in semi-annual reports. Data will be in the form of aggregated data tables detailing the frequencies of these events by blinded treatment group. These events will be reported to the Central IRB in blinded aggregate form at the time of continuing review.

Adverse events which develop into Serious Adverse Events, as defined below, will be reported as such.

## 2. Expected Serious Adverse Events

Serious adverse events (SAEs) are a subset of adverse events defined in 21 CFR 312.32(a) and VA Handbook 1058.01 paragraph 4(w), as follows:

Definition of SAE from CFR 312.32 (a): Serious adverse event. An adverse event or suspected adverse reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of the following outcomes: Death, a life-threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, or a congenital

540 anomaly/birth defect. Important medical events that may not result in death, be life-  
541 threatening, or require hospitalization may be considered serious when, based upon  
542 appropriate medical judgment, they may jeopardize the patient or subject and may require  
543 medical or surgical intervention to prevent one of the outcomes listed in this definition.

544 Definition of SAE according to VA Handbook 1058.01: An SAE is an AE in human research that  
545 results in death, a life-threatening experience, inpatient hospitalization, prolongation of  
546 hospitalization, persistent or significant disability or incapacity, congenital anomaly, or birth  
547 defect. An AE is also considered serious when medical, surgical, behavioral, social, or other  
548 intervention is needed to prevent such an outcome.

549 The intervention in this study is the switch from hydrochlorothiazide to an equivalent dose of  
550 chlorthalidone, two widely-used diuretics with well-known risk profiles. There are no safety  
551 events that are unanticipated in regard to these two drugs. Thus, serious adverse events  
552 defined above that are feasibly identified through the medical record will be reported in  
553 aggregate to the DMC at 6 month intervals and to the Central IRB at continuing review.

554 Informatics staff at the MAVERIC CSPCC will extract medical record data on all subjects  
555 monthly and will identify adverse events through ICD-9 codes, laboratory values, medication  
556 files and the VA vital status files (i.e., BIRLS and the Master Death File). Expected serious  
557 adverse events will be reported to the IRB at the time of continuing review in aggregated data  
558 tables detailing the frequencies of these events. Study reports will also be circulated to  
559 appropriate members, including the study chairmen and DMC.

560 This study will not use MedDRA coding of AE and SAE data. The study team will define events  
561 using the data sources described above and categorize events by system organ class and  
562 assessment type for reporting.

### 563 3. Unanticipated Problems Involving Risks to Subjects and Others

564 Any unanticipated problems involving risks to subjects or others (UPRs), but not qualifying as a  
565 serious adverse event by definition (such as errant distribution of study medication), will also  
566 be reported. Unanticipated problems related to the study design will be reported to the IRB in  
567 an expedited fashion (within 5 business days of identifying the problem). Possible events  
568 include failure to distribute study drug, patient continuing previous prescription while taking  
569 study drug, or patient randomized without provider knowledge. Informatics staff at the  
570 MAVERIC CSPCC will extract medical record data on all subjects monthly allowing for the  
571 identification of UPRs at fixed intervals. Study reports will be circulated to appropriate  
572 members, including the study chairmen.

UPRs that result in an SAE, pursuant to the definition above, will be reported as an SAE to the VA Central IRB within 5 business days by the MAVERIC Boston CSP Coordinating Center after becoming aware of the event.

## **XVIII. Study Organization and Administration**

### **A. Administration**

The administrative structure of this study is similar to others in CSP and includes:

The Cooperative Studies Program (VA Central Office) establishes overall policies and procedures that are applied to all VA cooperative studies through the Study Chair's office and the CSPCC.

The CSPCC and the Study Chair's office jointly will perform the day-to-day scientific and administrative coordination of the study. These include developing and revising the study protocol; abstracting data from the national databases (CSPCC Only); ensuring the appropriate support for the participating centers; scheduling meetings and conference calls; answering questions about the protocol; conducting site visits; publishing newsletters. The CSPCC will also prepare interim and final progress reports; and archive study data at the end of the study. Study progress reports will be produced every 6 months. Patient accrual, patient safety, and data quality will be monitored closely by the CSPCC, the study executive committee, and the DMC to ensure that the study is progressing satisfactorily. Further delineation of responsibilities will be documented in communications with the Study Chair's office.

The CSPCC will be responsible for monitoring and reporting the safety of trial participants through the review, assessment, and communication of adverse events and serious adverse events detected within the national data systems. The CSPCC will document trends and analyze safety data to prepare reports for various committees including the DMC, VA Central IRB (CIRB), Executive Committee(s), and Study Group meetings.

The Canandaigua VA Medical Center will serve as a centralized call center for this study. The CSPCC will work closely with Canandaigua to track eligible participants as they move through the recruitment and enrollment workflow. The primary responsibilities for the Canandaigua call center include contacting patients by telephone to obtain verbal informed consent and receiving incoming patient phone calls. .

The CSP Clinical Research Pharmacy Coordinating Center (CSPCRPCC) will provide advice and consultation about drug-related matters, review safety information, and serve as a regulatory affairs expert and liaison to the FDA for regulatory matters.

The Clinical Sciences Scientific Evaluation Committee (CSSEC) reviews the scientific merit of all new cooperative study proposals and all ongoing cooperative studies. The committee is composed of both VA and non-VA clinical research scientists, most of whom have had experience in managing their own cooperative studies.

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The Study Group will be composed of the SLs from each participating center, the Study Chair, Study Director, and CSP staff (biostatistician, project manager, and others). The Study Chair will

711 head the group, which will meet once a year to discuss the progress of the study, any problems  
712 that the study team has encountered, and any suggestions for improving the study.

### 713 B. Monitoring

714 The following groups monitor the various aspects of the study. These committees will meet  
715 according to current Cooperative Studies Program guidelines.

716 The Executive Committee is responsible for the operations of the study, including protocol  
717 amendments, and overall management of the study. It will be headed by the Study Chair and  
718 Study Director and consist of the study biostatistician, study project manager, CSP Center  
719 Director, selected VA experts, and outside consultants as needed. This committee will meet  
720 regularly to review blinded data (not broken down by treatment group), decide upon changes  
721 in the study, determine the fate of hospitals whose performance is substandard, initiate any  
722 subprotocols, and discuss publication of the study results. This Committee must grant  
723 permission before any study data may be used for presentation or publication.

724 The Technical Committee will advise the Executive Committee on informatics and database  
725 related issues pertaining to study operations. This committee will serve as subject matter  
726 experts for the study database, web application, ETL procedures and primary data source, the  
727 Corporate Data Warehouse. It will consist of a VINCI representative, MAVERIC Director of  
728 Informatics, and other informaticians/SMEs as needed.

729 The Data Monitoring Committee (DMC) will review the progress of the study and will monitor  
730 patient intake, outcomes, adverse events, and other issues related to patient safety. Interim,  
731 independent, and unbiased reviews of the study's ongoing progress will be provided. The DMC  
732 will consist of experts in the study's subject matter field(s), clinical trials, biostatistics, and  
733 ethics. These individuals will not be participants in the trial and will not have participated in the  
734 planning of the protocol. The DMC will consider safety or other circumstances as grounds for  
735 early termination, including either compelling internal or external evidence of treatment  
736 differences or the unfeasibility of addressing the study hypothesis (e.g., poor patient intake,  
737 poor adherence to the protocol).

738 At each of its meetings during the study period, the DMC will review the randomization rates  
739 and assess the difference between the actual and the projected rates, as well as the impact of  
740 these assessments on overall trial size. If the study enrollment is inadequate, the reasons for  
741 exclusion may be scrutinized and actions may be suggested. An assessment of whether the  
742 trial should be continued will be made followed by recommendations, as appropriate. All  
743 serious adverse events will be reported regularly to the DMC for review. Unexpected, related  
744 serious adverse events will be reported to the DMC as soon as they become known based  
745 upon the consensus of the Study Chair, the study biostatistician, the Study Director. The study

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biostatistician will provide the appropriate data to the DMC at specified intervals for this purpose. Conditional power estimates may be provided to the DMC to assist them in making

748 their decisions and recommendations at their request. To help them make their assessment,  
749 the Study Chair and study biostatistician will furnish the Data Monitoring Committee with  
750 appropriate monitoring data before each meeting. The DMC makes recommendations after  
751 each meeting to the Director of the Clinical Science Research and Development (CSRD) Service  
752 about whether the study should continue or be stopped.

753 The VA Central IRB will be the IRB of record for all VA sites. They will monitor the study's  
754 serious adverse events on a continual basis. They will conduct annual reviews of the study. In  
755 addition, some study materials (such as subject correspondence and protocol changes) will  
756 have to be reviewed by the VA CIRB, and approved prior to implementation.

757 The CSPCC Human Rights Committee (HRC) is composed primarily of lay people and is  
758 responsible for ensuring that patients' rights and safety are upheld prior to study initiation and  
759 during the conduct of the study. The committee reviews all new protocols, periodically makes  
760 site visits to participating centers to monitor firsthand the progress of the study, and may be  
761 asked to review any ethical and human rights issues that arise during the conduct of the study.



## **XIX. Publications**

### **A. Publication policy**

It is the policy of the CSP that outcome data will not be revealed to the participating investigators until the data collection phase of the study is completed. This policy safeguards against possible biases affecting the data collection. All presentations and publications from this study will be done in accordance with current CSP Guidelines, including the Authorship Policy. The most current version of the Guidelines should be referenced when planning any study publication.

The presentation or publication of any or all data collected by participating investigators on patients entered into the VA Cooperative Study is under the direct control of the study's Executive Committee. No individual participating investigator has any inherent right to perform analyses or interpretations or to make public presentations or seek publication of any or all of the data other than under the auspices and approval of the Executive Committee.

The Executive Committee has the authority to establish one or more publication subgroups of investigators and members of the Executive Committee for producing scientific presentations and publications. Authors with VA appointments must list their VA affiliation first. The VA contributions to the research project should be acknowledged in all written and oral presentations of the research results, including scientific articles, news releases, news conferences, public lectures, and media interviews.

All study reports and journal manuscripts must be reviewed and approved by the MAVERIC CSPCC Director prior to submission for publication. After approval for submission is granted by the MAVERIC CSPCC Director, VA Central Office must be notified upon acceptance of any publications. This includes minor publications such as abstracts and poster presentations.

### **B. Planned Publications**

A list of planned publications is below:

- I. Editorial: The first large clinically integrated VA trial
- II. Design of the DCP
- III. Ascertainment of urgent revascularization from administrative data
- IV. Ascertainment of acute heart failure episodes from administrative data
- V. Main outcomes paper
- VI. Blood pressure control and drug compliance in the DCP
- VII. Blood chemistries in the DCP

## XX. References

1. [http://www.cdc.gov/bloodpressure/hypertension\\_iom.htm](http://www.cdc.gov/bloodpressure/hypertension_iom.htm)
2. <http://www.webmd.com/news/20110420/the-10-most-prescribed-drugs>
3. [http://www.healthquality.va.gov/hypertension/htn04\\_pdf1.pdf](http://www.healthquality.va.gov/hypertension/htn04_pdf1.pdf)
4. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. *JAMA* 2003;289:2560-72.
5. Psaty BM, Lumley T, Furberg CD, Schellenbaum G, Pahor M, Alderman MH, Weiss NS. Health outcomes associated with various antihypertensive therapies used as first-line agents: a network meta-analysis. *JAMA* 2003;289:2534-44.
6. Messerli FH, Bangalore S. Half a century of hydrochlorothiazide: facts, fads, fiction, and follies. *Am J Med* 2011;124:896-9.
7. Ernst ME, Lund BC. Renewed interest in chlorthalidone: evidence from the Veterans Health Administration. *J Clin Hypertens (Greenwich)*. 2010;12:927-34.
8. Kaplan NM. Chlorthalidone versus hydrochlorothiazide: a tale of tortoises and a hare. *Hypertension* 2011;58:994-5.
9. Mitka M. Experts argue not all diuretics the same. *JAMA* 2007;298:31.
10. Kaplan NM. The case for low dose diuretic therapy. *Am J Hypertens* 1991;4:970-1.
11. Materson BJ, Cushman WC, Goldstein G, Reda DJ, Freis ED, Ramirez EA, Talmers FN, White TJ, Nunn S, Chapman RH, et al. Treatment of hypertension in the elderly: I. Blood pressure and clinical changes. Results of a Department of Veterans Affairs Cooperative Study. *Hypertension* 1990;15:348-60.
12. Cushman WC, Khatri I, Materson BJ, Reda DJ, Freis ED, Goldstein G, Ramirez EA, Talmers FN, White TJ, Nunn S, et al. Treatment of hypertension in the elderly. III. Response of isolated systolic hypertension to various doses of hydrochlorothiazide: results of a Department of Veterans Affairs cooperative study. Department of Veterans Affairs Cooperative Study Group on Antihypertensive Agents. *Arch Intern Med* 1991;151:1954-60.
13. Materson BJ, Oster JR, Michael UF, Bolton SM, Burton ZC, Stambaugh JE, Morledge J. Dose response to chlorthalidone in patients with mild hypertension. Efficacy of a lower dose. *Clin Pharmacol Ther* 1978;24:192-8.

14. Morledge JH, Ettinger B, Aranda J, McBarron F, Barra P, Gorwit J, Davidov M. Isolated systolic hypertension in the elderly. A placebo-controlled, dose-response evaluation of chlorthalidone. *J Am Geriatr Soc* 1986;34:199-206.
15. Neff KM, Nawarskas JJ. Hydrochlorothiazide versus chlorthalidone in the management of hypertension. *Cardiol Rev* 2010;18:51-6.
16. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA* 2014;311:507-20.
17. Dorsch MP, Gillespie BW, Erickson SR, Bleske BE, Weder AB. Chlorthalidone reduces cardiovascular events compared with hydrochlorothiazide: a retrospective cohort analysis. *Hypertension* 2011;57:689-94.
18. Ernst ME, Neaton JD, Grimm RH Jr, Collins G, Thomas W, Soliman EZ, Prineas RJ; Multiple Risk Factor Intervention Trial Research Group. Long-term effects of chlorthalidone versus hydrochlorothiazide on electrocardiographic left ventricular hypertrophy in the multiple risk factor intervention trial. *Hypertension* 2011;58:1001-7.
19. Wing LM, Reid CM, Ryan P, Beilin LJ, Brown MA, Jennings GL, Johnston CI, McNeil JJ, Macdonald GJ, Marley JE, Morgan TO, West MJ; Second Australian National Blood Pressure Study Group. A comparison of outcomes with angiotensin-converting--enzyme inhibitors and diuretics for hypertension in the elderly. *N Engl J Med* 2003;348:583-92.
20. ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic: The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *JAMA*. 2002;288:2981-97.
21. Roush GC, Holford TR, Guddati AK. Chlorthalidone compared with hydrochlorothiazide in reducing cardiovascular events: systematic review and network meta-analyses. *Hypertension* 2012;59:1110-7.
22. Carter BL, Ernst ME, Cohen JD. Hydrochlorothiazide versus chlorthalidone: evidence supporting their interchangeability. *Hypertension* 2004;43:4-9.
23. Ernst ME, Carter BL, Goerdts CJ, Steffensmeier JJ, Phillips BB, Zimmerman MB, Bergus GR. Comparative antihypertensive effects of hydrochlorothiazide and chlorthalidone on ambulatory and office blood pressure. *Hypertension* 2006;47:352-8.
24. Kwon BJ, Jang SW, Choi KY, Kim DB, Cho EJ, Ihm SH, Youn HJ, Kim JH. Comparison of the efficacy between hydrochlorothiazide and chlorthalidone on central aortic pressure

when added on to candesartan in treatment-naïve patients of hypertension. *Hypertens Res.* 2013;36:79-84.

25. [https://vaww.cmopnational.va.gov/cmop/PBM/Clinical Guidance/Archived Criteria, Guidelines and Reviews/Clinical Recommendations \(Archive\)/Thiazides in Hypertension, Review of Recent Evidence \(Archived Dec 2014\).doc](https://vaww.cmopnational.va.gov/cmop/PBM/Clinical%20Guidance/Archived%20Criteria,%20Guidelines%20and%20Reviews/Clinical%20Recommendations%20(Archive)/Thiazides%20in%20Hypertension,%20Review%20of%20Recent%20Evidence%20(Archived%20Dec%202014).doc)
26. Ernst ME, Carter BL, Zheng S, Grimm RH Jr. Meta-analysis of dose-response characteristics of hydrochlorothiazide and chlorthalidone: effects on systolic blood pressure and potassium. *Am J Hypertens* 2010;23:440-6.
27. Peterzan MA, Hardy R, Chaturvedi N, Hughes AD. Meta-analysis of dose-response relationships for hydrochlorothiazide, chlorthalidone, and bendroflumethiazide on blood pressure, serum potassium, and urate. *Hypertension* 2012;59:1104-9.
28. Lund BC, Ernst ME. The comparative effectiveness of hydrochlorothiazide and chlorthalidone in an observational cohort of veterans. *J Clin Hypertens (Greenwich)*. 2012 Sep;14(9):623-9.
29. Dhalla IA, Gomes T, Yao Z, Nagge J, Persaud N, Hellings C, Mamdani MM, Juurlink DN. Chlorthalidone versus hydrochlorothiazide for the treatment of hypertension in older adults: a population-based cohort study. *Ann Intern Med* 2013;158:447-55.
30. Bakris GL, Sica D, White WB, Cushman WC, Weber MA, Handley A, Song E, Kupfer S. Antihypertensive efficacy of hydrochlorothiazide vs chlorthalidone combined with azilsartan medoxomil. *Am J Med.* 2012;125:1229.e1-1229.e10.
31. Cushman WC, Bakris GL, White WB, Weber MA, Sica D, Roberts A, Lloyd E, Kupfer S. Azilsartan medoxomil plus chlorthalidone reduces blood pressure more effectively than olmesartan plus hydrochlorothiazide in stage 2 systolic hypertension. *Hypertension.* 2012;60:310-8.
32. Ernst ME, Moser M. Use of diuretics in patients with hypertension. *N Engl J Med.* 2009 Nov 26;361(22):2153-64.
33. Dolan E, Stanton A, Thijs L, Hinedi K, Atkins N, McClory S, Den Hond E, McCormack P, Staessen JA, O'Brien E. Superiority of ambulatory over clinic blood pressure measurement in predicting mortality: the Dublin outcome study. *Hypertension.* 2005 Jul;46(1):156-61.
34. Fagard RH, Celis H, Thijs L, Staessen JA, Clement DL, De Buyzere ML, De Bacquer DA. Daytime and nighttime blood pressure as predictors of death and cause-specific cardiovascular events in hypertension. *Hypertension.* 2008 Jan;51(1):55-61.
35. Woodman R, Brown C, Lockette W. Chlorthalidone decreases platelet aggregation and vascular permeability and promotes angiogenesis. *Hypertension.* 2010 Sep;56(3):463-70.

36. Kurtz TW. Chlorthalidone: don't call it "thiazide-like" anymore. *Hypertension* 2010;56:335-7.
37. Rodenburg EM, Hoorn EJ, Ruiter R, Lous JJ, Hofman A, Uitterlinden AG, Stricker BH, Visser LE. Thiazide-Associated Hyponatremia: A Population-Based Study. *Am J Kidney Dis.* 2013 Apr 18. [Epub ahead of print]
38. Alderman MH, Piller LB, Ford CE, et al; Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial Collaborative Research Group. Clinical significance of incident hypokalemia and hyperkalemia in treated hypertensive patients in the antihypertensive and lipid-lowering treatment to prevent heart attack trial. *Hypertension.* 2012;59(5):926-33.
39. Barzilay JI, Davis BR, Cutler JA, Pressel SL, Whelton PK, Basile J, Margolis KL, Ong ST, Sadler LS, Summerson J; ALLHAT Collaborative Research Group. Fasting glucose levels and incident diabetes mellitus in older nondiabetic adults randomized to receive 3 different classes of antihypertensive treatment: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). *Arch Intern Med.* 2006 Nov 13;166(20):2191-201.
40. Barzilay JI, Davis BR, Pressel SL, Cutler JA, Einhorn PT, Black HR, Cushman WC, Ford CE, Margolis KL, Moloo J, Oparil S, Piller LB, Simmons DL, Sweeney ME, Whelton PK, Wong ND, Wright JT Jr; ALLHAT Collaborative Research Group. Long-term effects of incident diabetes mellitus on cardiovascular outcomes in people treated for hypertension: the ALLHAT Diabetes Extension Study. *Circ Cardiovasc Qual Outcomes.* 2012 Mar 1;5(2):153-62.
41. McAdams DeMarco MA, Maynard JW, Baer AN, Gelber AC, Young JH, Alonso A, Coresh J. Diuretic use, increased serum urate levels, and risk of incident gout in a population-based study of adults with hypertension: the Atherosclerosis Risk in Communities cohort study. *Arthritis Rheum.* 2012 Jan;64(1):121-9.
42. Siegel D, Hulley SB, Black DM, Cheitlin MD, Sebastian A, Seeley DG, Hearst N, Fine R. Diuretics, serum and intracellular electrolyte levels, and ventricular arrhythmias in hypertensive men. *JAMA* 1992;267:1083-9.
43. Mount DB, et al. Clinical manifestations and treatment of hypokalemia. UpToDate. Accessed July 2013.
44. Roush GC, Buddharaju V, Ernst ME, Holford TR. Chlorthalidone: Mechanisms of Action and Effect on Cardiovascular Events. *Curr Hypertens Rep.* 2013 Jul 10. [Epub ahead of print]

- 028 45. Rahman M, Pressel S, Davis BR, et al. Renal outcomes in high-risk hypertensive patients  
029 treated with an angiotensin-converting enzyme inhibitor or a calcium channel blocker vs a  
030 diuretic: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent  
031 Heart Attack Trial (ALLHAT). *Arch Intern Med.* 2005 Apr 25;165(8):936-46.
- 032 46. Rahman M, Ford CE, Cutler JA, et al; ALLHAT Collaborative Research Group. Long-term  
033 renal and cardiovascular outcomes in Antihypertensive and Lipid-Lowering Treatment to  
034 Prevent Heart Attack Trial (ALLHAT) participants by baseline estimated GFR. *Clin J Am  
035 Soc Nephrol.* 2012 Jun;7(6):989-1002.
- 036 47. Prevention of stroke by antihypertensive drug treatment in older persons with isolated  
037 systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program  
038 (SHEP). SHEP Cooperative Research Group. *JAMA* 1991;265:3255-64.
- 039 48. Hueskes BA, Roovers EA, Mantel-Teeuwisse AK, Janssens HJ, van de Lisdonk EH,  
040 Janssen M. Use of diuretics and the risk of gouty arthritis: a systematic review. *Semin  
041 Arthritis Rheum.* 2012 Jun;41(6):879-89.
- 042 49. Mortality findings for stepped-care and referred-care participants in the hypertension  
043 detection and follow-up program, stratified by other risk factors. The Hypertension  
044 Detection and Follow-up Program Cooperative Research Group. *Prev Med* 1985;14:312-  
045 35.
- 046
- 047 50. Wilson L, Nair KV, Saseen JJ. Comparison of New-Onset Gout in Adults Prescribed  
048 Chlorthalidone vs Hydrochlorothiazide for Hypertension. *J Clin Hypertens.* 2014 Sep 25.  
049 doi: 10.1111/jch.12413. [Epub ahead of print]
- 050
- 051 51. Khosla N, Chua DY, Elliott WJ, Bakris GL. Are chlorthalidone and hydrochlorothiazide  
052 equivalent blood-pressure-lowering medications? *J Clin Hypertens* 2005;7:354-6.
- 053
- 054 52. Matthews KA, Brenner MJ, Brenner AC. Evaluation of the Efficacy and Safety of a  
055 Hydrochlorothiazide to Chlorthalidone Medication Change in Veterans With Hypertension.  
056 *Clin Ther.* 2013 Aug 28.[Epub ahead of print]
- 057
- 058 53. van Blijderveen JC, Straus SM, Rodenburg EM, Zietse R, Stricker BH, Sturkenboom MC,  
059 Verhamme KM. Risk of hyponatremia with diuretics: chlorthalidone versus  
060 hydrochlorothiazide. *Am J Med* 2014;127:763-71.
- 061 54. Roush GC, Buddhharaju V, Ernst ME. Is chlorthalidone better than hydrochlorothiazide in  
062 reducing cardiovascular events in hypertensives? *Curr Opin Cardiol* 2013;28:426-32.
- 063 55. Dhalla IA, Mamdani MM, Juurlink DN. Chlorthalidone versus hydrochlorothiazide. *Ann  
064 Intern Med.* 2013;158:923-4.

- 065 56. Einhorn PT, Cushman WC, Whelton PK; ALLHAT Collaborative Research Group.  
066 Chlorothalidone versus hydrochlorothiazide. *Ann Intern Med* 2013;158:922-3.
- 067 57. Asche C, Yang J, Yu S, Hagan M. A profiling of hypertension patients treated with  
068 chlorthalidone or hydrochlorothiazide. *Value Health*. 2013 May;16(3):A295.
- 069 58. Krause T, Lovibond K, Caulfield M, McCormack T, Williams B; Guideline Development  
070 Group. Management of hypertension: summary of NICE guidance. *BMJ* 2011;343:d4891.
- 071 59. Mancia G, Fagard R, Narkiewicz K, et al; Task Force Members. 2013 ESH/ESC  
072 Guidelines for the management of arterial hypertension: the Task Force for the  
073 management of arterial hypertension of the European Society of Hypertension (ESH) and  
074 of the European Society of Cardiology (ESC). *J Hypertens* 2013;31:1281-357.
- 075 60. Floyd JS, Psaty BM. Observational Comparative Effectiveness Studies of Drug Therapies:  
076 High-Quality Answers or Important Clinical Questions? Comment on "Comparative  
077 Effectiveness of 2  $\beta$ -Blockers in Hypertensive Patients". *Arch Intern Med* 2012;172:  
078 1412-4.
- 079 61. Lauer MS, D'Agostino RB. The randomized registry trial — the next disruptive technology  
080 in clinical research? *N Engl J Med* 2013; 369:1579-1581.
- 081 62. Jansen JP, Fleurence R, Devine B, Itzler R, Barrett A, Hawkins N, Lee K, Boersma C,  
082 Annemans L, Cappelleri JC. Interpreting indirect treatment comparisons and network meta-  
083 analysis for health-care decision making: report of the ISPOR Task Force on Indirect  
084 Treatment Comparisons Good Research Practices: part 1. *Value Health* 2011;14:417-28.
- 085 63. Pletcher MJ, Lo B, Grady D. Informed consent in randomized quality improvement trials: a  
086 critical barrier for learning health systems. *JAMA Intern Med* 2014;174:668-70.
- 087 64. Peto R, Collins R, Gray R. Large-scale randomized evidence: large, simple trials and  
088 overviews of trials. *J Clin Epidemiol*. 1995 Jan;48(1):23-40.
- 089 65. Vickers AJ, Scardino PT. The clinically-integrated randomized trial: proposed novel  
090 method for conducting large trials at low cost. *Trials*. 2009;10:14.
- 091 66. van Staa TP, Goldacre B, Gulliford M, Cassell J, Pirmohamed M, Taweel A, Delaney B,  
092 Smeeth L. Pragmatic randomised trials using routine electronic health records: putting  
093 them to the test. *BMJ*. 2012 Feb 7;344:e55.
- 094 67. Fiore LD, Brophy M, Ferguson RE, D'Avolio L, Hermos JA, Lew RA, Doros G, Conrad  
095 CH, O'Neil JA Jr, Sabin TP, Kaufman J, Swartz SL, Lawler E, Liang MH, Gaziano JM,  
096 Lavori PW. A point-of-care clinical trial comparing insulin administered using a sliding  
097 scale versus a weight-based regimen. *Clin Trials*. 2011;8:183-95.

- 098 68. D'Avolio L, Ferguson R, Goryachev S, Woods P, Sabin T, O'Neil J, Conrad C, Gillon J,  
099 Escalera J, Brophy M, Lavori P, Fiore L. Implementation of the Department of Veterans  
000 Affairs' first point-of-care clinical trial. *J Am Med Inform Assoc*. 2012 Jun 1;19(e1):e170-  
001 e176. Epub 2012 Feb 24.
- 002 69. IOM Roundtable on Evidence-Based Medicine. Appendix A. Learning what works best:  
003 the nation's need for evidence on comparative effectiveness in health care: an issue  
004 overview. In: *Learning What Works: Infrastructure Required for Comparative*  
005 *Effectiveness Research: Workshop Summary*. Institute of Medicine (US) Roundtable on  
006 *Value & Science-Driven Health Care*. Washington (DC): National Academies Press (US);  
007 2011. <http://www.ncbi.nlm.nih.gov/books/NBK64784/>
- 008 70. Eapen ZJ, Lauer MS, Temple RJ. The imperative of overcoming barriers to the conduct of  
009 large, simple trials. *JAMA* 2014;311:1397-8.
- 010 71. Smith DH, Neutel JM, Lacourcière Y, Kempthorne-Rawson J. Prospective, randomized,  
011 open-label, blinded-endpoint (PROBE) designed trials yield the same results as double-  
012 blind, placebo-controlled trials with respect to ABPM measurements. *J Hypertens*. 2003  
013 Jul;21(7):1291-8.
- 014 72. Kerr EA, Lucatorto MA, Holleman R, Hogan MM, Klamerus ML, Hofer TP; VA Diabetes  
015 Quality Enhancement Research Initiative (QUERI) Workgroup on Clinical Action  
016 Measures. Monitoring performance for blood pressure management among patients with  
017 diabetes mellitus: too much of a good thing? *Arch Intern Med*. 2012;172:938-45.
- 018 73. Berry SD, Kiel DP. Treating hypertension in the elderly: should the risk of falls be part of  
019 the equation? *JAMA Intern Med* 2014;174:596-7.
- 020 74. Nord J, Stults B, Rose R, Underwood AE, Williams T, West G, Huhtala T, Milne CK.  
021 Optimizing office blood pressure measurement at a VAMC. *Fed Pract* 2012;29(5):35-39.
- 022 75. Kim JW, Bosworth HB, Voils CI, Olsen M, Dudley T, Gribbin M, Adams M, Oddone EZ.  
023 How well do clinic-based blood pressure measurements agree with the mercury standard? *J*  
024 *Gen Intern Med* 2005;20:647-9.
- 025 76. Freeman MK, White W, Iranikhah M. Tablet splitting: a review of the clinical and  
026 economic outcomes and patient acceptance. *Consult Pharm* 2012;27:421-30.
- 027 77. Kalsbeek WD, Botman SL, Massey JT, Liu PW. Cost-Efficiency and the Number of  
028 Allowable Call Attempts in the National Health Interview Survey. *Journal of Official*  
029 *Statistics* 1994;10(2): 133–52
- 030 78. Hörngren J, Lundquist P, Westling S. Effects of number of call attempts on nonresponse  
031 rates and nonresponse bias – result from some case studies at Statistics Sweden. *Statistics*



Canada's International Symposium Series: Proceedings, 2009.

<http://www.statcan.gc.ca/pub/11-522-x/2008000/article/10999-eng.pdf>

79. Fowler FJ, Jr., Gallagher PM, Stringfellow VL, Zaslavsky AM, Thompson JW, Cleary PD. Using telephone interviews to reduce nonresponse bias to mail surveys of health plan members. *Med Care*. 2002;40:190-200.
80. Fu SS, van Ryn M, Burgess DJ, Nelson D, Clothier B, Thomas JL, Nyman JA, Joseph AM. Proactive tobacco treatment for low income smokers: study protocol of a randomized controlled trial. *BMC Public Health* 2014;14:337.
81. Koepsell T, McGuire V, Longstreth W, Nelson L, Belle G. Randomized trial of leaving messages on telephone answering machines for control recruitment in an epidemiologic study. *Am J Epidemiol*. 1996;144:704-706.
82. Andrade SE, Kahler KH, Frech F, Chan KA. Methods for evaluation of medication adherence and persistence using automated databases. *Pharmacoepidemiol Drug Saf*. 2006;15:565-74.
83. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD; Joint ESC/ACCF/AHA/WHF Task Force for the Universal Definition of Myocardial Infarction, et al. Third universal definition of myocardial infarction. *Circulation*. 2012;126:2020-35.
84. Systolic Blood Pressure Intervention Trial (SPRINT) Protocol
85. Braunwald E, Domanski MJ, Fowler SE, et al; PEACE Trial Investigators. Angiotensin-converting-enzyme inhibition in stable coronary artery disease. *N Engl J Med* 2004;351:2058-68.
86. Morrow DA, Braunwald E, Bonaca MP, et al; TRA 2P-TIMI 50 Steering Committee and Investigators. Vorapaxar in the secondary prevention of atherothrombotic events. *N Engl J Med* 2012;366:1404-13.
87. Tricoci P, Huang Z, Held C, et al; TRACER Investigators. Thrombin-receptor antagonist vorapaxar in acute coronary syndromes. *N Engl J Med* 2012;366:20-33.
88. White WB, Bakris GL, Bergenstal RM, Cannon CP, Cushman WC, et al. EXamination of cardiovascular outcoMes with alogliptIN versus standard of care in patients with type 2 diabetes mellitus and acute coronary syndrome (EXAMINE): a cardiovascular safety study of the dipeptidyl peptidase 4 inhibitor alogliptin in patients with type 2 diabetes with acute coronary syndrome. *Am Heart J* 2011;162:620-6.
89. Einhorn PT, Davis BR, Massie BM, Cushman WC, Piller LB, Simpson LM, Levy D, Nwachuku CE, Black HR; ALLHAT Collaborative Research Group. The Antihypertensive

and Lipid Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) Heart Failure Validation Study: diagnosis and prognosis. *Am Heart J.* 2007 Jan;153(1):42-53.

90. Go AS, Mozaffarian D, Roger VL, et al; AHA Statistics Committee and Stroke Statistics Subcommittee. Heart disease and stroke statistics--2013 update: a report from the American Heart Association. *Circulation* 2013;127:e6-e245.
91. Kannel WB. Blood pressure as a cardiovascular risk factor: prevention and treatment. *JAMA* 1996;275:1571-6.
92. Roger VL, Weston SA, Redfield MM, Hellermann-Homan JP, Killian J, Yawn BP, Jacobsen SJ. Trends in heart failure incidence and survival in a community based population. *JAMA* 2004;292:344-50.
93. Hicks KA, Hung HMJ, Mahaffey KW, et al. Standardized definitions for cardiovascular and stroke end point events in clinical trials. FDA draft report, 2012.
94. Ron E, Carter R, Jablon S, Mabuchi K. Agreement between death certificate and autopsy diagnoses among atomic bomb survivors. *Epidemiology.* 1994 Jan;5(1):48-56.
95. Sesso HD, Gaziano JM, Glynn RJ, Buring JE. Value of an Endpoints Committee versus the use of nosologists for validating cause of death. *Contemp Clin Trials.*2006 Aug;27(4):333-9.
96. German RR, Fink AK, Heron M, et al. The accuracy of cancer mortality statistics based on death certificates in the United States. *Cancer epidemiology* 2011;35(2):126-31.
97. Prieto-Merino D, Smeeth L, Staa TP, Roberts I. Dangers of non-specific composite outcome measures in clinical trials. *BMJ* 2013;347:f6782.
98. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure: the Framingham study. *N Engl J Med.* 1971;285:1441-6.
99. Sohn MW, Arnold N, Maynard C, Hynes DM. Accuracy and completeness of mortality data in the Department of Veterans Affairs. *Popul Health Metr.* 2006 Apr 10;4:2.
100. Fletcher RD, Amdur RL, Kolodner R, McManus C, Jones R, Faselis C, Kokkinos P, Singh S, Papademetriou V. Blood pressure control among US veterans: a large multiyear analysis of blood pressure data from the Veterans Administration health data repository. *Circulation* 2012;125:2462-8.
101. ACCORD Study Group, Cushman WC, Evans GW, Byington RP, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. *N Engl J Med.* 2010;362:1575-85(+ online supplement).

- 098 102. Jennison, C and Turnbull, B. Group Sequential Methods with Applications to Clinical  
099 Trials. Boca Raton, FL: Chapman & Hall/CRC Interdisciplinary Statistics, 2000.
- 100 103. Daniels MJ and Hogan JW. Missing Data in Longitudinal Studies: Strategies for Bayesian  
101 Modeling and Sensitivity Analysis. Boca Raton, FL: Chapman and Hall/CRC, 2008.
- 102 104. Beyersmann J, Allignol A, and Schumacher M. Competing Risks and Multistate Models  
103 with R. New York, NY: Springer, 2012.
- 104 105. <http://answers.hhs.gov/ohrp/questions/7276>
- 105 106. Morris MC; Nelson RM. Randomized, controlled trials as minimal risk: An ethical  
106 analysis. Crit Care Med 2007; 35:940–4.
- 107 107. Nelson K, Garcia RE, Brown J, Mangione CM, Louis TA, Keeler E, Cretin S. Do patient  
108 consent procedures affect participation rates in health services research? Med Care  
109 2002;40:283-8.
- 110
- 111 108. Cann CI, Rothman KJ. IRBs and epidemiologic research: how inappropriate restrictions  
112 hamper studies. IRB 1984;6(4):5-7.
- 113
- 114 109. Armstrong D, Kline-Rogers E, Jani SM, Goldman EB, Fang J, Mukherjee D, Nallamothe  
115 BK, Eagle KA. Potential impact of the HIPAA privacy rule on data collection in a registry  
116 of patients with acute coronary syndrome. Arch Intern Med 2005;165:1125-9.
- 117
- 118 110. Kaiser J. Patient privacy. Rule to protect records may doom long-term heart study. Science  
119 2006;311:1547-8.
- 120
- 121 111. Ellickson PL, Hawes JA. An assessment of active versus passive methods for obtaining  
122 parental consent. Eval Rev 1989;13:45-55.

2123  
2124  
2125  
2126  
2127  
2128  
2129  
2130  
2131  
2132  
2133  
2134  
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**Department of Veterans Affairs Cooperative Studies Program**

**CSP#597: Diuretic Comparison Project (DCP)**

**A proposal from the Point of Care Program**

**Study Chair: Areef Ishani, MD**

**Version 4.4**

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2195 **A. Executive Summary**

2196 Thiazide-type diuretics have been in use for more than 50 years and are considered in JNC-7 and VA  
2197 guidelines to be the first-line treatment for hypertension. Of the more than 1 million veterans  
2198 prescribed a thiazide-type diuretic each year, more than 95% receive hydrochlorothiazide, and fewer  
2199 than 2.5% receive chlorthalidone. However, indirect evidence has been accumulating for many years  
2200 that chlorthalidone may be more effective than hydrochlorothiazide at preventing cardiovascular  
2201 events, by about 20% according to a recent network meta-analysis. Possible mechanisms for such an  
2202 effect include longer duration of action, better nighttime blood pressure control, and pleiotropic effects  
2203 of chlorthalidone. A randomized trial comparing the effect of the two drugs on cardiovascular outcomes  
2204 has never been conducted, primarily for reasons of cost.

2205 We are proposing a new type of efficient, less expensive randomized trial (termed a “clinically  
2206 integrated” or “point of care” trial) to answer the question of whether chlorthalidone is more effective  
2207 than hydrochlorothiazide at preventing cardiovascular outcomes in older patients with hypertension.  
2208 Our primary outcome will be a composite consisting of: stroke, myocardial infarction, non-cancer death,  
2209 urgent coronary revascularization, and hospitalization for acute congestive heart failure. We plan to  
2210 enroll patients over age 65 years currently prescribed hydrochlorothiazide 25 or 50 mg daily with no  
2211 recent systolic blood pressure below 120 mm Hg, and randomize them to either continue on  
2212 hydrochlorothiazide or receive open-label chlorthalidone at suggested doses of 12.5 or 25 mg,  
2213 respectively.

2214 To have a 90% power with 2-sided  $\alpha = 0.05$  to detect a 17.5% reduction in the expected 3% per year  
2215 primary outcome occurrence rate in the hydrochlorothiazide group, we plan to randomize  
2216 13,700 patients over 3 years and follow them for a mean of 3 years, for a total study duration of 4.5  
2217 years.

2218 The key feature of our design is that, instead of employing local investigators, we substitute centralized  
2219 study processes and rely on usual primary care. Specifically, this involves: 1) identification of eligible  
2220 patients using the VA electronic medical record system (EMR), 2) centralized recruitment and  
2221 enrollment, involving permission from the patient’s primary care provider, a patient recruitment letter,  
2222 and informed consent obtained by telephone, 3) centralized placement of notes and orders using the VA  
2223 EMR, 4) all patient care including the study drug to be managed by the primary care provider, and 5)  
2224 centralized passive collection of outcomes and process variables using the VA EMR, Medicare, and other  
2225 national VA and non-VA databases.



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**I. Abbreviations and Acronyms**

|      |            |   |
|------|------------|---|
| 2239 | ACCOMPLISH | Avoiding Cardiovascular Events in Combination Therapy in Patients         |
| 2240 |            | Living with Systolic Hypertension   |
| 2241 | ACCORD     | Action to Control Cardiovascular Risk in Diabetes Trial                   |
| 2242 | ACE        | Angiotensin Converting Enzyme   |
| 2243 | ACEI       | Angiotensin Converting Enzyme Inhibitors                                  |
| 2244 | ACME       | Automated Classification of Medical Entities                              |
| 2245 | AHA        | American Heart Association  |
| 2246 | ALLHAT     | Antihypertensive and Lipid-Lowering Therapy to Prevent Heart Attack Trial |
| 2247 | ANBP2      | Second Australian National Blood Pressure Study                           |
| 2248 | ARB        | Angiotensin Receptor Blocker  |
| 2249 | ARIC       | Atherosclerosis Risk in Communities                                       |
| 2250 | BIRLS      | Beneficiary Identification and Records Locator Subsystem database         |
| 2251 | CAC        | Clinical Application Coordinator  |
| 2252 | CBOC       | Community Based Outpatient Clinics  |
| 2253 | CDW        | Corporate Data Warehouse  |
| 2254 | CFR        | Code of Federal Regulations   |
| 2255 | CHD        | Coronary Heart Disease  |
| 2256 | CHF        | Congestive Heart Failure  |
| 2257 | CI         | Confidence Interval   |
| 2258 | CPRS       | VA Computerized Patient Record System                                     |
| 2259 | CPT        | Current Procedural Terminology  |
| 2260 | CSP        | Cooperative Studies Program   |
| 2261 | CSPCC      | Cooperative Studies Program Coordinating Center                           |
| 2262 | CSSEC      | Clinical Sciences Scientific Evaluation Committee                         |
| 2263 | CVD        | Cardiovascular Disease  |

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|      |         |  |
|------|---------|--|
| 2266 | DM      | Diabetes Mellitus  |
| 2267 | DMC     | Data Monitoring Committee  |
| 2268 | DoD     | US Department of Defense   |
| 2269 | ECG     | Electrocardiography  |
| 2270 | EMR     | Electronic Medical Record  |
| 2271 | EHR     | Electronic Health Record   |
| 2272 | EXAMINE | EXamination of cArdiovascular outcoMes with alogliptIN versus standard of carE |
| 2273 |         | in patients with type 2 diabetes mellitus and acute coronary syndrome          |
| 2274 | FDA     | US Food and Drug Administration  |
| 2275 | HCTZ    | Hydrochlorothiazide  |
| 2276 | HDFP    | Hypertension Detection and Follow-up Program                                   |
| 2277 | HF      | Heart Failure  |
| 2278 | HIPAA   | Health Insurance Portability and Accountability Act                            |
| 2279 | HR      | Hazard Ratio   |
| 2280 | ICD-9   | International Classification of Disease, 9th edition                           |
| 2281 | ICD-10  | International Classification of Disease, 10 <sup>th</sup> edition              |
| 2282 | ICD     | Internal Cardiac Defibrillator   |
| 2283 | IRM     | Information Resource Management  |
| 2284 | ISO     | Information Security Officer   |
| 2285 | JNC-7   | Seventh Report of the Joint Committee on Prevention, Detection, Evaluation and |
| 2286 |         | Treatment of High Blood Pressure   |
| 2287 | meq/L   | Milli-equivalents per liter  |
| 2288 | mg      | Milligram  |
| 2289 | MI      | Myocardial Infarction  |
| 2290 | mmH     | Millimeters of Mercury   |
| 2291 | MRFIT   | Multiple Risk Factor Intervention Trial  |





|      |                  |  |
|------|------------------|--|
| 2293 | NHLBI            | National Heart, Lung, Blood Institute                              |
| 2294 | NIH              | National Institutes of Health                                      |
| 2295 | PACT             | Patient Aligned Care Team  |
| 2296 | PBM              | VA Pharmacy Benefits Management                                    |
| 2297 | PCP              | Primary Care Provider  |
| 2298 | PEACE Trial      | Prevention of Events with Angiotensin-Converting Enzyme Inhibition |
| 2299 | PHI              | Protected Health Information                                       |
| 2300 | POC-CT           | Point of Care Clinical Trial                                       |
| 2301 | PROBE            | Prospective, Randomized, Open-label, Blinded-Endpoint Trial        |
| 2302 | SBP              | Systolic Blood Pressure  |
| 2303 | SHEP             | Systolic Hypertension in the Elderly Population Trial              |
| 2304 | SPRINT           | Systolic Blood Pressure Intervention Trial                         |
| 2305 | SOP              | Standard Operating Procedure                                       |
| 2306 | SME              | Subject Matter Expert  |
| 2307 | TOMHS-T          | Treatment of Mild Hypertension Study                               |
| 2308 | TRACER           | Thrombin-Receptor Antagonist Vorapaxar in Acute Coronary Syndromes |
| 2309 | (TRA2°P)-TIMI 50 | Thrombin Receptor Antagonist in Secondary Prevention of            |
| 2310 |                  | Atherothrombotic Ischemic Events Trial                             |
| 2311 | UK NICE          | United Kingdom National Institute for Health and Care Excellence   |
| 2312 | VA               | US Department of Veterans Affairs                                  |
| 2313 | VAMC             | VA Medical Center  |
| 2314 | VIREC            | VA Information Resource Center                                     |
| 2315 | VISN             | Veterans Integrated Service Network                                |
| 2316 | WHO              | World Health Organization  |

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**II. Study Question**

Does treatment with chlorthalidone reduce cardiovascular outcomes compared with hydrochlorothiazide in older patients with hypertension?

**III. Background and Rationale**

**A. Diuretics for hypertension**

Hypertension is the most common primary diagnosis in America (1), and 3 of the 10 most commonly prescribed drugs in the US are antihypertensive agents (2). Thiazide-type diuretics are recommended as first line therapy by VA/DoD hypertension guidelines (3) and by the Seventh Report of the Joint Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC-7). JNC-7 noted that “diuretics have been virtually unsurpassed in preventing complications of hypertension” and as a result “should be used in drug treatment for most patients with uncomplicated hypertension” (4). In a network meta-analysis of 42 trials involving 192,478 patients randomized to active drug treatment for hypertension vs. placebo, low-dose diuretics (usually hydrochlorothiazide or the thiazide-type diuretic chlorthalidone) were “the most effective first-line treatment for preventing the occurrence of cardiovascular disease morbidity and mortality” (5).

**B. Hydrochlorothiazide and chlorthalidone**

Nearly all thiazide-type diuretic prescriptions in the U.S. are for hydrochlorothiazide. Hydrochlorothiazide is among the top 10 most commonly prescribed drugs in the US (2), with 135 million prescriptions written annually (6). In the VA national outpatient prescription database, of the more than 1 million veterans prescribed a thiazide-type diuretic each year from 2003-8, more than 95% received hydrochlorothiazide, and fewer than 2.5% received chlorthalidone (7). From our own search of the subsequent 3-year period 2009-11, 1.5 million veterans received hydrochlorothiazide from the VA and 50,000 received chlorthalidone.

The nearly universal use of hydrochlorothiazide has been attributed to a variety of factors, including 1) early aggressive marketing by its manufacturer (Merck) using “the largest pharmaceutical sales force in the world” (8), 2) its use in the early landmark VA hypertension treatment trials, 3) its early and frequent inclusion into combination pills, numbering at least 28 preparations (8), and 4) the ease of abbreviation to “HCTZ”, which may influence physician preference (9).

Both drugs have been approved by the FDA and in use for more than 50 years, have long been available as generics, and are included in the VA national formulary in the same drug class: USP code CV 701, thiazide-related diuretics. There is no patient characteristic that influences the choice between these two drugs - it is based solely on physician preference.

**C. Drug dosages**

Both drugs were once commonly used at doses of 100 mg per day and higher, but by 1990, concern over the lack of reduction in coronary events from blood pressure reduction by thiazides (despite proven



2360 efficacy for stroke), and further concern that this might be due to competing harms (particularly  
2361 ventricular arrhythmias) from thiazide-induced metabolic abnormalities, led to recommendations to use  
2362 lower doses of diuretics, including suggestions to use 12.5 mg of hydrochlorothiazide (10).

2363 In the early 1990's, publications of randomized dosing trials from the VA cooperative study group  
2364 concluded that the doses of 25-50 mg of hydrochlorothiazide were nearly as effective as higher doses at  
2365 controlling blood pressure with fewer adverse metabolic effects, favoring the use of 25 mg and a  
2366 maximum dose of 50 mg (11,12). Several randomized dosing trials of chlorthalidone found 12.5 mg per  
2367 day to be effective, and found 25 mg per day to be nearly as effective as higher doses with fewer  
2368 adverse metabolic effects (13,14). Since then, doses of 12.5-25 mg per day have been widely used (15)  
2369 and rarely exceeded for both drugs, with higher doses accounting for only 7% of VA prescriptions in  
2370 2008 (7). However, several authors have pointed out that hydrochlorothiazide doses lower than 25 mg  
2371 have not been shown to reduce cardiovascular outcomes and have performed poorly in randomized  
2372 trials (6). As a result, JNC-8 recommends target doses of 25-50 mg per day for hydrochlorothiazide and  
2373 12.5-25 mg per day for chlorthalidone (16).

2374 D. MRFIT – the first evidence that chlorthalidone may be more effective

2375 Despite the near universal use of hydrochlorothiazide in the U.S., evidence has accumulated over the  
2376 past 30 years suggesting that chlorthalidone may be more effective at reducing cardiovascular  
2377 outcomes. The first indication was from the Multiple Risk Factor Intervention Trial (MRFIT), a large  
2378 randomized trial of a multi-component 'special intervention' to prevent cardiovascular events in which  
2379 either hydrochlorothiazide or chlorthalidone could be used as first-line treatment of hypertension in the  
2380 special intervention arm. During the study, clinics that used hydrochlorothiazide were noted to have  
2381 44% more coronary heart disease deaths than those using chlorthalidone. In 1980, the MRFIT Policy  
2382 Advisory Board changed the protocol, recommending chlorthalidone over hydrochlorothiazide for initial  
2383 therapy, and lowered the maximum dose to 50 mg. Mortality in the former hydrochlorothiazide clinics  
2384 subsequently dropped 28% (which could, of course, partially reflect regression to the mean). A recent  
2385 analysis of the use of chlorthalidone and hydrochlorothiazide within MRFIT reported significantly fewer  
2386 cardiovascular events with chlorthalidone, though the findings of this non-randomized comparison are  
2387 confounded by large differences in dosage, randomized group, and lipid lowering (17). A separate non-  
2388 randomized analysis of MRFIT data concluded that chlorthalidone was associated with less left  
2389 ventricular hypertrophy than hydrochlorothiazide (18).

2390 E. Indirect comparisons of randomized trial data

2391 Because of the MRFIT observations, most subsequent NIH-funded blood pressure trials have used  
2392 chlorthalidone, including the Hypertension Detection and Follow-up Program (HDFP), the Systolic  
2393 Hypertension in the Elderly Program (SHEP), the Treatment of Mild Hypertension Study (TOMHS), and  
2394 the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), and in the  
2395 ongoing Systolic Blood Pressure Intervention Trial (SPRINT), it is 'preferred'. The use of chlorthalidone in  
2396 these trials and of hydrochlorothiazide in many other trials has enabled indirect comparisons of the  
2397 effects of the two drugs against a third drug or class. Thus, hydrochlorothiazide resulted in worse  
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2401 outcomes than an ACE inhibitor (enalapril) in men in the Second Australian National Blood Pressure  
2402 Study (ANBP2) (19), and worse outcomes than amlodipine (with all patients receiving benazepril) in the  
2403 Avoiding Cardiovascular Events in Combination Therapy in Patients Living with Systolic Hypertension  
2404 (ACCOMPLISH) trial (6), whereas in ALLHAT, chlorthalidone was found to be superior to an ACE inhibitor  
2405 (lisinopril) or amlodipine “in preventing 1 or more major forms of CVD” (though there was no difference  
2406 in the primary outcome) (20). These and other indirect comparisons have recently been combined into a  
2407 focused network meta-analysis that estimated a 21% risk reduction ( $p < .0001$ ) in cardiovascular events  
2408 with chlorthalidone relative to hydrochlorothiazide that persisted (as 18%,  $p = .024$ ) in an analysis  
2409 adjusted for attained blood pressure (21).

#### 2410 F. Relative Potency

2411 Several studies have found chlorthalidone to have about twice the potency of hydrochlorothiazide  
2412 (22,23,24) and this is reflected in the VA Pharmacy Benefits Management (PBM) 2009 evidence review  
2413 (25). Two indirect meta-analyses have reported similar conclusions. Ernst et al (26) found that at  
2414 identical doses, chlorthalidone had a greater effect than hydrochlorothiazide on lowering blood  
2415 pressure. Pederzan et al (27) considered the 2 drugs to have equivalent effects at equally potent doses,  
2416 which they considered to be 3 to 1. Despite these indications of greater potency, in practice  
2417 chlorthalidone is not used in lower doses than hydrochlorothiazide (7,28,29). This may reflect greater  
2418 awareness of appropriate thiazide dosing by the small proportion of prescribers who use chlorthalidone,  
2419 rather than widespread belief that the potencies are equivalent. There is essentially universal  
2420 agreement among experts that chlorthalidone at 12.5 or 25 mg is equipotent to hydrochlorothiazide at  
2421 25 or 50 mg (respectively).

#### 2422 G. Possible differences between the two diuretics

2423 No randomized trials have been conducted that directly compare clinical (e.g., cardiovascular) outcomes  
2424 of chlorthalidone and hydrochlorothiazide, but several short-term randomized trials have examined  
2425 blood pressure and metabolic effects. Two recent short-term (10 and 12 weeks) randomized double-  
2426 blind trials of 609 and 1071 patients (respectively) compared blood pressure control and adverse effects  
2427 when taking chlorthalidone 25 mg or hydrochlorothiazide 25 mg in patients also taking an angiotensin  
2428 receptor blocker (ARB) (30,31). In both studies, chlorthalidone resulted in lower systolic blood pressure  
2429 by at least 5 mmHg in clinic and, in the larger study, by 24 hour ambulatory recording.

2430 Chlorthalidone is known to have a longer duration of action than hydrochlorothiazide. The elimination  
2431 half-life of chlorthalidone is 50-60 hours compared with 9-10 hours for hydrochlorothiazide (32). Ernst et  
2432 al (23) randomized 30 patients to either chlorthalidone 12.5mg/day, titrated to 25 mg/day or  
2433 hydrochlorothiazide 25 mg/day, titrated to 50mg/day. After 8 weeks, there was no significant difference  
2434 in office systolic blood pressure (SBP), but 24-h ambulatory SBP favored chlorthalidone over  
2435 hydrochlorothiazide:  $-12.4 (\pm 1.8)$  vs.  $-7.4 (\pm 1.7)$  mmHg, respectively,  $P = 0.054$ , an effect primarily  
2436 driven by the lower nighttime SBP for chlorthalidone compared with hydrochlorothiazide:  $-13.5 (\pm 1.9)$   
2437 and  $-6.4 (\pm 1.8)$  mmHg, respectively,  $P = 0.009$ . Of note in this regard, large observational studies have

2439 found nighttime blood pressure to be a better predictor of cardiovascular outcomes than daytime blood  
2440 pressure (33,34).

2441 A recent in vitro study reported that chlorthalidone reduced epinephrine-induced platelet aggregation  
2442 and increased angiogenesis more than the thiazide bendroflumethiazide (35). There have been no  
2443 reports of any related clinical effects (e.g., increased bleeding), but these mechanisms could help to  
2444 explain differences between thiazides in reducing vascular events (36).

2445 In summary, given the longer duration of action, better nighttime blood pressure control, and possible  
2446 pleiotropic effects of chlorthalidone, it is possible that chlorthalidone and hydrochlorothiazide could  
2447 have different long-term effects on cardiovascular outcomes even at doses that result in similar office  
2448 blood pressures.

#### 2449 H. Drug costs

2450 Although both drugs are inexpensive generic products, chlorthalidone costs the VA seven times as much  
2451 as hydrochlorothiazide. According to VA Pharmacy Benefits Management (PBM), the cost to the VA for  
2452 hydrochlorothiazide 50 mg is 1.6¢ per tablet and for chlorthalidone 25mg is 11¢ per tablet (with half  
2453 doses costing half as much). Thus if the approximately 1 million VA patients using hydrochlorothiazide  
2454 (nearly all on 12.5 or 25 mg) were switched over to chlorthalidone 12.5 mg at an additional cost of 5¢  
2455 per day, the total increased cost would be about \$18 million per year.

#### 2456 I. Comparative metabolic effects

2457 Thiazide diuretics have a variety of metabolic effects. They generally lower serum sodium (36) and  
2458 potassium (27,38) levels and increase blood sugar (39,40) and uric acid (27,41) levels. In a small  
2459 randomized trial (42), hydrochlorothiazide 50 mg per day lowered potassium by a mean of 0.44 meq/L  
2460 more than placebo, regardless of whether potassium supplements or triamterene were added. Perhaps  
2461 the best source of information on the effect of thiazides comes from ALLHAT, which randomized 33,357  
2462 patients with hypertension: 15,255 to chlorthalidone and 9000 each to amlodipine and lisinopril.  
2463 Overall, chlorthalidone was considered superior to the other drugs in preventing cardiovascular events  
2464 (20). The year-1 incidence of hypokalemia (<3.5 meq/L) was higher with chlorthalidone (12.9%) than  
2465 with lisinopril (1.0%) or amlodipine (2.1%), but only 3.5% of the chlorthalidone group had a level <3.2  
2466 meq/L, and, in the chlorthalidone group, hypokalemia was associated with fewer cardiovascular  
2467 outcomes than was normokalemia (38).

2468 According to UpToDate (43): “The severity of the manifestations of hypokalemia tends to be  
2469 proportionate to the degree and duration of the reduction in serum potassium. Symptoms generally do  
2470 not become manifest until the serum potassium is below 3.0 meq/L, unless the serum potassium falls  
2471 rapidly or the patient has a potentiating factor, such as a predisposition to arrhythmia due to the use of  
2472 digitalis. Symptoms usually resolve with correction of the hypokalemia. ... Muscle weakness usually does  
2473 not occur at serum potassium concentrations above 2.5 meq/L if the hypokalemia develops slowly. ... In  
2474 addition to causing muscle weakness, severe potassium depletion (serum potassium less than 2.5  
2475 meq/L) can lead to muscle cramps, rhabdomyolysis, and myoglobinuria.” In one study, occurrence of  
2476

2479 premature ventricular contractions was twice as common when serum potassium was below 3.0 meq/L  
2480 (43).

2481 In ALLHAT (39,40), chlorthalidone was also associated with more incident diabetes (defined as any  
2482 fasting blood sugar >125 mg/dL) than were the other drugs (chlorthalidone: 14%, amlodipine: 11.1%,  
2483 lisinopril: 9.5%). While overall, those with incident diabetes had more cardiovascular deaths, incident  
2484 diabetes in the chlorthalidone group had lower cardiovascular deaths than incident diabetes in other  
2485 groups, leading the ALLHAT investigators to conclude that “there is no conclusive or consistent evidence  
2486 that this diuretic-associated increase in DM risk increases the risk of clinical events” (39), so “concerns  
2487 regarding potential adverse diabetic effects associated with thiazide-type diuretic therapy should not  
2488 inhibit its use” (40). Roush et al (44) recently reviewed this literature and concluded that  
2489 “Chlorthalidone-induced diabetes mellitus (DM) is “chemical diabetes” rather than DM leading to  
2490 cardiovascular pathology.”

2491 Also in ALLHAT, chlorthalidone did not increase the rate of development of either end-stage renal  
2492 disease or of a 50% or greater decrease in glomerular filtration rate compared with lisinopril or  
2493 amlodipine (45,46).

2494 Sodium, uric acid, and gout were not followed in ALLHAT. Thiazides have been associated with  
2495 hyponatremia in observational studies. In the Rotterdam study, about 50 of 3400 patients treated with  
2496 thiazides over 6 years developed Na < 130 meq/L, 4.5 times as many as controls (36). However, in SHEP,  
2497 patients randomized to chlorthalidone did not differ from those receiving placebo in sodium levels after  
2498 1 year (47).

2499 Similarly, in the observational Atherosclerosis Risk in Communities (ARIC) study, thiazides were  
2500 associated with an increased risk of incident gout mediated by increased uric acid levels (41). A recent  
2501 systematic review concluded “There is a trend toward a higher risk for acute gouty arthritis attacks in  
2502 patients on loop and thiazide diuretics, but the magnitude and independence is not consistent.  
2503 Therefore, stopping these useful drugs in patients who develop gouty arthritis is not supported by the  
2504 results of this review” (48). In HDP, patients randomized to chlorthalidone had reduced mortality  
2505 compared with usual care regardless of baseline uric acid level (49). In a matched sample comparison of  
2506 national pharmacy records, new onset gout episodes occurred with similar frequency in the year  
2507 following prescription for chlorthalidone or hydrochlorothiazide, despite the 2 drugs being used in equal  
2508 milligram doses (50).

2509 The above comparisons involving thiazide vs. no thiazide demonstrate effects that are minor and of  
2510 uncertain clinical importance. In addition, two studies from university (51) and VA (52) settings changed  
2511 19 and 40 patients (respectively) on a stable dose of hydrochlorothiazide to an equal milligram dose of  
2512 chlorthalidone. Both reported reduced blood pressure with no significant metabolic effects except for  
2513 one instance of hypokalemia in the university study.

2514 Changing from hydrochlorothiazide to a roughly equipotent half dose of chlorthalidone (the intervention  
2515 proposed in this study) should result in even smaller effects. In the randomized study by Ernst et al (23),  
2516 hypokalemia < 3.5 meq/L occurred in nearly identical proportions at 2:1 doses: 50% of patients on



2518 hydrochlorothiazide 25/50mg and 46% on chlorthalidone 12.5/25mg. Within the commonly used dosing  
2519 range of 12.5-25 mg per day, potassium reduction was found to be equivalent for the 2 drugs in one  
2520 meta-analysis (26), whereas the other found it to mirror the potency results, i.e. greater for  
2521 chlorthalidone at equal milligram doses (27). In a Dutch population-based case-control study,  
2522 hyponatremia was twice as common with chlorthalidone compared with hydrochlorothiazide at equal  
2523 doses, but no difference was observed comparing 2:1 dosing (53). In the short-term randomized trials of  
2524 609 and 1071 patients that compared equal doses (25 mg) of the 2 drugs in patients also taking an  
2525 angiotensin receptor blocker, hypokalemia was rare, occurring in 1-2% (30,31). Summarizing the  
2526 metabolic data available for the 2 drugs, a recent review (54) concluded that “factors such as serum  
2527 potassium, glucose, lipids, endothelial function, and oxidative status” “are either favorable to  
2528 chlorthalidone or are neutral in arriving at a decision as to which drug is superior.”

2529 More recently, a population-based observational study from Ontario compared effects of starting  
2530 treatment with chlorthalidone (10,384 patients) vs. hydrochlorothiazide (propensity matched sample of  
2531 19489 patients) with a mean follow-up of about one year (29). Patients treated with chlorthalidone  
2532 received higher doses (despite its greater potency), and were less likely to also be treated with an ACEI  
2533 or ARB (drugs that raise potassium levels). Chlorthalidone was associated with a small non-significant  
2534 reduction in the composite cardiovascular outcome, from 3.4 to 3.2 per 100 patient-years (adjusted HR  
2535 0.93, CI: 0.81-1.06). However, treatment with chlorthalidone was associated with significantly more  
2536 hospitalizations with (not necessarily “for”) hypokalemia (0.69 vs 0.27 events per 100 patient-years,  
2537 adjusted HR 3.06, CI: 2.04-4.58) and hyponatremia (0.69 vs 0.49 events per 100 patient-years, adjusted  
2538 HR 1.68, CI: 1.24-2.28). The authors included hospitalizations that listed electrolyte abnormalities as  
2539 secondary diagnoses noted during hospitalizations for other reasons. Hypokalemia and hyponatremia  
2540 were each recorded as a secondary outcome noted during hospitalization less than once per 100  
2541 patient-years. In response to a letter suggesting that the analysis should be restricted to hospitalizations  
2542 “for” hypokalemia (as primary diagnosis), the authors responded that doing so would result in so few  
2543 hospitalizations that “such an analysis would be severely underpowered” (55). So while it is not known  
2544 whether chlorthalidone caused more hospitalizations “for” hypokalemia, it is clear that such  
2545 hospitalizations were rare.

2546 The Ontario study had the advantages of large size and direct comparison of the two drugs in a  
2547 population. The principal disadvantages were the observational design and the very small (and therefore  
2548 potentially quite different) proportion taking chlorthalidone. Incomplete adjustment for known  
2549 confounders (e.g., for dose and co-treatment) or from unrecognized confounders in the treated  
2550 populations could have influenced the findings, as noted in a letter by the ALLHAT investigators (56). For  
2551 example, chlorthalidone is likely used more often by hypertension specialists who might have been  
2552 more attentive to recording electrolyte abnormalities on discharge summaries. Review of US data  
2553 indicates that chlorthalidone is used in patients with more severe co-morbidities than those given  
2554 hydrochlorothiazide (57). The Ontario study nevertheless raises questions regarding the possible  
2555 superiority of chlorthalidone. In the correspondence following its publication, both the ALLHAT  
2556 investigators and the Ontario authors stress the need for a randomized trial, such as the one we are  
2557 proposing, to resolve this uncertainty (55,56).

2559 In summary, the metabolic effects of thiazides are minor and have little or no clinical effect. Evidence  
2560 from a variety of studies indicates that substitution of an equipotent dose of chlorthalidone for  
2561 hydrochlorothiazide can be expected to have no more metabolic effect than might occur if the patient  
2562 remained on hydrochlorothiazide without the substitution. **This is the basis for our assertion that this**  
2563 **substitution constitutes minimal risk.**

2564 J. Expert views on the choice of drugs and the need for a randomized trial

2565 The evidence summarized above is consistent with a substantial benefit from using chlorthalidone  
2566 rather than hydrochlorothiazide, but is not compelling, as the Ontario study illustrates. Many of the  
2567 studies describing a possible advantage of chlorthalidone were conducted by Ernst and colleagues at the  
2568 University of Iowa (7,18,22,23,26,28), but those authors have stated that “we do not believe there is  
2569 strong evidence to support the use of chlorthalidone over HCTZ” (22). Ernst and Marvin Moser (who  
2570 pioneered thiazide use in the 1950’s) wrote in 2009: “Whether hydrochlorothiazide and chlorthalidone  
2571 are interchangeable in reducing the risk of cardiovascular events is questionable”(32). On the other  
2572 hand, Messerli et al reviewed the literature and concluded that “there is no evidence showing that HCTZ  
2573 in the dose of 12.5-25 mg reduces myocardial infarction, stroke, or death” and argue that “if a thiazide-  
2574 type diuretic is indicated, either chlorthalidone or indapamide should be selected” (6). The 2011 UK  
2575 National Institute for Health and Care Excellence (NICE) guidelines for hypertension (58) recommend “a  
2576 thiazide like diuretic, such as chlorthalidone..., in preference to a conventional thiazide diuretic such as  
2577 bendroflumethiazide or hydrochlorothiazide”, whereas the 2013 European Society guidelines dispute  
2578 this and conclude that “no recommendation can be given to favor a particular diuretic agent” (59).

2579 A recent review from investigators at the New Mexico VA (15) concludes: “The available evidence  
2580 therefore supports both HCTZ and chlorthalidone as safe and effective drugs for treating hypertension.  
2581 Although there are favorable trends both in terms of antihypertensive efficacy as well as clinical  
2582 outcomes data with chlorthalidone compared with HCTZ, the results are not conclusive, and as such may  
2583 not be enough to shift the treatment paradigm in favor of chlorthalidone, given the comfort level that  
2584 most prescribers have with HCTZ. A head-to-head study looking at hard clinical outcomes, which may or  
2585 may not ever be performed, may be the only way to resolve the ongoing debate as to which is the  
2586 preferred thiazide for treating hypertension.” Floyd and Psaty noted in 2012 (60) that “In the area of  
2587 pharmacological drug treatment for high blood pressure, the current question of primary interest is  
2588 whether health outcomes associated with the use of hydrochlorothiazide and chlorthalidone may differ.  
2589 ...Reliable and valid comparisons between hydrochlorothiazide and chlorthalidone will require a large,  
2590 long-term clinical trial.”

2591 As suggested by the New Mexico authors, it is extremely unlikely that a randomized clinical outcomes  
2592 trial of hydrochlorothiazide vs. chlorthalidone will ever be undertaken except by the inexpensive  
2593 methodology we are proposing. Neaton and Grimm, University of Minnesota Professors who  
2594 participated in MRFIT, SHEP, and subsequent NIH hypertension trials, have been lobbying for such a trial  
2595 since the end of SHEP more than 20 years ago. They have discussed the idea with the NHLBI project  
2596 office numerous times over conference calls and had a meeting in Bethesda about this issue. According  
2597 to Dr. Grimm, NHLBI project officers have maintained that they will only consider a 5 year proposal  
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2601 capped at \$1.5 million a year. The Director of the NHLBI Cardiovascular division has recently written that  
2602 “we can no longer afford to undertake randomized effectiveness trials that cost tens or hundreds of  
2603 millions of dollars” (61). Apart from a trial design such as we are proposing, which may be unique to the  
2604 VA system, these investigators found it impossible to design a study for an amount close to this budget.  
2605 Richard Grimm concluded a 7/29/13 email to the principal proponent (FAL) with: “It looks like the last  
2606 chance of getting a definitive answer for this incredibly important question is your VA proposal.”

2607 K. Summary of evidence and potential impact of the proposed trial

2608 Direct evidence shows chlorthalidone to be more potent and longer-lasting than hydrochlorothiazide,  
2609 and indirect interventional evidence from the Roush network meta-analysis (21) suggests that  
2610 chlorthalidone may have a more beneficial effect on cardiovascular events, whereas the large Ontario  
2611 observational study (29) did not find a significant reduction in adverse cardiovascular events. In  
2612 comparing these 2 methodologies, the International Society for Pharmacoeconomics and Outcomes  
2613 Research Indirect Treatment Comparisons Good Research Practices Task Force concluded that “a  
2614 network meta-analysis must be considered observational evidence, but is arguably less prone to  
2615 confounding bias than an observational comparative (prospective) cohort study” (62).

2616 Currently available data thus favor a likely substantial benefit from chlorthalidone compared with  
2617 hydrochlorothiazide, but these data have had little effect on prescribing, which continues to  
2618 overwhelmingly favor hydrochlorothiazide.

2619 If cardiovascular events were reduced by even a small amount by chlorthalidone, the public health  
2620 effect would be considerable because of the large number of patients who take diuretics. For the VA, it  
2621 would likely justify the effort and cost of implementing a national policy to change drugs. However, the  
2622 evidence is not yet persuasive enough to justify active measures directed at increasing chlorthalidone  
2623 use. A randomized head-to-head comparison of the effectiveness of these two drugs at reducing  
2624 cardiovascular events is clearly necessary to determine whether chlorthalidone is superior and if so, to  
2625 justify efforts to change practice.

2626 **IV. The Point of Care Program within the VA’s Office of Research and Development**

2627 A. Program Background

2628 Medical decision making is informed by clinical trials and observational studies. While clinical trials are  
2629 the gold standard in clinical research the high cost of conducting these studies combines with issues of  
2630 generalizability to limit their contribution to changes in medical practice. Observational studies are far  
2631 less expensive and thus more numerous, addressing a broader scope of clinical issues. However, their  
2632 primary failing is that the lack of randomization often leaves open the possibility of bias due to selection  
2633 by indication, and residual confounding of results due to unobserved prognostic factors that influence  
2634 treatment decisions.

2635 Point of care (POC) randomization represents an intermediate strategy between these two approaches.  
2636 The intent is to introduce the opportunity to randomize patients at decision points in clinical care where

2638 two or more alternatives are considered equivalent on average by the medical community (that is,  
2639 clinical equipoise exists). Patients who agree to be randomly assigned to treatment options will become  
2640 subjects in the clinical experiment.

2641 POC randomization preserves the experimental quality of clinical trials without the cost of the clinical  
2642 trial apparatus; recruitment and randomization is done at the point of care with minimal perturbation of  
2643 work flow, and outcomes are assessed by automated extraction of data from the medical record.  
2644 Reduction of the need for research staff interaction with potential subjects (limited to obtaining  
2645 informed consent) greatly reduces cost and generates data that reflects the *effectiveness* (rather than  
2646 efficacy) of experimental interventions in clinical care.

2647 To be effective, the additional burden on patients and health care providers imposed by POC  
2648 randomization must be minimal. The VA electronic medical record system (VistA) can be customized to  
2649 identify, enroll and randomize patients and serve as the source of outcomes data and is thus well suited  
2650 for such a trial design. Subject recruitment and enrollment will be accomplished by embedding  
2651 processes within the VistA system through a series of dialog boxes. Furthermore, an external system  
2652 will extract consent and randomization data from the databases supporting VistA.

2653 As noted in a recent editorial (63), “With optimal use of EMRs, the administrative costs of a trial need  
2654 not increase with the sample size; this decoupling of costs and size facilitates large, simple, and  
2655 inexpensive trials that have the potential to transform health systems into entities that learn and  
2656 continuously improve.”

2657 As the VA system continues to lead in the development of EMR that support increasingly sophisticated  
2658 monitoring for outcome-based evaluation of care, we anticipate that the methods we test using POC  
2659 randomization will have even greater scope for application. The methods are also a natural fit for testing  
2660 personalized and precision medicine strategies and for experimental comparative effectiveness  
2661 research.

## 2662 B. POC Pilot Study

2663 The first implementation of POC randomization is a pilot study that was conducted at 3 VAMC across 2  
2664 VISNs. The goal of the pilot was fivefold:

- 2666 1. To test the feasibility of the method for modification of VistA/CPRS screens and the ability to  
2667 randomize within the system;
- 2668 2. To assess patient and provider acceptance of the new methodology;
- 2669 3. To assess the regulatory acceptance of:
  - 2670 a. Informed consent procedures;
  - 2671 b. Safety monitoring;
  - 2672 c. Ethical considerations;
- 2673 4. To test the method for data extraction and passive collection of endpoint data using the EMR;
- 2674 5. To apply Informatics techniques to refine and improve efficiencies in the identification of  
2675 endpoints, etc.

2680 The pilot is a comparison of two standard strategies of insulin administration for hospitalized patients  
2681 and is designed as an open-label, randomized trial comparing sliding scale regular insulin (ssRI) to a  
2682 weight based regimen for control of hyperglycemia in non-ICU inpatients. The strategy is to enroll  
2683 patients into the study directly from the point of contact with clinical care within all inpatient facilities.  
2684 All non-ICU patients who require in-hospital insulin therapy are eligible for this study. Clinicians decide  
2685 at the time of care (through the VistA order entry screen for insulin) whether or not they will allow their  
2686 patient to be contacted by POC study staff. If the treating clinician agrees, consenting patients are  
2687 randomized to treatment arms and treated by their clinicians according to usual practices. All technical  
2688 modifications necessary are executed within the “Clinical Alert” package. Consenting patients are then  
2689 followed through VistA from randomization until 30 days post discharge. Comparisons of effectiveness  
2690 will be formally conducted using length of hospital stay measured in days as our primary outcome  
2691 measure.

2692 The pilot has demonstrated the feasibility of the POC method as an alternative design to traditional  
2693 trials. To date, 92% of eligible patients have accepted participation and have been consented into the  
2694 pilot protocol. Additionally, 71% of all clinicians that are able to order medications have accepted  
2695 randomization within the clinic and have referred their patients to the protocol. All patient data has  
2696 been extracted from the EMR and has been validated with chart review by a qualified clinician. There  
2697 have been no significant safety events and no findings from regulatory audits or the local institutional  
2698 review boards.

#### 2699 C. The POC National Program

2700 The goal of POC program is to deliver state of the art treatments to patients simultaneously with  
2701 enrolling them as subjects to redefine that care. By institutionalizing a process of statistically sound and  
2702 efficient learning, and by integrating that learning with automatic implementation of best practice, the  
2703 participating VA health care systems will accelerate improvements in the effectiveness of care for  
2704 veterans. With this goal in mind, Point of Care Research has been designated as one of the Secretary’s  
2705 (SECVA) Transformational Initiatives within the VA and within the Office of Research and Development  
2706 (ORD). Accordingly, this initiative has a national scope and an operating budget of approximately  
2707 \$10.2Million (exclusive of study budgets).

2708 The Boston CSPCC has been tasked with leading the effort to implement POC randomization within the  
2709 VA. To that end, our mission is to build the infrastructure necessary to support POC research; to educate  
2710 providers, veterans and investigators on the initiative; to build consensus for support of the initiative  
2711 among the VA community as a whole; and to explore the ethical, scientific, and regulatory aspects of the  
2712 POC method itself. In order to fulfill its mission, the Boston CSPCC collaborates with national leaders in  
2713 the fields of medical ethics and pragmatic clinical trials to produce scholarly works and it will conduct  
2714 focus groups of veterans, veteran service organizations, and providers in order to develop a national  
2715 educational campaign for all VA stakeholders.

#### 2716 V. Relevance of our trial design to current needs of VA healthcare

2721 The most reliable way to learn if medical interventions provide more benefit than harm for our patients  
2722 is through large randomized trials (64). However, large randomized trials that enroll thousands of  
2723 patients can cost hundreds of millions of dollars, placing them out of range for most payers, including  
2724 VA. As a result, many important questions remain unanswered.

2725 We are proposing herein a ‘clinically integrated’ study design (65,66) that will incorporate and extend  
2726 previously described VA ‘Point of Care’ Clinical Trial methodology (67,68). This is an efficient and  
2727 inexpensive design, that will rely on a centralized processes involving mail, phone, and data extraction  
2728 from the VA electronic medical records (EMR) , assisted by a designated study champion at each site  
2729 (the Site Liaison) and by local Clinical Application Coordinators (CACs). These methods will allow us to  
2730 avoid having to employ study personnel at each site to manage patients and collect data. As a result, the  
2731 infrastructure costs typically dedicated to these activities can be reinvested to answer other questions  
2732 for the healthcare system. The goal, as Lauer and D’Agostino suggest, is “to design and conduct  
2733 megatrials with what we have: bigger data and smaller budgets” (61).

2734 The following quotes, excerpted from the 2011 Institute of Medicine report “Learning what works best -  
2735 the nation’s need for evidence on comparative effectiveness in health care”(69), provide support for our  
2736 study objectives and design:

2737 “A core objective for the nation is achieving the best health outcome for every patient. This objective  
2738 simply cannot be accomplished until we have better evidence on which to base healthcare decisions”;  
2739 “the most rapidly growing problem is that of our inability to produce the needed evidence in a timely  
2740 fashion”; “Estimates of the proportion of medical care in the United States that is based on, or  
2741 supported by, adequate evidence range widely. However, given concerns about the extent to which this  
2742 information may be generalized, and the quality of the evidence which is used, some place this figure at  
2743 well below half.”; “Within the overall umbrella of clinical effectiveness research, the most practical need  
2744 is for studies of comparative effectiveness, the comparison of one diagnostic or treatment option to one  
2745 or more others.”; “issues in need of additional systematic evaluation ... include issues related to the  
2746 comparative evaluation of different drugs within a single class”; “A learning healthcare system is one in  
2747 which the clinical research paradigm depends more judiciously on the serial conduct of randomized  
2748 controlled trials—important, but often too expensive, untimely, and of limited applicability—and draws  
2749 more heavily on electronic health records (EHRs) to generate evidence as a natural by-product of the  
2750 clinical experience.”

2751 More recently, the FDA has launched a Clinical Trials Transformation Initiative intended to promote and  
2752 enable the conduct of larger, simpler, less expensive randomized trials using streamlining methodologies  
2753 such as use of electronic health records (70).

2754 In addition to addressing an important clinical question, our proposed trial is responsive to all these  
2755 needs. This trial represents a new efficient methodology designed to provide reliable answers to  
2756 practical clinical questions at a greatly reduced cost.

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**VI. Study Design**

The study design is a multicenter clinically integrated (65) [or “point of care” (67,68)] prospective randomized open-label blinded-endpoint (PROBE) trial (71).

**VII. Study Population**

A. Inclusion Criteria

Eligible patients are those (including women and minorities) who:

1. Are over age 65 years
2. Are receiving hydrochlorothiazide from the VA pharmacy at a daily dose of 25 or 50 mg
3. Have a most recent SBP in EHR  $\geq$  120 mm Hg, with no SBP  $<$  120 mm Hg recorded in EHR in the previous 90 days

B. Exclusion Criteria

Patients will be excluded if they are known to have any of the following:

1. Impaired decision-making capacity rendering the patient unable to provide informed consent (i.e., if there is any question during the nurse’s EHR chart review that the individual does not have the ability to make an autonomous decision or the PCP declines permission to randomize)
2. Death expected within 6 months (inferred by PCP permission to randomize)
3.  $K < 3.1$  meq/L (or 3.5 meq/L if on digoxin) in the past 90 days (assessed by EHR review)
4.  $Na < 130$  meq/L in the past 90 days (assessed by EHR review)
5. Known to be enrolled in Medicare Part C (assessed through administrative data or on consent phone call). This exclusion will only be employed if we determine that we cannot obtain sufficient information from Part C data (see below under Rationale).

Enrollment in another CSP interventional study is not an exclusion criteria for DCP. Dual enrollment is addressed in **Section IX. Study Procedures**.

C. Rationale

We limit to age over 65 years to allow data collection through Medicare (which is only widely available starting at this age) [and will exclude known Part C enrollees (those enrolled in Health Maintenance Organizations), for whom usual encounter data is not available through Medicare if we determine that we cannot obtain sufficient information from Part C data].



2796 We limit randomization to patients receiving hydrochlorothiazide because a) 95% of thiazide-type  
2797 diuretic prescriptions are for hydrochlorothiazide, b) there is little evidence to suggest that  
2798 chlorthalidone is inferior to hydrochlorothiazide, and c) the few PCPs who have deliberately chosen to  
2799 use chlorthalidone over the much more commonly used hydrochlorothiazide are less likely to be willing  
2800 to change drugs.

2801 We limit to hydrochlorothiazide doses of 25 or 50 mg because lower doses may not be effective and  
2802 cannot be easily converted to chlorthalidone (which is available only in 25mg tablets), and because  
2803 higher doses are not recommended and are rarely used.

2804 We limit to SBP  $\geq$  120 mmHg primarily to minimize risk from hypotension, and also to avoid enrolling  
2805 patients whose blood pressure is already low enough that a potentially more effective drug would not  
2806 be expected to add benefit (72, 73). The cutoff point of 120 mmHg was selected, in part, because we are  
2807 using routine clinic blood pressures recorded in EHR to determine study eligibility. These are obtained  
2808 using a less rigorous measurement protocol than is normally used in randomized trials and that tends to  
2809 overestimate blood pressure (74), in one study by a mean of 8 mmHg (75).

2810 **VIII. We will attempt to exclude patients in Part C as long as it appears that we will not be able to**  
2811 **obtain adequate data. Part C data have not been available for research purposes in the past,**  
2812 **but CMS plans to make the Healthcare Effectiveness Data and Information Set (HEDIS) for the**  
2813 **years 2006-2011 available sometime in 2015. We plan to check with CMS periodically, and if,**  
2814 **before or during enrollment, adequate Part C data appear to be accessible, we will**  
2815 **discontinue the exclusion and attempt to enroll these patients. Study Intervention**

2816 Participants will be randomly assigned to remain on their current dose of hydrochlorothiazide (25 or 50  
2817 mg), or to replace it with half that dose of chlorthalidone (12.5 or 25 mg, respectively), both changeable  
2818 by the PCP. Chlorthalidone 12.5 mg will require tablet splitting, and a splitter will be mailed with the  
2819 prescription. [Tablet splitting is a common procedure in VA pharmacy, sometimes including the splitting  
2820 of hydrochlorothiazide 50 mg to get 25 mg. A recent review (76) concluded that “Tablet splitting does  
2821 not seem to significantly affect clinical outcomes related to management of hypertension, cholesterol,  
2822 or psychiatric disorders, nor influence overall patient adherence.”]

2823 **IX. Rationale for the default use of 1:2 chlorthalidone dose: Because chlorthalidone is not used at**  
2824 **lower doses than hydrochlorothiazide in practice (7,28,29), it could be argued that the most**  
2825 **appropriate pragmatic comparison would be a 1:1 substitution. We selected the 1:2 dose**  
2826 **default for 3 reasons: 1) as noted above, the use of similar doses in practice probably reflects**  
2827 **greater awareness of appropriate thiazide dosing by the small proportion of prescribers who**  
2828 **use chlorthalidone, rather than belief that the potencies are equivalent, 2) a 1:1 design would**  
2829 **change the study question from assessment of a possible inherent difference between the two**  
2830 **diuretics to an assessment whether low doses of hydrochlorothiazide are less effective,**  
2831 **whereas our interest is in the former question , and 3) an equal dose of chlorthalidone would**  
2832 **represent an intensification of diuretic therapy, resulting in increased effects on blood**  
2833 **pressure and blood chemistries (51,52,53), whereas the 1:2 design results in virtually no**  
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2837 **change in blood pressure or metabolic effects (see Background and Rationale, parts F and**  
2838 **I).Study Procedures**

2839 A. Procedures prior to patient enrollment

2840 We will attempt to identify a “Liaison” at each site, usually a physician in primary care and/or  
2841 hypertension management whose role will be limited to identifying key personnel at the site and  
2842 introducing the study by giving presentations to local Primary Care Providers (PCPS), pharmacy, the  
2843 Information Resource Management service (IRM), Clinical Application Coordinators (CACs), and  
2844 Information Security Officers (ISOs) and subsequently referring all questions and comments to Boston  
2845 CSPCC. The Liaison will not be involved in recruitment or have patient interaction related to the study.  
2846 Because we are introducing a new design and intend to evaluate its success, PCPs are also considered to  
2847 be research subjects (see XI. Biostatistical Considerations, F. Secondary Data Analysis, 4. Primary Care  
2848 Provider Metrics of Interest).

2849 Our procedures are summarized in a flow diagram (**Appendix C**). Working through the VA national ISO  
2850 structure and local CAC’s and pharmacy personnel, we will obtain permission for Boston CSPCC to have  
2851 the necessary access to local EHR systems to enter notes and post orders as View Alerts to PCPs and to  
2852 collect the study data on enrolled patients. Research staff at the Boston CSPCC will be responsible for  
2853 communicating with local PCPs, coordinating and implementing all patient recruitment activities and  
2854 completing the enrollment process including randomization and placing assigned treatment orders for  
2855 signature by the PCP in EHR. The Boston CSPCC will partner with the Minneapolis VA Medical Centers to  
2856 conduct centralized calling activities, including contacting potential participants and obtaining informed  
2857 consent by telephone.

2858 We plan to roll out the study in blocks of sites. When a site starts up, the Boston CSPCC will generate a  
2859 local list of PCPs along with their eligible patients. We will also identify local PCP and pharmacy email  
2860 groups and obtain the PCPs’ and pharmacists VA Outlook email addresses. The Boston CSPCC will send  
2861 an introductory letter (by mail and email) to local PCPs signed by the Study Chair providing information  
2862 about the study (**Appendix A.1, A.7**). Introductory emails (**Appendix A.7**) will be sent by the study team  
2863 via ProjectFlow, while letters will be sent via external mail contractor. The Site Liaison or study team will  
2864 present information about the study at primary care staff meetings and other forums (individual PACT  
2865 meetings, video staff meetings for Community-Based Outpatient Clinics, etc.). If no meetings are  
2866 available the study may use a video of slides accompanied by an audio track to conduct site education  
2867 for providers. This video can also be accessed at any time by consented providers that would like to  
2868 review the study information. To further provider education, a second reminder email with an attached  
2869 summary document and a link to the video will be sent to providers prior to being contacted within the  
2870 EHR system (**Appendix A.8**). The second email is to act as a brief reminder of the study to providers, not  
2871 to act as an informed consent document.

2872 After these activities are completed, a View Alert ‘testpatient’ order will be sent to each PCP identified  
2873 by the method above. The testpatient order will accompany a progress note containing the text of the  
2874 Provider Information Sheet, which will contain the elements of informed consent and detail the study

2876 procedures (**Appendix B.3**). By signing the ‘testpatient’ view alert order, the PCP is agreeing to  
2877 participate in the study as a research subject and allowing the recruitment letter (**Appendix A.2**) to be  
2878 sent to eligible patients. Alternatively, the PCP can “discontinue” the order, in which case that PCP will  
2879 not be enrolled in the study and his/her patients will not be contacted at this time. As some PCPs may  
2880 discontinue the order because they did not recognize the purpose of the ‘testpatient’ order we may  
2881 send a second View Alert ‘testpatient’ order approximately 8 weeks later to PCPs who decline to give  
2882 the PCP the opportunity to participate and/or confirm their desire not to participate.

## 2883 B. Enrollment procedures

2884 The procedures described below are summarized in a flowchart (**Appendix C**). Provider and patient mail  
2885 will be sent primarily through an external mail contractor and also by the study team, as needed. The  
2886 external contracted mailing vendor will receive participants’ names, addresses, information about  
2887 treatment assignment, and other protocol procedures. No other patient health information will be sent  
2888 to the mail vendor.

2889 Using the VA electronic medical record, the Boston CSPCC will identify eligible patients of PCPs who  
2890 signed the testpatient order. The mailing vendor or study staff will mail the study recruitment letter  
2891 (**Appendix A.2**) with Informed Consent Information Sheet (**Appendix B.2**), which contains the text of the  
2892 consent script (**Appendix B.1**), to these patients. The study team will attempt to send the letter 3-4  
2893 months before the patient’s next planned appointment with the PCP to make it easier for the PCP to  
2894 obtain any follow up on blood pressure and laboratory tests that the PCP might want. The VA Advanced  
2895 Clinical Access/Recall system may prevent early detection of these appointments. The study Invitation  
2896 Letter and the Informed Consent Information Sheet will provide information about the study and the  
2897 opportunity for the patient to opt out of future contact from the study. Patients can opt out by leaving a  
2898 voicemail with their name, date of birth, and the last four digits of their social security number. Patients  
2899 that leave an opt-out message will only be contacted in the rare case that the their identity cannot be  
2900 confirmed. Additional Spanish letters will be sent to all patients in Puerto Rico and any patients that  
2901 request a Spanish version. Any Spanish speaking Veteran will speak to a Spanish speaking study team  
2902 member, contact a voicemail box recorded in Spanish, and will consent in Spanish.

2903 If no ‘opt out’ call is received within 2 weeks after the Patient Information Letter is sent, the patient will  
2904 be contacted to determine if they wish to participate. This will be done in majority by trained callers  
2905 using a telephone line that displays the calling source as the VA on caller ID. Trained research staff may  
2906 also consent patients and may also contact patients during follow-up calls. We will make multiple  
2907 attempts to reach the patient, only leaving a maximum of 3 spaced out messages. More than 3 will only  
2908 be left if the caller is returning the patient’s call. The U.S. National Health Interview Survey used a  
2909 maximum of 15 call attempts and a 1994 study confirmed this number to be optimal (77). In 2 surveys  
2910 conducted by Statistics Sweden, nonresponse rates stabilized at 15 and 20 maximum call attempts (78).  
2911 In the Consumer Assessment of Health Plans Study, “most hard-to reach non-respondents were called  
2912 10 or more times” (79). A recent study at the University of Minnesota (80) had an amendment approved  
2913 by the UMN IRB in 2011 to increase the maximum number of call attempts from 6 to 12. Regarding left  
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messages, Koepsell (81) “found that leaving a brief message about the study and promising a call-back improved the response rate by nearly 20 percentage points”. If a Veteran expresses interest on the last

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2968 call or leaves a voicemail after 15 calls, 3 additional call attempts will be made. On the phone call, the  
2969 information included in the letter will be reviewed and the patient’s informed consent will be sought  
2970 using a pre-approved Telephone Consent Script (**Appendix B.1**). Research staff and study nurses may  
2971 occasionally call consented patients to evaluate consent call procedures, discuss any concerns the  
2972 patient’s raise, and to complete withdrawal procedures. Additional study information may be  
2973 transmitted to Veterans, per their request, in the format that best suits their needs (**Appendix A. 12**). All  
2974 email communication between the study team and Veterans will occur over My Healthy Vet. The mail  
2975 vendor or study staff may also re-send introductory study materials to Veterans if they have not been  
2976 reached after 5 calls. The mail vendor or study staff may also send a newsletters or reminder  
2977 information to enrolled patients as needed (**Appendix A.15, A.10, A.11**). At the end of recruitment a  
2978 letter (**Appendix A.20**) will be sent to any patient who has not been given a study status. Meaning they  
2979 have not declined, agreed to participate, or were otherwise found to be ineligible in the study. This  
2980 letter will not be sent to patients who have received 6 or more calls, to avoid confusion. Study data will  
2981 be dispersed to all randomized patients via an end of recruitment letter (**Appendix A. 23**), consented  
2982 PCPs will receive a the same information via email (**Appendix A.22**)

2983 At the end of recruitment all consented providers will receive an email (**Appendix A.24**) inviting them to  
2984 participate in a participation survey (**Appendix A.21**). In addition, Minneapolis providers will have the  
2985 opportunity to take an in-person interview (Appendix A.25). The survey data will be aggregated to  
2986 inform and improve future designs of pragmatic studies.

2987 After telephone consent is obtained, a preliminary eligibility check will be performed to prevent sending  
2988 randomization View Alerts to providers for ineligible patients. If a patient is deemed eligible, a View  
2989 Alert order will be sent to the PCP which, if signed by the PCP, will indicate permission to randomize that  
2990 particular patient. If a patient is deemed ineligible at that time, a determination will be made whether  
2991 they are temporarily or permanently ineligible. Temporary ineligibility may be due to lab values or  
2992 blood pressure measurements out of inclusion range that could change over the subsequent months.  
2993 Temporarily ineligible patients may receive a letter indicating that they are not presently eligible, but  
2994 will continue to be considered for randomization if their eligibility criteria change. Eligibility will be re-  
2995 assessed for temporarily ineligible participants periodically. If a patient becomes eligible again six  
2996 months or more after consent, a study team member will attempt to call the patient to reaffirm consent.  
2997 After three attempts the study team will proceed with randomization. Randomization will yield a letter  
2998 with study information allowing the Veteran to withdraw or contact the study if needed. Permanently  
2999 ineligible patients will receive a letter indicating that they will no longer be considered for  
3000 randomization. Alternatively, if the PCP believes that patient should be excluded for any reason (e.g.,  
3001 incompetence or short life expectancy), the order can be “discontinued” and the patient will then  
3002 receive a letter saying that their PCP declined their participation in the study (**Appendix A.3**).

3003 If an eligible patient is enrolled into another CSP interventional study prior to randomization in DCP, the  
3004 DCP PI will initiate a conversation regarding dual enrollment with the other study’s PI. If the  
3005 investigators of both studies agree, they will sign a memo describing that agreement and any additional  
3006 study activities or safety reporting requirements resulting from enrollment in both studies. Additionally,  
3007 this memo must be signed by the studies’ respective CSPCC directors prior to randomization into DCP.



3010 DCP will dual enroll with CSP577: CONFIRM, CSP2005: VALOR, and CSP2016 per the guidance from the  
3011 signed memos.

3012 C. Randomization

3013 After the PCP signs the order allowing the patient to be randomized, the patient will be randomized by  
3014 the Boston CSPCC. Randomization will be to chlorthalidone or hydrochlorothiazide with equal  
3015 probability. Randomized group will be open label, but allocation will be concealed before randomization  
3016 and irrevocable afterwards. All randomized patients will be included in the analysis according to the  
3017 intent-to-treat principle. Outcome assessment will be conducted by investigators blinded to treatment  
3018 assignment.

3019 We are thus proposing a “prospective randomized open-label blinded-endpoint” (PROBE) trial (71). The  
3020 rationale for our open-label design is several fold: 1) since there is no local coordinator, it is essential  
3021 that the PCP manage the diuretic therapy, and we are concerned that this may not always occur if we  
3022 use a blinded study drug, 2) there is no local investigator to assist with emergency unblinding, 3) we  
3023 believe that keeping patients on open label therapy, being more familiar and straightforward from the  
3024 patient’s perspective, will enhance recruitment, thereby improving both feasibility and generalizability,  
3025 4) local pharmacy management of blinded drug would require a level of effort and local engagement in  
3026 research incompatible with our streamlined study structure, 5) the expense of producing a study  
3027 preparation that is identical for the two drugs, and then labeling and tracking each patient’s therapy,  
3028 would greatly increase cost, defeating the purpose of our highly efficient clinically integrated design. A  
3029 recent meta-analysis found PROBE trials to be comparable to blinded trials in terms of assessing  
3030 antihypertensive drug effect on blood pressure measurements, though clinical outcomes were not  
3031 examined (71).

3032 At the time of randomization, a templated text order placed by the Boston CSPCC will appear as a View  
3033 Alert to the PCP. The order will indicate randomized assignment and reference the associated progress  
3034 note that provides the following reminders: 1) when resolving the view-alert orders, the PCP can accept  
3035 the order by signing as is or change the dose, 2) the PCP can discontinue the order to continue their  
3036 patient on his/her current diuretic, 3) the PCP may wish to order any desired laboratory tests or blood  
3037 pressure checks, and 4) the PCP should manage the diuretic in the future according to the patient’s  
3038 needs.

3039 Patients will be sent a letter informing them of their randomized group (**Appendix A.4**). Patients  
3040 assigned to hydrochlorothiazide will simply remain on their current prescription. For patients  
3041 randomized to chlorthalidone, the Boston CSPCC will also generate View Alert orders to the PCP  
3042 cancelling the hydrochlorothiazide prescription and replacing it with chlorthalidone. Patients  
3043 randomized to chlorthalidone will be instructed to discard their hydrochlorothiazide pills, and will be  
3044 reimbursed for their co-pay on the discarded pills. The change from hydrochlorothiazide to  
3045 chlorthalidone is a typical pharmacy action in usual care and will otherwise be handled with usual  
3046 pharmacy procedures and information at that medical center.

3048 In the unlikely event that the PCP, having very recently signed the “permission to randomize” view alert  
3049 order, does not sign (i.e., “discontinues”) the initial study drug order for chlorthalidone, the patient will  
3050 still be analyzed in the randomized group according to intent to treat. In these instances, we may  
3051 contact the PCP to ask the reason for the discontinuation of the order.

3052 **X. We will monitor drug prescribing for study patients throughout the study. If the study drug is**  
3053 **discontinued, a prescription is written for the other diuretic (cross-over), or the**  
3054 **prescription is not refilled for 90 days after expected, a View Alert may be sent to**  
3055 **remind the PCP about the study. If the situation persists after 2 weeks, we will review**  
3056 **the chart to determine if the lapse was intentional and if so, try to determine the**  
3057 **reason. If questions remain after the review, we may query the PCP. Outcome**  
3058 **Measures**

3059 A. Primary outcome

3060 The primary outcome measure will be time to a major cardiovascular event, defined as a composite  
3061 outcome comprised of the first occurrence (after randomization) of any of the following:

- 3062 1. Stroke
- 3063 2. Myocardial infarction
- 3064 3. Urgent coronary revascularization (completed or attempted) because of unstable angina
- 3065 4. Hospitalization for acute congestive heart failure
- 3066 5. Non-cancer death

3067 B. Secondary outcomes

3068 Secondary outcomes will include:

- 3069 1. All deaths
- 3070 2. The composite outcome substituting all deaths for non-cancer deaths
- 3071 3. “Possibly vascular deaths” defined as all deaths caused by vascular diseases, diabetes,  
3072 external causes, and unknown causes
- 3073 4. The composite outcome substituting “possibly vascular deaths” for non-cancer deaths
- 3074 5. Each of the 5 components of the composite primary outcome
- 3075 6. Any revascularization of any artery
- 3076 7. Erectile dysfunction, defined as first prescription for PDE5 inhibitor or referral for ED

3077 C. Process variables  
3078  
3079  
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- 3082 1. Mean blood pressure during the study (outpatient clinics only; excludes inpatient,  
3083 Emergency Department and Operating Room)
- 3084 2. Time to discontinuation of the randomly assigned diuretic (defined as discontinue order or  
3085 no prescription for  $\geq 6$  months at last observation during study period)
- 3086 3. Mean compliance with study drug using “Medication Possession Ratio” (82) (used by VA  
3087 Pharmacy Benefits Management Services)
- 3088 4. Other antihypertensive drug use

3089 D. Tertiary Outcomes

- 3090 1. Hospitalization for primary diagnosis of hypokalemia, hyponatremia, or renal failure
- 3091 2. Renal failure. Defined as dialysis or renal transplant. (Doubling of serum creatinine from  
3092 baseline will also be recorded and reported in the final analyses).
- 3093 3. Other recorded hypokalemia ( $< 3.1$  meq/L), or hyponatremia ( $< 130$  meq/L)
- 3094 4. New diabetes, defined as first use of a medication for diabetes
- 3095 5. Acute gout episodes
- 3096 6. New allergic reaction to thiazide-type diuretic to be found in EMR allergy data

3097 E. Rationale for elements of composite primary outcome

3098 The elements of the composite primary outcome are intended to represent the clinically important  
3099 effects of diuretic therapy for hypertension. Myocardial infarction and stroke are traditional outcomes  
3100 for cardiovascular clinical trials and will not be further justified here.

3101 Stroke. Stroke is defined from the American Heart Association/American Stroke Association updated  
3102 definition of stroke for the 21<sup>st</sup> century (83) and includes central nervous system infarction (brain, spinal  
3103 cord, or retinal) attributable to ischemia based on neuropathological, imaging, and/or clinical evidence;  
3104 ischemic stroke accompanied by overt symptoms; and stroke caused by intracerebral hemorrhage,  
3105 subarachnoid hemorrhage, or cerebral venous thrombosis. Stroke also includes any episode of acute  
3106 neurological dysfunction presumed to be caused by ischemia or hemorrhage, persisting  $\geq 24$  hours or  
3107 until death, but without sufficient evidence to be classified as one of the above. We exclude silent  
3108 central nervous system (CNS) infarction, silent cerebral hemorrhage, major brain trauma including  
3109 subdural hematoma or hemorrhaging, intracranial neoplasm or metastasis, coma due to metabolic  
3110 disorders or disorders of fluid or electrolyte balance, peripheral neuropathy, or central nervous system  
3111 infections.

3112 Myocardial infarction. Myocardial infarction is defined from the third universal definition as evidence of  
3113 myocardial necrosis in a clinical setting consistent with myocardial ischemia (84).

3115 Urgent coronary revascularization. Urgent coronary revascularization is an important outcome because  
3116 these events accurately reflect both the progression of underlying atherosclerotic vascular disease and  
3117 represent an important contributor to cardiovascular morbidity and healthcare costs. Disease  
3118 progression that formerly resulted in myocardial infarction now frequently results in revascularization  
3119 that aborts the infarction. Furthermore, because of increasingly sensitive troponin assays, many patients  
3120 having urgent coronary revascularization attributed to unstable angina actually have mild troponin  
3121 positivity and would be classified as myocardial infarctions in a classic trial design with in-depth outcome  
3122 review (Christopher P. Cannon, MD, personal communication, Aug 2013). Including urgent coronary  
3123 revascularization in our study will prevent us from missing these infarctions. Urgent coronary  
3124 revascularization is more restrictive than the revascularization outcome usually reported in previous  
3125 trials and selects for the most clinically relevant events. For example, in the PEACE trial of patients with  
3126 stable coronary artery disease and normal ejection fraction (85), “all coronary revascularizations” were  
3127 more frequent than all the other events combined that make up our composite. On the other hand, in  
3128 the (TRA2°P)-TIMI 50 trial of an antiplatelet agent in patients with vascular disease (86), urgent coronary  
3129 revascularization because of unstable angina was less frequent than myocardial infarction and similar in  
3130 frequency to cardiovascular death or stroke, and increased the composite rate in the placebo group  
3131 from 10.5% for those 3 outcomes to 12.4% for those 3 outcomes plus urgent revascularization.

3132 Reductions in urgent coronary revascularization represent an important contribution to the overall  
3133 effectiveness of therapy. The observed reductions in urgent revascularizations in randomized trials are  
3134 concordant with changes in other major outcomes. In (TRA2°P)-TIMI 50 (86), the hazard ratio for the  
3135 primary composite outcome of cardiovascular death, myocardial infarction, or stroke was 0.87, and for  
3136 urgent coronary revascularization was 0.88. Urgent coronary revascularization has also been used in  
3137 TRACER (87) and is being used in EXAMINE (88). CSSEC recently approved a broader revascularization  
3138 outcome for VA CSP #593, the VA Fenofibrate Intervention Trial (VA-FIT) (for which the indications  
3139 included stable angina with a >50% target lesion).

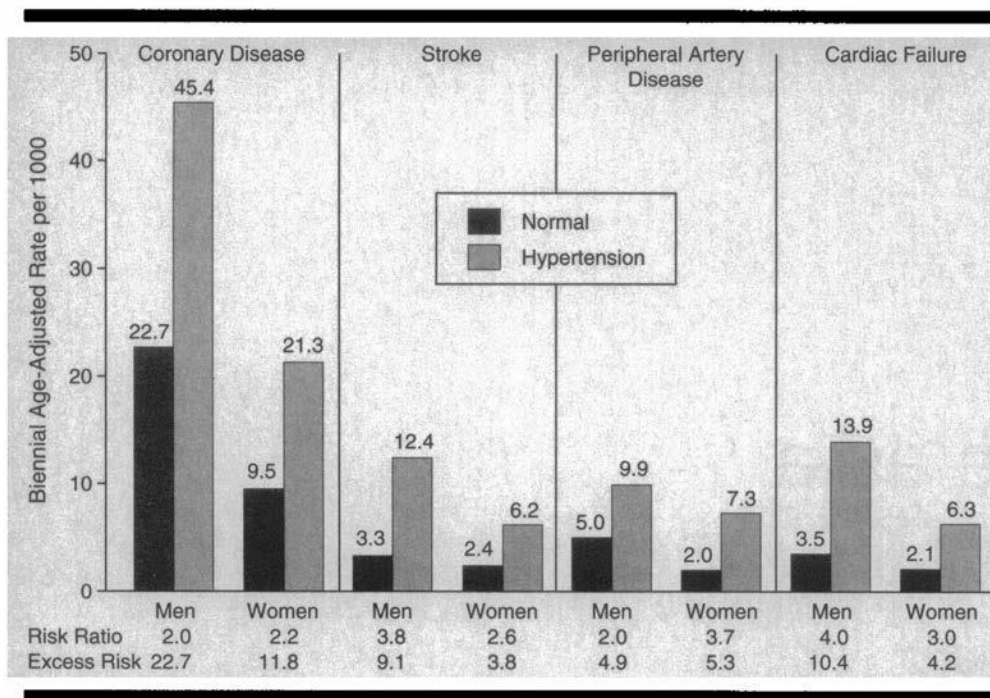
3140 In summary, urgent coronary revascularization is a significant contributor to cardiovascular morbidity  
3141 and health care costs, its inclusion will allow assessment of the full impact of therapy, and its relative  
3142 contribution to overall endpoints is not anticipated to be disproportionate to that of other study  
3143 outcomes. Our definition of urgent coronary revascularization will consider completed or attempted  
3144 coronary revascularization procedures performed because of unstable angina. Unstable angina is further  
3145 defined as any increase in angina, and/or inadequate response to increased anti-anginal therapy cited as  
3146 the reason(s) for the procedure, and with the medical record citing that increased angina and/or  
3147 inadequate response to increased anti-anginal therapy occurred within 30 days before the inpatient  
3148 procedure code for coronary revascularization.

3149 Hospitalization for acute congestive heart failure. Hospitalization for acute congestive heart failure is  
3150 another important component of our primary outcome. It will, in most instances, represent a new  
3151 diagnosis of heart failure because most patients with established heart failure are maintained on a loop  
3152 diuretic such as furosemide and are not treated with hydrochlorothiazide and thus would not be  
3153 enrolled in our study. We will seek to identify clinical exacerbations of symptoms (e.g., not

3155 hospitalization for ICD placement), which should be associated with intensification of treatment, which  
3156 we will assess in our algorithm.

3157 Heart failure is a major public health problem with a profound impact on prognosis and also on costs,  
3158 and is the most frequent cause of hospitalization among people older than 65 years (89). Its impact is  
3159 summarized in the AHA 2013 update (90): “HF incidence approaches 10 per 1000 population after 65  
3160 years of age”, ...“approximately 50% of people diagnosed with HF will die within 5 years”, ...“One in 9  
3161 deaths has HF mentioned on the death certificate”, ...“In 2009, HF any-mention mortality was 274 601”  
3162 and “HF was the underlying cause in 56 410 of those deaths”.

3163 Heart failure and stroke are the two major cardiovascular outcomes most related to hypertension and  
3164 most benefited by treatment of hypertension. Seventy-five percent of heart failure cases have  
3165 antecedent hypertension (90). The Framingham Heart Study (91) found the highest risk ratio from  
3166 hypertension to be for heart failure in men (Figure 1).  
3167



3168 Figure 1. A prospective analysis of the 36-year follow-up data from the Framingham Heart Study (91)  
3169 demonstrates that hypertension (blood pressure  $\geq 140/90$  mmHg) predisposes to all major  
3170 atherosclerotic cardiovascular disease outcomes, but the largest risk ratios are for cardiac failure and  
3171 stroke in men.

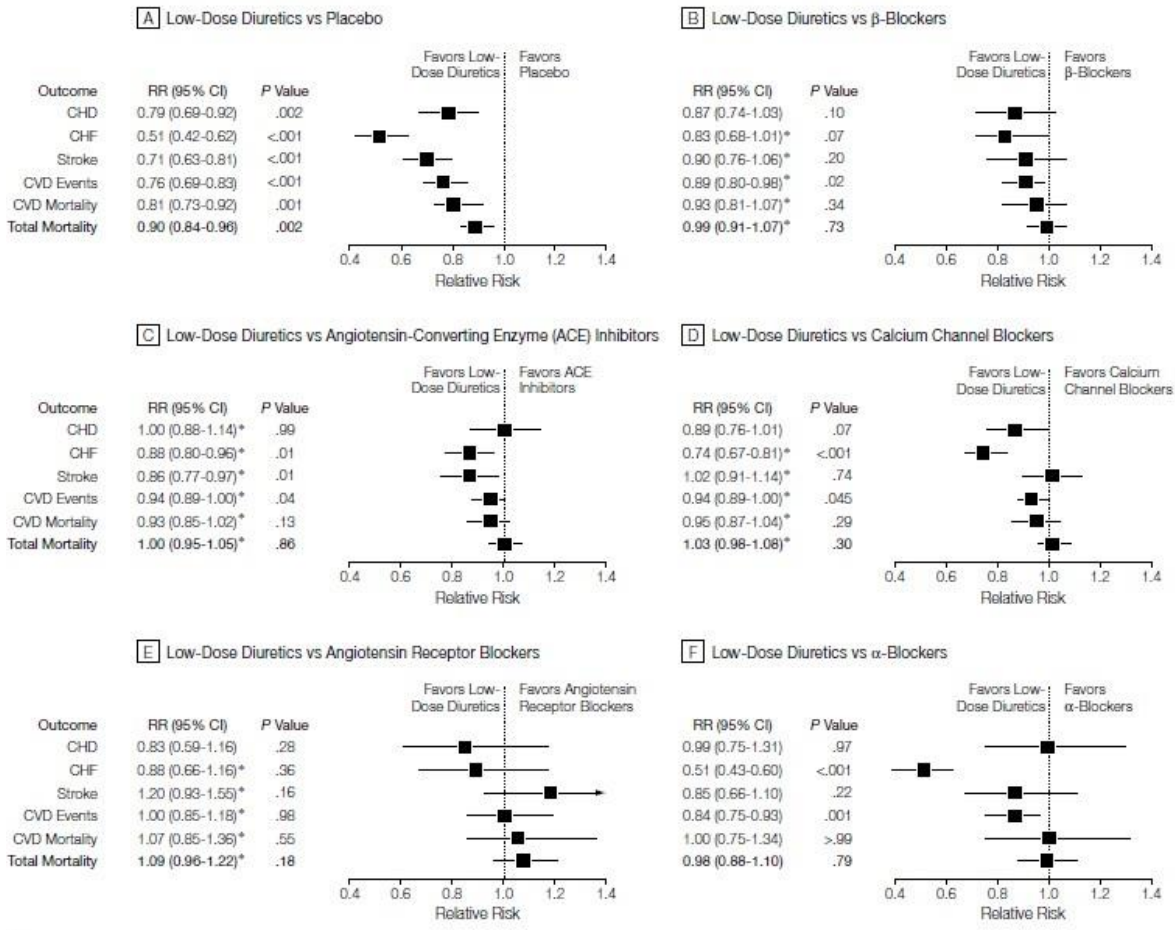
3172 Diuretic-based treatment arms in outcome trials have reduced HF by an average of 50% over placebo  
3173 (compared with 30-40% reduction for stroke), and more effectively than calcium channel blockers and  
3174 ACE inhibitors in comparative trials (Figure 2) (5). In ALLHAT (89), the alpha blocker doxazosin, the  
3175 calcium channel blocker amlodipine, and the ACE inhibitor lisinopril were associated with 80%, 38% and  
3176 19% higher risk of heart failure compared with chlorthalidone. Therefore, heart failure is likely to be one



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of the most sensitive outcomes for detecting a true difference in reducing cardiovascular disease between the two diuretics in our study.

**Figure 2.** Network Meta-analysis of First-Line Treatment Strategies in Randomized Controlled Clinical Trials in Hypertension



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Figure 2. From a network meta-analysis of hypertension trials (5). Heart failure (CHF) can be seen to be a particularly effective outcome for discriminating between diuretics and other drugs. “CVD Events” include CHD, CHF, stroke and CVD deaths.

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Hospitalized heart failure is not disproportionately common compared with our other outcomes. In the principal ALLHAT report (20), there were 885 non-fatal MIs, 724 hospitalized or fatal heart failure events, and 675 strokes. Hospitalized heart failure events in ALLHAT attracted close scrutiny because they were reported by site investigators and not adjudicated. The authors undertook a separate study in which they successfully validated these events (89), and from which they concluded “Heart failure proved to be a common outcome in ALLHAT and one that was affected differentially by the randomized treatment assignments. In addition, patients who developed HF had significantly poorer survival than those who did not. Whether this poor prognosis can be altered presents an important clinical and public health question. Thus, *in planning future hypertension treatment trials* (and perhaps also treatment trials in other populations at high risk of HF, such as diabetics and survivors of acute coronary

3196



3197 syndromes) *serious consideration should be given to including HF in the primary end point*, along with  
3198 death, MI, and stroke” (italics added).

3199 Heart failure is reasonably well identified using discharge diagnoses. In a population-based study of 4537  
3200 cases of heart failure from Olmsted County MN, ICD-9 code 428 constituted 80% of heart failure codes,  
3201 and 82% of the cases coded as 428 met Framingham criteria for heart failure when records were  
3202 reviewed by experienced abstractors (92).

3203 Identification of clinically important episodes can be improved by looking for evidence of treatment  
3204 intensification. The draft report of the FDA expert panel on Cardiovascular Endpoints in Clinical Trials  
3205 (93) recommends inclusion of the following criteria for determining a heart failure hospitalization event:  
3206 “The patient receives initiation or intensification of treatment specifically for HF, including at least one  
3207 of the following: a. augmentation in oral diuretic therapy, b. intravenous diuretic, inotrope, or  
3208 vasodilator therapy, or c. Mechanical or surgical intervention, such as i. mechanical circulatory support  
3209 (e.g., intra-aortic balloon pump, ventricular assist device) or ii. mechanical fluid removal (e.g.,  
3210 ultrafiltration, hemofiltration, dialysis).” We will employ these criteria and others, such as exclusion of  
3211 admissions for ICD placement, in our algorithms to maximize the likelihood that the events we capture  
3212 are clinically relevant.

3213 Non-cancer deaths. We include non-cancer deaths in our primary composite outcome as a compromise  
3214 between total mortality, which includes many irrelevant events that dilute the effect of the intervention,  
3215 and cardiovascular mortality, which is less accurately distinguished on death certificates and may miss  
3216 relevant deaths. We exclude cancer deaths because they are numerous, relatively accurately identified  
3217 on death certificates (94,95,96), and believed to be unrelated to diuretic use, so excluding them reduces  
3218 “noise” relative to expected effects of the intervention. In the Physicians’ Health Study (95), cancer  
3219 deaths in patients older than 65 years were identified from death certificates using standard nosology  
3220 protocols and the Automated Classification of Medical Entities (ACME) Decision Tables with specificity  
3221 well over 99% compared with an adjudication committee, meaning that the deaths excluded from our  
3222 primary outcome will almost certainly be due to cancer.

3223 Prieto-Merino and colleagues (97) note: “If outcomes that are causally related to the trial treatment are  
3224 combined with those that are not, the estimate of the treatment effect is diluted towards the null and  
3225 we may fail to identify potentially important benefits or harms.... Because few treatments will be  
3226 causally related to all causes of death, all-cause mortality is a composite outcome that combines causally  
3227 related causes of death with those unrelated to the treatment.” We did not restrict to cardiovascular  
3228 deaths because some other deaths may be relevant, such as accidents due to syncope from hypotension  
3229 and deaths from unknown causes (which could have been cardiovascular), and other deaths (e.g.,  
3230 pneumonia, COPD) that are not accurately distinguished from cardiovascular deaths by death certificate  
3231 diagnoses. Competing risk from cancer deaths will be considered in a secondary analysis.

#### 3232 F. Ascertainment of Outcome Data

3233 Data collection will be via electronic medical records, administrative data, Medicare and death records.  
3234 We will use VA, CMS, and National Death Index data. Assessment of outcomes and relevant data

3237 elements as well as adverse event is by passive collection of data in electronic health records; the study  
3238 will not attempt to generate any additional tests or procedures. All outcome processing will be  
3239 conducted by investigators at the Boston CSPCC unaware of treatment group. In this section we describe  
3240 our approach to ascertainment and assessment of these outcomes.

3241 The Boston CSP Coordinating Center has 15 years of experience in ascertainment and assessment of  
3242 cardiovascular outcomes using the VA electronic health record (EHR) and CMS data. We will build on  
3243 this extensive experience to refine a specific procedure for doing the same in this trial in order to  
3244 accurately identify and assess outcomes. The process involves several clearly defined steps. First, we  
3245 develop a method to screen the electronic medical records of all participants on a periodic basis for  
3246 potential cases. This screening consists of comparing discharge diagnosis and procedure codes for  
3247 enrolled patients to a list of outcome-relevant ICD 10 and CPT codes. Admissions that do not match  
3248 codes on our list will be considered non-events. The development of the screening process and the  
3249 algorithms for confirming cases follows a systematic approach that we have used at the Boston CSPCC  
3250 for a number of years. The screening approach is used to identify all potential cases using key elements  
3251 in the EHR. The screening tool varies for each outcome (i.e. outcome-specific administrative diagnosis  
3252 codes).

3253 Second, algorithms are developed to collect and analyze data elements that are used to confirm or  
3254 refute the potential cases (e.g. presence of imaging during a stroke). The algorithms are based on  
3255 elements of the clinical definitions of the outcomes, and are applied to potential cases to determine if  
3256 the case is confirmed, disconfirmed or deemed indeterminate. Algorithms for cases are constructed  
3257 using “gold standard” cases (identified by manual chart review) and data elements obtained from the  
3258 medical record that are found in the outcome definitions, such as cardiac enzymes for MI. Once the  
3259 algorithm for a specific case is defined, the algorithm’s accuracy is checked by manual review of cases  
3260 identified by the algorithm.

3261 Third, indeterminate cases will undergo manual adjudication. We expect to be left with a relatively small  
3262 number of events that cannot be resolved by the algorithm, but all of these will be referred for  
3263 adjudication to an outcomes committee. This will greatly lessen the workload for manual adjudication.  
3264 All patients will be followed until death or the end of the study (even if the primary outcome is  
3265 determined to have occurred) to collect secondary outcomes, including death.

3266 A pilot study using VA EHR was conducted to determine the availability of potential cases and core data  
3267 elements that would be needed to develop algorithms to assess the primary outcomes. A total of 150  
3268 medical records were reviewed, 30 in each category for stroke, myocardial infarction and urgent  
3269 coronary revascularization and 60 records of patients with a diagnosis of acute congestive heart failure.  
3270 A medical record abstraction form for each outcome was developed based on standard diagnostic  
3271 definitions that included information on symptom presentation, physical findings, critical laboratory  
3272 values, radiographic or imaging findings, electrocardiographic results, hemodynamic data and  
3273 administration of medications and therapeutic interventions (84, 98) During this study these data will be  
3274 augmented with CMS data for all participants. Below we describe the approach to ascertainment of

3276 potential cases. Definition criteria and ICD diagnostic and procedure codes for each outcome can be  
3277 found in Appendix F (Outcome Definitions)

3278 G. Adjudication of events

3279 In cases where the outcome diagnosis is not clear based on the screening mechanism and algorithms  
3280 developed, we will resort to manual adjudication to determine the validity of the diagnosis. Based on  
3281 our 150 chart review, it is expected that fewer than 300 to 400 cases will require this form of  
3282 adjudication. The adjudication will consist of a chart review by qualified clinicians of medical records  
3283 pertaining to the hospital admission for VA admissions and a chart review of VA inpatient and outpatient  
3284 records as well as CMS data following the discharge date for non-VA hospitalizations. In some cases, we  
3285 may query the PCP as to whether a possible event occurred.

3286 Additionally, we will also manually adjudicate 10% of all outcomes confirmed or refuted by our  
3287 algorithms to serve as a quality check on the algorithms. We will develop near-final algorithms during  
3288 the study and will continue to refine the algorithms and retrospectively apply these refinements to all  
3289 data. It is also important to note that between the time of study approval and study launch, the VA has  
3290 transitioned to using the ICD-10 classification system. We will be mapping the ICD-9 codes described in  
3291 this protocol to the equivalent ICD-10 codes as we continue to develop our algorithms.

3292 H. Ascertainment of potential cases, adverse events and other case data

3293 **XI. Investigators at the Boston CSPCC unaware of treatment group will process potential cases**  
3294 **and adverse events by collecting relevant codes, laboratory values, and prescription data from**  
3295 **EHR, the VA electronic medical record system, and Medicare (e.g., acute gout episode = ICD10**  
3296 **M10.00). Blood pressures will be collected from routine clinic visits, and not from emergency**  
3297 **room visits or inpatient stays, and only the reading with the lowest SBP of the day will be**  
3298 **retained (99). Section XIII details the data sources and the data collection (i.e., data**  
3299 **extraction) procedures that will be used. When the study drug is discontinued, we may query**  
3300 **the PCP as to the reason if not clear from the charBiostatistical Considerations**

3301 **A. Overview of the Study Design**

3302 The proposed study is a prospective randomized open-label blinded-endpoint, multicenter, two arm  
3303 intervention trial testing the effectiveness of chlorthalidone for prevention of cardiovascular events and  
3304 non-cancer death among patients currently receiving hydrochlorothiazide. The primary hypothesis is  
3305 that chlorthalidone is superior to hydrochlorothiazide for the prevention of cardiovascular events and  
3306 non-cancer death over time.

3307 The primary outcome measure is time from enrollment in the study to the first occurrence of a  
3308 cardiovascular event or non-cancer death. Cardiovascular (CVD) events are defined as stroke,  
3309 myocardial infarction, urgent coronary revascularization, and hospitalization for acute congestive heart  
3310 failure. The results for CVD and non-cancer death event-free survival will be analyzed by means of a  
3311 two-sided log-rank test.

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3315 The study will have one interim analysis and one final analysis.

3316 **1. Estimated Incidence of the Primary Endpoint**

3317 This study will randomize up to 13,700 patients, in 50:50 allocation to hydrochlorothiazide and  
3318 chlorthalidone, in order to achieve 1,055 primary outcome events. . All subjects will be followed  
3319 through the end of the four and one-half (4.5) year study period yielding an estimated average follow-up  
3320 time of three (3) years. We posit a four and one-half year rate of 13.5% of the composite outcome in the  
3321 hydrochlorothiazide group and 11.1% in the chlorthalidone group. We utilized the VA National data  
3322 from fiscal years 2010 to 2012 to identify a subgroup of subjects who would be potentially eligible for  
3323 the proposed study. Details of the analysis can be found in **Section XII. Feasibility and Recruitment**  
3324 **Plan.**

3325 The cardiovascular event rate, using a composite similar to that proposed here, was 2% per year in  
3326 ALLHAT (20) and ACCORD (101), and is projected as 2% for the ongoing SPRINT. Unlike those studies, we  
3327 are limiting enrollment to patients over age 65 years and are not excluding very old or seriously ill  
3328 patients (unless life expectancy is known to be less than 6 months), and we are including all non-cancer  
3329 deaths rather than only cardiovascular deaths, all of which would be expected to increase the event  
3330 rate. For patients 65-79 years old with no serious illness (and creatinine <1.5 mg/dL) in ACCORD, the  
3331 composite event rate (stroke, myocardial infarction, and cardiovascular death) was 2.8% per year (96).  
3332 Our event rate should be higher because we include urgent revascularization, acute heart failure, and  
3333 non-cancer deaths. ANBP2 enrolled patients over 65 years but included all deaths in the composite, and  
3334 observed an event rate of >4% per year (19).

3335 We believe that the most relevant event rates for our study come from the Ontario observational study  
3336 (29) comparing chlorthalidone with hydrochlorothiazide, discussed above. The Ontario study is both  
3337 recent, published in 2013 and reporting data from 1993 to 2010, large (nearly 30,000 patients), and  
3338 shares important features with our proposed trial, including: 1) study patients are aged 66 and older and  
3339 taking diuretics for hypertension, 2) outcome data were collected passively from administrative  
3340 databases, and 3) the primary outcome was a composite similar to the one we are proposing, with two  
3341 differences: a) they did not include urgent revascularization, and b) they included all deaths whereas we  
3342 do not include cancer deaths.

3343 We expect these 2 differences to very nearly cancel each other's effect. The rate for the Ontario  
3344 composite outcome was 3.4% per year in the hydrochlorothiazide group. The rate for all deaths was  
3345 1.8% per year, or 45% of the total number of individual outcomes (some patients had more than one of  
3346 the composite outcome elements). Many studies, such as the Physicians Health Study (95) have found  
3347 that all deaths in this age group are comprised of roughly 1/3 each of deaths due to cardiovascular  
3348 disease, cancer and other causes, suggesting that our exclusion of cancer deaths would reduce the  
3349 composite rate by 15%. In the (TRA2°P)-TIMI 50 trial (86), urgent coronary revascularization was less  
3350 frequent than myocardial infarction (0.82% in the Ontario study, or 20% of the total number of  
3351 individual outcomes) and similar in frequency to stroke (0.46% in the Ontario study, or 11% of the total

3353 number of individual outcomes), suggesting that our inclusion of this outcome will raise the composite  
3354 by 10-15%.

3355 These adjustments result in a best estimate for the expected composite rate of about 3.2% per year. For  
3356 the proposed study, because event rates tend to decrease over time, we conservatively project a 3% per  
3357 year event rate in the hydrochlorothiazide group.

## 3358 2. Effects of the Intervention

3359 Of 125,000 VA patients started on drug in routine practice in 2004, 72% of hydrochlorothiazide users  
3360 and 62% of chlorthalidone users remained on the drug 1 year later (28). Onsite coordinators in standard  
3361 trials may be able to maintain better drug adherence than occurs in usual practice. ACCORD (101) and  
3362 SPRINT (84) considered a 20% relative reduction to be an appropriate minimum important difference for  
3363 power calculations. Because the difference in outcomes in our study could be reduced by patients  
3364 coming off drug more often than in previously published trials, we reduce the minimum important  
3365 difference value to **17.5%**. A reduction in CVD events or non-cancer death of this magnitude or greater  
3366 would be considered clinically significant.

### 3367 B. The Primary Analysis

3368 We posit a four and one-half event rate of 13.5% in the hydrochlorothiazide group and a 17.5%  
3369 reduction of CVD events in the chlorthalidone group to inform our primary hypothesis.

#### 3370 Formal statement of the primary hypothesis

3371 Under the null hypothesis:

3372 The 4.5 year event rate will be 13.5% (or 578 primary events)

3373 Under the alternative hypothesis for study participants treated with chlorthalidone:

3374 The 4.5 year event rate will be 11.1% (or 477 primary events)

3375  
3376 The reductions attributed to chlorthalidone may be viewed in several ways. The absolute reduction  
3377 from 13.5% to 11.1% is 2.4%, the relative reduction is  $(13.5 - 11.1)/13.5 = 17.5\%$ , and the hazard ration  
3378 (chlorthalidone hazard rate/hydrochlorothiazide hazard rate) of 0.81 is approximately midway between  
3379 the simple odds ratio,  $11.1(100-13.5)/13.5(100-11.1) = 0.80$  and the risk ratio  $11.1/13.5 = 0.82$ .

3380  
3381 Formally, the null hypothesis is that the two treatment groups do not differ in their time-to-event hazard  
3382 rates. The alternative hypothesis is that chlorthalidone has a lower or higher hazard rate than  
3383 hydrochlorothiazide therapy with a hazard ratio for chlorthalidone compared to hydrochlorothiazide  
3384 less than 0.82 or greater than 1.22. We will test this hypothesis with a two-sided log-rank test.

### 3385 3386 C. Sample Size and Statistical Power Considerations for the Primary Hypothesis

3387 The formal hypothesis test is two-sided allowing for chlorthalidone to be either more or less effective  
3388 than hydrochlorothiazide. A significant difference showing that the intervention chlorthalidone  
3389 compared to the control hydrochlorothiazide decreases (or increases) the hazard of a major  
3390 cardiovascular event will be regarded a positive result. The results for the primary outcome measure will

3393 be analyzed by means of the two-sided log-rank test to detect either a hazard ratio that exceeds 1.22 or  
3394 is less than 0.82. The test will have a two-sided 4.9% type I error. The test has 90% power to detect a  
3395 hazard ratio of 1.22 or larger or 0.82 or less with a total of 1,055 primary outcome events. The  
3396 remaining Type I error of 0.1% is used for the interim analysis.

3397 If the annual event rate is 2.5% (rather than the posited 3%), then the study has 84% power; if 2%, it has  
3398 75% power.

#### 3399 **D. Primary Data Analysis**

3400 The primary outcome hypothesis will be a time-to-event analysis with the use of a two-sided log-rank  
3401 test based on intention-to-treat principles. The model will not include any covariates. Analytic reports  
3402 will include hazard rates, their ratio, and the 95% confidence interval about the ratio.

3403 This will be followed by further refined covariate-adjusted exploratory analyses, using Cox proportional  
3404 hazards regression modeling, controlling for baseline factors. Covariates will include demographic  
3405 factors (e.g., age, sex, smoking status, education) and clinical factors (e.g., blood pressure, medications,  
3406 comorbidities, history of disease, and BMI). We will test the proportional hazards assumption by  
3407 including a time-treatment interaction term in the model.

#### 3408 **E. Interim Analysis**

3409 We will perform one interim analysis when the 500<sup>th</sup> event occurs, approximately 3.5 years after  
3410 initiation of enrollment. Assuming a uniform rate of enrollment over time, the first patient entered will  
3411 potentially have 3.5 years of follow-up and the last patient entered will potentially have 0.5 years of  
3412 follow-up. Thus, we will have an average follow-up time of approximately 2 years on 13,500 subjects.

3413 Using the O'Brien Fleming procedure, this interim analysis will have a type I error of 0.1%, which  
3414 negligibly decreases the overall type I error and has virtually no effect on the power to show that  
3415 chlorthalidone is different from hydrochlorothiazide. The sample size of 13,532 accounts for the interim  
3416 analysis with a corresponding inflation factor, for increase in sample size of 1.001, resulting in 14 more  
3417 subjects per arm (102). We will confer with the Data Monitoring Committee (DMC) members and the  
3418 program leadership for potential stopping guidelines based on findings from the interim analysis.

#### 3419 **F. Secondary Data Analysis**

##### 3420 1. Treatment Effect in Subgroups

3421 The Cox regression modeling will explore the possibilities of treatment variation across pre-  
3422 specified subgroups based on status at time of enrollment including:

- 3423 a) gender,
- 3424 b) age (dichotomized at median),
- 3425 c) baseline SBP (dichotomized at median),
- 3426 d) history of MI or stroke,
- 3427 e) black race vs. not,
- 3428 f) diabetes vs. not,

- g) eGFR < 60, and
- h) good compliance (medication possession ratio  $\geq$  80%) with hydrochlorothiazide over the year before randomization.

## 2. Individual Components of Primary Outcome

In addition to the subgroup analyses listed above, each component of the composite primary outcome measure (stroke, myocardial infarction, urgent coronary revascularization, hospitalization for acute congestive heart failure, and non-cancer death) will be separately analyzed using log-rank and Cox proportional hazards models to compare chlorthalidone and hydrochlorothiazide. The Cox analyses will include the covariates considered in the primary data analysis.

## 3. Additional Outcomes of Interest (Analysis of Secondary and Tertiary Objectives)

In addition we will run time-to-event analyses comparing the treatment effect on:

- a) all-cause mortality,
- b) the composite outcome substituting all deaths for non-cancer deaths,
- c) vascular deaths defined as all deaths caused by diabetes, vascular diseases, external causes, and unknown causes,
- d) the composite outcome substituting vascular deaths for non-cancer deaths,
- e) any revascularization of an artery,
- f) hospitalization for primary diagnosis of hypokalemia, hyponatremia, or renal failure,
- g) other hypokalemia (< 3.5 meq/L), hyponatremia (< 130 meq/L), or renal failure,
- h) new diabetes, requiring medications, defined as first use of medication for diabetes,
- i) acute gout episode,
- j) erectile dysfunction (ED), defined as first prescription for PDE5 inhibitor or referral for ED, and
- k) new allergic reaction to thiazide-like diuretic, defined as new flag warning in EHR

This may include characterizing healthcare utilization associated with these outcomes, evaluation of incidence of the conditions, and defining these conditions with algorithms using administrative healthcare data.

## 4. Primary Care Provider Metrics of Interest.

- a) percent of patients approved
- b) percent of approved patients for whom order signed
- c) reasons order not signed
- d) rate of discontinuation of both drugs
- e) reasons for discontinuation of both drugs

## 5. Medication Compliance

We will compare treatments with respect to overall compliance (adherence) to the randomly assigned medication, indirectly measured by the medication possession ratio (MPR) and average daily dose (ADD). The comparison will be made using a GEE analysis to account for varying



3474 periods of follow-up. The potential period ends if the subject dies, has an outcome event, or  
3475 changes medication. Subjects categorized as medication compliant will make up the per-  
3476 protocol subgroup of the study cohort.

3477 6. Non-acute Outcomes

3478 The repeated measures of systolic blood pressure during the disease-free intervals (free of  
3479 component events) will be compared by treatment. We will use a mixed effects repeated  
3480 measures model allowing for irregular time intervals, the spatial power law extension of AR(1)  
3481 covariance option where  $r(t_1, t_2) = \exp(-\lambda |t_1 - t_2|)$ . In each model we will assume linear  
3482 growth over time. A random effect will be included for both intercept and linear time. The  
3483 hypotheses will test if SBP increases/decreases over time for subjects receiving chlorthalidone, if  
3484 SBP increases/decreases over time for subjects receiving hydrochlorothiazide, and if both have  
3485 non-zero slopes, a test of whether they differ or are equal.

3486 We will conduct a time-to-event analysis comparing treatments for the outcome of time to first  
3487 discontinuation of assigned diuretic (defined as no prescription for  $\geq 3$  months at last  
3488 observation during study period) and time to first protocol deviation from assigned diuretic.

3489 **G. Exploratory Objectives**

3490 1. Per-protocol analysis

3491 The primary intent to treat analyses of randomly assigned treatments takes no account of post-  
3492 baseline changes such as protocol deviations and treatment switches from chlorthalidone to  
3493 hydrochlorothiazide (and vice versa). Thus, exploratory analyses will model such changes to  
3494 assess robustness of conclusions.

3495 The per-protocol analysis will determine if chlorthalidone and hydrochlorothiazide differ among  
3496 the subset of protocol compliant subjects. We will run other analyses that include all subjects  
3497 and attempt to model the time-dependent effects of protocol deviations such as medication  
3498 changes and levels of compliance. Frailty analyses will assess center effects. We will explore  
3499 censoring patterns such as models that assume not missing-at-random censoring (103).

3500 A change in medication may alter the subsequent risk of a cardiovascular event. First, we will  
3501 add time-dependent covariates to a Cox model, such as binary indicators of a switch from  
3502 chlorthalidone to hydrochlorothiazide, switch from hydrochlorothiazide to chlorthalidone, and  
3503 the start of new medication that interacts with chlorthalidone or hydrochlorothiazide. To  
3504 directly estimate subsequent risk, we will use a multistage model (MSM) to assess the hazard  
3505 rate of a major cardiovascular event after a switch (104). MSM models extend the time-to-first-  
3506 event models to second, third, and more events. This extension of the Cox model allows direct  
3507 estimation of the hazard rate associated with any transition adjusted for previous history and  
3508 baseline characteristics. Within MSM we will carry out a competing risks analysis to assess the  
3509 effect of cancer deaths.

3510 2. COVID-19

3512 COVID-19 is understood to more severely impact older patients with pre-existing conditions.  
3513 There is also evidence from the Centers for Disease Control and Prevention that many patients  
3514 with major medical events are not seeking the care they require during the COVID-19 pandemic.

3515  
3516 The DCP patient population is 65 or older with known baseline cardiovascular disease, and many  
3517 overweight with diabetes. With a primary outcome consisting of components that often require  
3518 immediate medical attention, there is a possibility that the observed rate of the study's primary  
3519 outcome will be impacted by the pandemic. We will characterize event rates throughout the  
3520 study to assess the impact of COVID-19. We will also assess primary outcome event rates in  
3521 COVID-positive patients and in geographic locations with particularly high rates of infection.

## 3522 H. Randomization

3523 To control for potential imbalance in randomization, both stratification and blocking will be employed.  
3524 The randomization scheme will be stratified by participating site to account for possible regional  
3525 differences in clinical practice. Participants will be randomized to either hydrochlorothiazide or  
3526 chlorthalidone within blocks of size 6.

3527 Enrollment and randomization of subjects will occur in accordance with **Section IX. Study Procedures**  
3528 and **Appendix C. Recruitment Flowchart.**

## 3530 XII. Feasibility and Recruitment Plan

### 3531 A. Feasibility

3532  
3533 In 2012, 69 VA medical centers prescribed single-agent hydrochlorothiazide 25 mg or 50 mg to at least  
3534 2000 patients over age 65 (**Appendix E.1**). In VISN1, 80% of these had SBP  $\geq 120$  mm Hg at last  
3535 measurement with no SBP measurement below 120 mm Hg in the previous 90 days (**Appendix E.2**).  
3536 Applying these regional SBP data to the national medical center data, in 2012 there would have been 76  
3537 VA medical centers with  $\geq 1500$  eligible patients and 104 centers with  $\geq 1000$  eligible patients.

3538 Based on experience with the CONFIRM study (CSP #577) and the Million Veteran Program and other  
3539 sources, we estimate that: 15% of PCPs will opt out; PCPs who don't opt out will exclude 5% of their  
3540 patients; 5% of patients mailed the initial letter will opt out; we will reach 65% of patients we attempt to  
3541 call; 60% of those we reach by phone will agree to be randomized; 2% of those who agree by phone will  
3542 opt out or be removed by their PCP before randomization. Combining these rates:  $(.85)(.95)(.95)(.65)(.6)$   
3543  $(.98) = .29$ , suggesting we should expect to enroll about 30% of eligible patients identified.

3544 Based on these considerations, randomization of 13,700 patients (270 per site at 50 sites) should be  
3545 feasible. We anticipate that this process will take 3 years, a duration that could be adjusted by the level  
3546 of staffing of the central call center. If recruitment falls short of our expectations, our primary strategy  
3547 will be to add additional sites as needed.

3551 B. Recruitment Plans

3552 As previously described the primary recruitment plan will be to enroll patients who have been identified  
3553 through the VA Corporate Data Warehouse as being eligible and cleared by their PCP through the direct  
3554 mailing of an information letter followed by telephone based consent. Enrollment will be initiated in 3  
3555 VISNs at the start of the study. This will allow the DCP team to learn about the feasibility of recruitment,  
3556 to identify issues with provider participation and EHR use, and to refine the primary recruitment plans  
3557 based on the experience from the vanguard sites. Patients will also be allowed to self-refer to the study  
3558 call center as well. In this regard, the DCP will allow all patients fitting the eligibility criteria to be  
3559 enrolled regardless of how they were identified.

3560 **XIII. In addition, we will initiate 20% more sites (i.e., 10 additional sites) than what is needed for**  
3561 **successful enrollment into the study. As sites fail at recruitment or as the potential**  
3562 **patient pool decreases at the vanguard sites, enrollment into the DCP will be**  
3563 **started at the 10 additional sites. Data Collection and Data Sources**

3564 Data for this study will be obtained from the medical and administrative data that are collected and  
3565 maintained by the United States Department of Veterans Affairs (VA) Corporate Data Warehouse  
3566 (CDW). This database covers the entire veteran population that utilizes the VA and contains individual  
3567 information on demographic factors, medical history, key laboratory values, procedure codes, and  
3568 diagnoses (inpatient and outpatient) coded with the ICD-9-CM and ICD-10 classification systems.  
3569 Healthcare encounters outside of the VA system will be captured using Medicare data that will be  
3570 obtained from VIREC for this project. Data from the various VA databases (including COVID-19 data from  
3571 the COVID-19 Shared Data Resource) will be linked together using a unique veteran identification  
3572 number that is assigned to each veteran at entry into the system.

3573 Vital status will be ascertained from the VA Vital Status File. This file allows for complete ascertainment  
3574 of death as it pulls data from multiple sources, including: the Beneficiary Identification and Records  
3575 Locator Subsystem database; the Death Master File from the Social Security Administration; and the  
3576 National Patient Care Database. Ascertainment of death with this method has demonstrated 98%  
3577 sensitivity and 98% agreement with the National Death Index. Cause of death will be collected from the  
3578 National Death Index, as the VA Vital Status File does not aggregate cause of death across the  
3579 aforementioned data sources.

3580 We will monitor for discontinuation or expiration of the assigned diuretic, detection of which will  
3581 prompt queries to the PCP asking the reason. No effort will be made by the study to influence blood  
3582 pressure goals or the prescribing of other drugs.

3583 **XIV. Data Management and Data Security Plans**

3584 The Boston CSPCC will create and maintain an electronic study database to manage the trial data. All  
3585 study data will be collected electronically from EHR and a study-specific web application by the  
3586 Coordinating Center throughout the duration of the study. There will be limited paper-based study  
3587 documents.

3589 Study data is housed on secure VA servers, encrypted and protected in accordance with VA policies  
3590 compliant with FDA requirements, Federal Information Security Management Act and the HIPAA Privacy  
3591 and Security rules. Data for this study will be stored in two locations: 1) on a VINCI-hosted server and 2)  
3592 on a Boston CSPCC-hosted server. Boston CSPCC personnel manage the data access request process for  
3593 the electronic systems to ensure that data access is appropriate for each individual and the level of the  
3594 individual access. Study project management will manage the Data Access Request Tracker (DART)  
3595 activities associated with granting VINCI access to study databases. VA's Office of Information &  
3596 Technology (OI&T) is responsible for managing other VA system access and ensuring the security and  
3597 integrity of VA information systems, including the databases and servers housing study data. In  
3598 accordance with VA Handbooks and Directives, OI&T is responsible for ensuring that appropriate  
3599 firewalls and data security is implemented and maintained, that data backups are performed and that  
3600 data may be restored in the event of a system malfunction.

3601 Data security incidents will be reported according to 1058.01. All Boston CSPCC staff will be expected to  
3602 report data security incidents to the responsible authority as they become aware of the breach.  
3603 Whenever possible, the reporting of data security incidents will be handled by the Boston CSPCC  
3604 Associate Center Director for Quality Assurance (ACDQA). This will be done to facilitate communication  
3605 between the center and the oversight bodies. In the event that an incident must be reported by a staff  
3606 member other than the ACDQA, all communication after the initial report will be handled by the Boston  
3607 CSPCC Center Director, the Boston CSPCC ACDPOC, or the Boston CSPCC ACDQA. [Note: all new and  
3608 current Boston CSPCC personnel will be trained on reporting data security incidents.]

3609 All local data security incidents will be reported in accordance with VA policy within one hour of  
3610 discovering the incident to:

- 3611 1. The Boston Information Security Officer (ISO)
- 3612 2. The Boston Privacy Officer (PO)
- 3613 3. The Boston ACOS for Research
- 3614 4. The Boston CSPCC Quality Assurance department

3615 Data security incidents will be treated as unanticipated problems by the Boston CSPCC and reported to  
3616 the VA Central IRB according to the procedure detailed below for unanticipated problems (Section  
3617 XVII.C.3).

3618 Study data will be coded and stored using a unique study identifier for each participant. Identifiable  
3619 information will be collected for patient tracking and safety purposes, and kept in an encrypted,  
3620 password protected file to which a small number of people will have access. Access to the cross-walk file  
3621 linking the participant's identifiers and their study data will be restricted to the approved personnel at  
3622 the CSP coordinating center. At the end of the study, study data will be stored according to CSP  
3623 guidelines and procedures. Retention of data will be conducted according to CSP operating procedures  
3624 and federal and local VA regulations. This file will be destroyed according to CSP policy well after the  
3625 close of the study.

3626  
3627  
3628

3629  
3630

3631 Access to the study data is restricted to individuals with CSP approval. Study team members must be  
3632 properly credentialed research staff and must be compliant with VA security trainings (e.g. HIPAA, Rules  
3633 of Behavior, and Good Clinical Practices). Once formal training is completed, user accounts for a study-  
3634 specific web application utilizing a URL specific to the study to access and use the system and enter  
3635 patient data will be activated for project management, study nursing staff, and call center staff.  
3636 Accounts will be password protected and unique to each user. The account permissions will correspond  
3637 with the users' functional study group. Furthermore, the permissions of the electronic systems are  
3638 heavily restricted. The site Liaisons will not have access to study data. Only properly approved  
3639 Coordinating Center personnel will have the ability to copy and export data. These individuals have  
3640 received training on the local standard operating procedure (SOP) governing their permissions. Access to  
3641 protected health information (PHI) will be restricted to individuals approved by CSP to have access to  
3642 the data, including the study's mailing vendor.

3643 At the Boston CSPCC the following staff will have access to all forms of PHI:

- 3644 1. Center Director
- 3645 2. Study Director
- 3646 3. Project Management
- 3647 4. Study Nurses
- 3648 5. Data Management
- 3649 6. Biostatisticians
- 3650 7. Quality Assurance Officer
- 3651 8. SAS/Database Programmer
- 3652 9. Research Assistant
- 3653 10. Clinical Applications Coordinator
- 3654 11. Informatics Team

3655 Periodic access control assessments will be made by Coordinating Center Quality Assurance personnel  
3656 to verify that access is controlled and appropriate for personnel. In addition, the CSPCC QA group will  
3657 provide continuing education on good clinical practices compliance and will evaluate clinical site  
3658 operations for violations of VA policies including VA data security policies and GCP.

3659 At the end of the study, the data for DCP will remain property of the Cooperative Studies Program and  
3660 be stored and shared according to CSP guidelines and procedures. Retention and destruction of data will  
3661 be conducted according to CSP operating procedures and federal and local VA regulations. This will  
3662 include electronic data stored at the Boston CSPCC, and at the VA facility housing our servers.

3664 Identifiable data will be kept according to CSP policy as outlined in the "CSP Guidelines for the Planning  
3665 and Conduct of Cooperative Studies".

3666 **XV. Human Subjects**

3667 A. Waiver of HIPAA authorization

3668 A waiver of HIPAA authorization to use VA data to determine eligibility will be requested because the  
3669 research could not practicably be conducted without access to and use of this information. In order to  
3670 conduct the study, it is necessary to first be able to identify eligible patients so that the recruitment  
3671 letter can be mailed to them.

3672 We will also request IRB approval for a waiver of HIPAA authorization to collect data prospectively.  
3673 Unlike traditional randomized clinical trials, a feature of the POC methodology is that data collection is  
3674 performed by passive data capture. All data elements will be collected electronically from EHR/VISTA  
3675 using both the Veteran's Information and Computing Infrastructure (VINCI), a collaborative effort  
3676 between the VA Office of Information Technology and the VA Office of Research and Development, and  
3677 the Office of Information Technology's Corporate Data Warehouse (CDW). Healthcare encounters  
3678 outside of the VA will be captured using Medicare data. Data from the various VA databases will be  
3679 linked together and maintained using a unique veteran identification number (not SSN). Access to the  
3680 cross-walk file linking the participant's identifiers and their study data will be restricted to approved  
3681 personnel at the CSP coordinating center.

3682 Because data abstraction is done electronically and not by staff perusing the electronic medical record  
3683 we believe that a waiver of HIPAA authorization is justified and involves no more than minimal risk to  
3684 the privacy of individuals. All protected health information, except participant address and treatment  
3685 assignment, will remain within the VA. The information will only be shared with the mailing contractor  
3686 using secure methods in alignment with VA policies. Moreover, it would be impractical to obtain a  
3687 signed authorization from patients in this study for use of their health information. The PCP's cannot  
3688 obtain a written HIPAA authorization for research purposes from patients who are subjects in this study  
3689 because they will not see the patient until weeks or months after the patient has been on the  
3690 randomized treatment. The PCPs are not study team members. We plan to identify and disclose to  
3691 participants in our information statement the health information to be collected and the specific  
3692 databases from which it will be obtained.

3693 In both instances, the patient eligibility screening and the prospective collection of patient data, the use  
3694 of the requested information involves no more than minimal risk to the privacy of individuals based on  
3695 the security measures used by the Boston CSPCC to protect the identifiers from improper use and  
3696 disclosure, and to destroy the identifiers at the earliest opportunity consistent with conduct of the  
3697 research. The requested information will not be reused or disclosed to any other person or entity,  
3698 except as required by law, for authorized oversight of the research study, or for other research for which  
3699 the use or disclosure of the requested information would be permitted by the Privacy Rule.

3700 B. Basis for Waiver of Documentation of Informed Consent

3701

3702

3703

3704 Though we are not planning to obtain written informed consent, multiple measures are in place to  
3705 ensure that all subjects are given all of the information they need in a manner that is understandable  
3706 before they consent and throughout the study. Primary care providers will receive information through  
3707 site liaisons as well as an introductory letter that is both mailed and emailed to their VA addresses prior  
3708 to receiving the initial testpatient order in EHR. The initial testpatient order will be sent together with a  
3709 progress note containing the Provider Information Sheet and by signing the testpatient order, the  
3710 providers are consenting to participate. Provider participation is completely voluntary and minimal risk,  
3711 facts that will be reiterated throughout this process.

3712 Patients are sent a transcript of the consent and an explanatory letter with study contact information  
3713 before the first phone call, full consent is obtained on the call, and they are informed of the randomized  
3714 group after the call.

3715 In this study, the relevant risks involved are those of changing therapy of half of the patients from  
3716 hydrochlorothiazide to the equivalent dose of chlorthalidone, a very similar drug with the same  
3717 indications and metabolic effects, plus the theoretical risk to confidentiality from compiling individual  
3718 data.

3719 Regarding the former, both drugs have been in use for more than 50 years, have long been available as  
3720 generics, and are included in the VA national formulary in the same drug class: USP code CV 701,  
3721 thiazide-type diuretics. The VA frequently selects one member of such a class to make available “on  
3722 formulary” based on cost or other considerations, and VA Pharmacy and Therapeutics Committees will  
3723 direct VA pharmacies to substitute drugs within a class when one drug becomes unavailable, so it is not  
3724 uncommon that VA physicians and patients have limited choice within a class.

3725 While thiazide-type diuretics affect some blood chemical levels as discussed above, these effects have  
3726 not demonstrated adverse clinical impact that would affect their being the preferred treatment for  
3727 hypertension. Furthermore, our plan to substitute an equivalent dose of chlorthalidone for the current  
3728 dose of hydrochlorothiazide, i.e. half the number of milligrams, would be expected to have an effect on  
3729 blood pressure and on blood chemical levels, small enough to be virtually indistinguishable from the  
3730 variation in these parameters that would ensue with remaining on the prescribed hydrochlorothiazide  
3731 (see Background and Rationale, parts F and I). We therefore propose that the study intervention  
3732 qualifies as minimal risk. Because the two drugs are used interchangeably, and the choice between them  
3733 is not influenced by any patient factors, but only by physician preference, randomization does not  
3734 reduce individualization of patient care. Care remains personalized after randomization because the PCP  
3735 manages the diuretic as usual. The patient’s needs are thus not subordinated to the needs of the trial.  
3736 Furthermore, because hypertension is a chronic condition, randomized patients will themselves be  
3737 among those expected to benefit from the information gained from this study.

3738 In their article “Randomized, controlled trials as minimal risk: an ethical analysis”, Morris and Nelson  
3739 (106) conclude that “A randomized, controlled trial poses no more than minimal risk only when all of the  
3740 following five criteria are met: 1) genuine clinical equipoise exists; 2) all of the treatment options  
3741 included in the research study fall within the current standard of care; 3) there is no currently available

3743 treatment with a more favorable risk-benefit profile than the treatments included in the research study;  
3744 4) the nontherapeutic components of the research are safely under the minimal risk threshold; and 5)  
3745 the research protocol provides sufficient latitude for treating physicians to individualize care when  
3746 appropriate.” We have designed this study to meet all of these criteria.

3747 We believe that the Waiver of Documentation of Informed Consent that we are requesting is necessary  
3748 to the successful completion of our study because obtaining the required sample size within the VA is  
3749 only feasible if recruitment is maximally efficient, as described in the Feasibility section (XII.A). Published  
3750 evidence demonstrates that requiring that written consent be returned by mail is likely to result in the  
3751 loss of the great majority of patients who intend to consent (107-111). If requirement of returned  
3752 written consent caused loss of most willing patients from our study, it is unlikely that it could be  
3753 completed within the VA system.

3754 Based on these considerations, we will request IRB approval of a Waiver of Documentation of Informed  
3755 Consent. Under the terms we are requesting for the Waiver, patients would be recruited by mail, and  
3756 the elements of consent obtained over the phone, a written summary of the consent will be sent to the  
3757 patient, but a signed returned document would not be required.

3758 Enrolled patients will be given study contact information for questions or withdrawal.

#### 3759 C. Engagement in Research

3760 **XVI. For this study, we consider the Site Liaison and the PCP’s to be not engaged in research. The**  
3761 **Site Liaison (sometimes called a “Champion” in other studies) serves to provide**  
3762 **information to local site personnel about the study and relays information and**  
3763 **questions back to the coordinating center, but in our view takes no action that**  
3764 **qualifies as research. The PCPs facilitate implementation of the intervention (after**  
3765 **patients provide consent and are randomized by study personnel) by signing an order**  
3766 **sent to them by study personnel. The PCPs are themselves research subjects in whom**  
3767 **we are studying the implementation of the protocol. Quality Control Procedures**

3768 Data that is extracted for the DCP will be cleaned and managed according to a rigorous data  
3769 management plan that will be written in conjunction with the statistical analysis plan and the study  
3770 operations manual (for chairs office and CSPCC personnel). However, the data will also be subject to  
3771 quality control procedures. As a first line effort to ensure the validity of the data, 100% of the data  
3772 elements collected from the first 10 individuals from each medical center will be subject to source  
3773 verification and validation through chart review that will be done by an experienced clinician and clinical  
3774 applications coordinator. In addition, chart review done through the creation of the algorithms to  
3775 identify outcomes for the DCP will also be used to perform QC procedures on the data. In brief, a  
3776 sample of the data will be verified periodically by the data management and clinical operations teams. If  
3777 errors are identified they will be referred to the data management teams at the Boston CSPCC or at  
3778 VINCI for resolution.



3784 In addition, the quality management system (QMS) in place at the CSPCC will ensure further quality  
3785 control for the DCP. The Quality Assurance Department of the CSPCC will subject the study to risk based  
3786 audits according to internal SOPs for conducting risk based monitoring and auditing. These audits will  
3787 evaluate the studys' compliance with QMS processes and procedures. If deviations or non-conformances  
3788 are identified they will be remedied through the internal corrective action/preventive action system of  
3789 the QMS.  
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3791 **XVII. Study Monitoring Plan**  
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3793 A. Introduction

3794 The safety issues related to hydrochlorothiazide and chlorthalidone are well established in the medical  
3795 literature and both diuretics are accepted first-line treatments for hypertension. Based on this  
3796 information the study poses minimal risks to participants beyond the expected adverse events (AE)  
3797 associated with the administration of either drug as part of "usual" care.

3798 Monitoring side effects and adverse events in the traditional manner of usual clinical trials is not feasible  
3799 for Point of Care studies since there are no site personnel and all data is captured passively through the  
3800 EMR. In addition, real-time monitoring will neither provide new information regarding the safety of  
3801 these two treatments nor assure adequate (or timely) safety of human subjects beyond that already  
3802 done by the medical staff as part of routine medical care. Accordingly, we propose an alternative safety  
3803 reporting plan for the DCP study that ensures protection of the participants and that complies with VHA  
3804 Policy (i.e., VHA Handbooks 1200.05 and 1058.01). In brief, health providers will identify, monitor, and  
3805 treat (as necessary) adverse events that occur during the course of the study. The CSPCC will identify  
3806 expected adverse events (as described below) through the EMR and report them to the monitoring  
3807 committees for the trial. The sections that follow describe in more detail the proposed safety monitoring  
3808 and reporting plan for this trial.

3809 B. Safety Monitoring Plan

3810 The participant's physicians, nurses, and other health providers will continue their usual monitoring of  
3811 the subject throughout the course of his/her treatment. If any treatments are indicated, they will be  
3812 provided by health providers as a part of the participant's routine medical care. The CSPCC staff will  
3813 collect safety data from the medical record from the time of consent through the end of the study  
3814 period. The safety data will then be aggregated and classified according to ICD-10 codes.

3815 Aggregated safety data will be reported to the Data Monitoring Committee, the study Executive  
3816 Committee, and the VA Central IRB using the processes described in Section C. Please refer to Section  
3817 XVIII Study Organization and Administration for a more detailed description of the oversight committees  
3818 for the trial.  
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3824 In addition to data culled from the EMR, the trial will allow for spontaneous reporting of events by study  
3825 participants. The informed consent script and information sheet will include the contact information for  
3826 the study call center should the participant wish to communicate safety concerns with the study team.

### 3827 C. Safety Reporting

#### 3828 1. Adverse Events

3829 Adverse events will be collected using the 21 CFR 312.32, International Conference on Harmonisation  
3830 (ICH) for Clinical Safety Data Management (ICH-E2A), and CSP Global SOP 3.6 definitions. Adverse  
3831 events (AEs) are defined by the 21 CFR 312.32 as "any untoward medical occurrence associated with the  
3832 use of a drug in humans, whether or not considered drug related."

3833 According to ICH-E2A, "an AE, therefore, can be any unfavorable or unintended sign (including an  
3834 abnormal laboratory finding), symptom, or disease temporally associated with the study interventions."

3835 Expected adverse events of interest related to diuretics will be culled from the EMR as part of the  
3836 outcome ascertainment activities of this protocol. The expected AEs of interest will be:

- 3837 1. Hospitalization for primary diagnosis of hypokalemia, hyponatremia, or renal failure
- 3838 2. Renal failure (dialysis or renal transplant)
- 3839 3. Other recorded hypokalemia (< 3.1 mEq/L), or hyponatremia (< 130 mEq/L)
- 3840 4. New diabetes, defined as first use of an outpatient medication for diabetes
- 3841 5. Acute gout episodes
- 3842 6. New allergic reaction to thiazide-type diuretic to be found in EMR allergy data

3843 These safety events are monitored and treated as part of routine medical care. These events will be  
3844 identified by the CSPCC through the electronic medical record (EMR). Informatics staff at the Boston  
3845 CSPCC will extract medical record data on all subjects and identify adverse events through ICD-10 codes,  
3846 laboratory values, and medication files. Expected adverse events will be reported to the DMC in semi-  
3847 annual reports. The DMC also reserves the right to request reporting on additional safety data not  
3848 specified above, as relevant to the study. Data will be in the form of aggregated data tables detailing  
3849 the frequencies of these events by blinded treatment group. These events will be reported to the  
3850 Central IRB in blinded aggregate form at the time of continuing review.

3851 Adverse events which develop into Serious Adverse Events, as defined below, will be reported as such.

#### 3852 2. Expected Serious Adverse Events

3853 Serious adverse events (SAEs) are a subset of adverse events defined in 21 CFR 312.32(a) and VA  
3854 Handbook 1058.01 paragraph 4(w), as follows:

3855 Definition of SAE from CFR 312.32 (a): Serious adverse event. An adverse event or suspected adverse  
3856 reaction is considered "serious" if, in the view of either the investigator or sponsor, it results in any of  
3857 the following outcomes: death, a life-threatening adverse event, inpatient hospitalization or

3859 prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of  
3860 the ability to conduct normal life functions, or a congenital anomaly/birth defect. Important medical  
3861 events that may not result in death, be life-threatening, or require hospitalization may be considered  
3862 serious when, based upon appropriate medical judgment, they may jeopardize the patient or subject  
3863 and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

3864 Definition of SAE according to VA Handbook 1058.01: An SAE is an AE in human research that results in  
3865 death, a life-threatening experience, inpatient hospitalization, prolongation of hospitalization, persistent  
3866 or significant disability or incapacity, congenital anomaly, or birth defect. An AE is also considered  
3867 serious when medical, surgical, behavioral, social, or other intervention is needed to prevent such an  
3868 outcome.

3869 The intervention in this study is the switch from hydrochlorothiazide to an equivalent dose of  
3870 chlorthalidone, two widely-used diuretics with well-known risk profiles. There are no safety events that  
3871 are unanticipated in regard to these two drugs. Thus, serious adverse events defined above that are  
3872 feasibly identified through the medical record will be reported in aggregate to the DMC at 6 month  
3873 intervals and to the Central IRB at continuing review.

3874 Expected serious adverse events will be reported to the IRB at the time of continuing review in  
3875 aggregated data tables detailing the frequencies of these events. Study reports will also be circulated to  
3876 appropriate members, including the study chairmen and DMC.

3877 This study will not use MedDRA coding of AE and SAE data. The study team will define events using the  
3878 data sources described above and categorize events by system organ class, major diagnostic category, or  
3879 assessment type for reporting.

### 3880 3. Unanticipated Problems Involving Risks to Subjects and Others

3881 Any unanticipated problems involving risks to subjects or others (UPRs), but not qualifying as a serious  
3882 adverse event by definition (such as errant distribution of study medication), will also be reported.  
3883 Unanticipated problems related to the study design will be reported to the IRB in an expedited fashion  
3884 (within 5 business days of identifying the problem). Possible events include failure to distribute study  
3885 drug, patient continuing previous prescription while taking study drug, or patient randomized without  
3886 provider knowledge. Informatics staff at the Boston CSPCC will extract medical record data on all  
3887 subjects regularly allowing for the identification of UPRs at fixed intervals. Study reports will be  
3888 circulated to appropriate members, including the study chairmen.

3889 UPRs that result in an SAE, pursuant to the definition above, will be reported as an SAE to the VA Central  
3890 IRB within 5 business days by the Boston CSP Coordinating Center after becoming aware of the event.

## 3891 **XVIII. Study Organization and Administration**

### 3892 A. Administration

3893 The administrative structure of this study is similar to others in CSP and includes:

3895 The Cooperative Studies Program (VA Central Office) establishes overall policies and procedures that are  
3896 applied to all VA cooperative studies through the Study Chair's office and the CSPCC.

3897 The CSPCC and the Study Chair's office jointly will perform the day-to-day scientific and administrative  
3898 coordination of the study. These include developing and revising the study protocol; abstracting data  
3899 from the national databases (CSPCC Only); ensuring the appropriate support for the participating  
3900 centers; scheduling meetings and conference calls; answering questions about the protocol. The CSPCC  
3901 will also prepare interim and final progress reports; and archive study data at the end of the study. Study  
3902 progress reports will be produced every 6 months. Patient accrual, patient safety, and data quality will  
3903 be monitored closely by the CSPCC, the study executive committee, and the DMC to ensure that the  
3904 study is progressing satisfactorily. Further delineation of responsibilities will be documented in  
3905 communications with the Study Chair's office.

3906 The CSPCC will be responsible for monitoring and reporting the safety of trial participants through the  
3907 review, assessment, and communication of adverse events and serious adverse events detected within  
3908 the national data systems. The CSPCC will document trends and analyze safety data to prepare reports  
3909 for various committees including the DMC, VA Central IRB (CIRB), Executive Committee(s), and Study  
3910 Group meetings.

3911 The CSPCC will work closely with the Minneapolis VAMC to track eligible participants as they move  
3912 through the recruitment and enrollment workflow. The primary responsibilities for the callers include  
3913 contacting patients by telephone to obtain verbal informed consent and receiving incoming patient  
3914 phone calls.

3915 The external mailing contractor will be primarily responsible for sending study communications to  
3916 providers and patients. The mailing contractor will be sent regular mailing files compiled by the  
3917 ProjectFlow application with participant name, address, and specific correspondence to be sent. PHI will  
3918 be sent to the mailing contractor [using secure methods in alignment with VA policies](#).

3919 The CSP Clinical Research Pharmacy Coordinating Center (CSPCRPCC) will provide advice and  
3920 consultation about drug-related matters, review safety information, and serve as a regulatory affairs  
3921 expert and liaison to the FDA for regulatory matters.

3922 The Clinical Sciences Scientific Evaluation Committee (CSSEC) reviews the scientific merit of all new  
3923 cooperative study proposals and all ongoing cooperative studies. The committee is composed of both VA  
3924 and non-VA clinical research scientists, most of whom have had experience in managing their own  
3925 cooperative studies.

## 3926 B. Monitoring

3927 The following groups monitor the various aspects of the study. These committees will meet according to  
3928 current Cooperative Studies Program guidelines.

3929 The Executive Committee is responsible for the operations of the study, including protocol amendments,  
3930 and overall management of the study. It will be headed by the Study Chair and Study Director and

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3933 consist of the study biostatistician, study project manager, CSP Center Director, selected VA experts, and  
3934 outside consultants as needed. This committee will meet regularly to review blinded data (not broken  
3935 down by treatment group), decide upon changes in the study, determine the fate of hospitals whose  
3936 performance is substandard, initiate any subprotocols, and discuss publication of the study results. This  
3937 Committee must grant permission before any study data may be used for presentation or publication.

3938 The Technical Committee will advise the Executive Committee on informatics and database related  
3939 issues pertaining to study operations. This committee will serve as subject matter experts (SMEs) for the  
3940 study database, web application, ETL procedures and primary data source, the Corporate Data  
3941 Warehouse. It will consist of a VINCI representative, Boston CSPCC Director of Informatics, and other  
3942 informaticians/SMEs as needed.

3943 The Data Monitoring Committee (DMC) will review the progress of the study and will monitor patient  
3944 intake, outcomes, adverse events, and other issues related to patient safety. Interim, independent, and  
3945 unbiased reviews of the study's ongoing progress will be provided. The DMC will consist of experts in the  
3946 study's subject matter field(s), clinical trials, biostatistics, and ethics. These individuals will not be  
3947 participants in the trial and will not have participated in the planning of the protocol. The DMC will  
3948 consider safety or other circumstances as grounds for early termination, including either compelling  
3949 internal or external evidence of treatment differences or the unfeasibility of addressing the study  
3950 hypothesis (e.g., poor patient intake, poor adherence to the protocol).

3951 At each of its meetings during the study period, the DMC will review the randomization rates and assess  
3952 the difference between the actual and the projected rates, as well as the impact of these assessments  
3953 on overall trial size. If the study enrollment is inadequate, the reasons for exclusion may be scrutinized  
3954 and actions may be suggested. An assessment of whether the trial should be continued will be made  
3955 followed by recommendations, as appropriate. All serious adverse events will be reported regularly to  
3956 the DMC for review. Unexpected, related serious adverse events will be reported to the DMC as soon as  
3957 they become known based upon the consensus of the Study Chair, the study biostatistician, the Study  
3958 Director. The study biostatistician will provide the appropriate data to the DMC at specified intervals for  
3959 this purpose. Conditional power estimates may be provided to the DMC to assist them in making their  
3960 decisions and recommendations at their request. To help them make their assessment, the Study Chair  
3961 and study biostatistician will furnish the Data Monitoring Committee with appropriate monitoring data  
3962 before each meeting. The DMC makes recommendations after each meeting to the Director of the  
3963 Cooperative Studies Program (CSP)Service about whether the study should continue or be stopped.

3964 The VA Central IRB will be the IRB of record for all VA sites. They will monitor the study's serious  
3965 adverse events on a continual basis. They will conduct annual reviews of the study. In addition, some  
3966 study materials (such as subject correspondence and protocol changes) will have to be reviewed by the  
3967 VA CIRB, and approved prior to implementation.

3968 **XIX. The CSPCC Human Rights Committee (HRC) is composed primarily of lay people and is**  
3969 **responsible for ensuring that patients' rights and safety are upheld prior to study**  
3970 **initiation and during the conduct of the study. The committee reviews all new**  
3971 **protocols, periodically**



3973 **makes site visits to participating centers to monitor firsthand the progress of the study, and**  
3974 **may be asked to review any ethical and human rights issues that arise during the conduct of**  
3975 **the study. Publications**

3976 **A. Publication policy**

3977 It is the policy of the CSP that outcome data will not be revealed to the participating investigators until  
3978 the data collection phase of the study is completed. This policy safeguards against possible biases  
3979 affecting the data collection. All presentations and publications from this study will be done in  
3980 accordance with current CSP Guidelines, including the Authorship Policy. The most current version of  
3981 the Guidelines should be referenced when planning any study publication.

3982 The presentation or publication of any or all data collected by participating investigators on patients  
3983 entered into the VA Cooperative Study is under the direct control of the study's Executive Committee.  
3984 No individual participating investigator has any inherent right to perform analyses or interpretations or  
3985 to make public presentations or seek publication of any or all of the data other than under the auspices  
3986 and approval of the Executive Committee.

3987 The Executive Committee has the authority to establish one or more publication subgroups of  
3988 investigators and members of the Executive Committee for producing scientific presentations and  
3989 publications. Authors with VA appointments must list their VA affiliation first. The VA contributions to  
3990 the research project should be acknowledged in all written and oral presentations of the research  
3991 results, including scientific articles, news releases, news conferences, public lectures, and media  
3992 interviews.

3993 All study reports and journal manuscripts must be reviewed and approved by the Boston CSPCC Director  
3994 prior to submission for publication. After approval for submission is granted by the Boston CSPCC  
3995 Director, VA Central Office must be notified upon acceptance of any publications. This includes minor  
3996 publications such as abstracts and poster presentations.

3997 **B. Planned Publications**

3998 A list of planned publications is below:

- 3999 I. Editorial: The first large clinically integrated VA trial
- 4000 II. Design of the DCP
- 4001 III. Ascertainment of urgent revascularization from administrative data
- 4002 IV. Ascertainment of acute heart failure episodes from administrative data
- 4003 V. Ascertainment of stroke episodes from administrative data
- 4004 VI. Use of and experiences with telephone informed consent
- 4005 VII. Challenges of embedding DCP into the electronic medical record

- 4008 VIII. Main outcomes paper
- 4009 IX. Blood pressure control and drug compliance in the DCP
- 4010 X. Blood chemistries in the DCP

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## XX. Provider Experience Survey

In order to improve the design of future point-of-care trials, a survey was designed to query providers that consented to participate in the CSP 597 study about their experience with the study (Appendix 21). The questions were designed to assess if education about the study was adequate and delivered in a convenient format, how interested providers are in the study question, time burden of study participation, and level of comfort with a pragmatic trial design. Demographic information is also requested. Survey results will be captured in a VA approved platform.. Completion of the survey is voluntary. The study will be reviewed by CIRB and the Organizational Assessment Committee (OAC) before being distributed to consented CSP 597 providers. Provider survey results will be made available through clinicaltrials.gov. Qualitative analysis will be performed for open text responses and sub-questions. Dichotomous responses and survey responses on a Likert scale will be analyzed using quantitative methods.

An additional interview will be made available to consented providers at Minneapolis VAHCS (Appendix 25). This interview will take place in person or via teleconference. Interview questions will focus on the providers individual experience throughout DCP and allow providers to give less structured feedback on the consent and randomization workflows. The aim is to further help structure future POC studies. All results will de-identified and made available on clinicaltrials.gov

## XX. References

1. [http://www.cdc.gov/bloodpressure/hypertension\\_iom.htm](http://www.cdc.gov/bloodpressure/hypertension_iom.htm)
2. <http://www.webmd.com/news/20110420/the-10-most-prescribed-drugs>
3. [http://www.healthquality.va.gov/hypertension/htn04\\_pdf1.pdf](http://www.healthquality.va.gov/hypertension/htn04_pdf1.pdf)
4. Chobanian AV, Bakris GL, Black HR, et al. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. JAMA 2003;289:2560-72.
5. Psaty BM, Lumley T, Furberg CD, Schellenbaum G, Pahor M, Alderman MH, Weiss NS. Health outcomes associated with various antihypertensive therapies used as first-line agents: a network meta-analysis. JAMA 2003;289:2534-44.
6. Messerli FH, Bangalore S. Half a century of hydrochlorothiazide: facts, fads, fiction, and follies. Am J Med 2011;124:896-9.
7. Ernst ME, Lund BC. Renewed interest in chlorthalidone: evidence from the Veterans Health Administration. J Clin Hypertens (Greenwich). 2010;12:927-34.
8. Kaplan NM. Chlorthalidone versus hydrochlorothiazide: a tale of tortoises and a hare. Hypertension 2011;58:994-5.
9. Mitka M. Experts argue not all diuretics the same. JAMA 2007;298:31.

- 4094 10. Kaplan NM. The case for low dose diuretic therapy. *Am J Hypertens* 1991;4:970-1.
- 4095 11. Materson BJ, Cushman WC, Goldstein G, Reda DJ, Freis ED, Ramirez EA, Talmers FN, White TJ,  
4096 Nunn S, Chapman RH, et al. Treatment of hypertension in the elderly: I. Blood pressure and clinical  
4097 changes. Results of a Department of Veterans Affairs Cooperative Study. *Hypertension*  
4098 1990;15:348-60.
- 4099 12. Cushman WC, Khatri I, Materson BJ, Reda DJ, Freis ED, Goldstein G, Ramirez EA, Talmers FN, White  
4100 TJ, Nunn S, et al. Treatment of hypertension in the elderly. III. Response of isolated systolic  
4101 hypertension to various doses of hydrochlorothiazide: results of a Department of Veterans Affairs  
4102 cooperative study. Department of Veterans Affairs Cooperative Study Group on Antihypertensive  
4103 Agents. *Arch Intern Med* 1991;151:1954-60.
- 4104 13. Materson BJ, Oster JR, Michael UF, Bolton SM, Burton ZC, Stambaugh JE, Morledge J. Dose  
4105 response to chlorthalidone in patients with mild hypertension. Efficacy of a lower dose. *Clin*  
4106 *Pharmacol Ther* 1978;24:192-8.
- 4107 14. Morledge JH, Ettinger B, Aranda J, McBarron F, Barra P, Gorwit J, Davidov M. Isolated systolic  
4108 hypertension in the elderly. A placebo-controlled, dose-response evaluation of chlorthalidone. *J Am*  
4109 *Geriatr Soc* 1986;34:199-206.
- 4110 15. Neff KM, Nawarskas JJ. Hydrochlorothiazide versus chlorthalidone in the management of  
4111 hypertension. *Cardiol Rev* 2010;18:51-6.
- 4112 16. James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high  
4113 blood pressure in adults: report from the panel members appointed to the Eighth Joint National  
4114 Committee (JNC 8). *JAMA* 2014;311:507-20.
- 4115 17. Dorsch MP, Gillespie BW, Erickson SR, Bleske BE, Weder AB. Chlorthalidone reduces cardiovascular  
4116 events compared with hydrochlorothiazide: a retrospective cohort analysis. *Hypertension*  
4117 2011;57:689-94.
- 4118 18. Ernst ME, Neaton JD, Grimm RH Jr, Collins G, Thomas W, Soliman EZ, Prineas RJ; Multiple Risk  
4119 Factor Intervention Trial Research Group. Long-term effects of chlorthalidone versus  
4120 hydrochlorothiazide on electrocardiographic left ventricular hypertrophy in the multiple risk factor  
4121 intervention trial. *Hypertension* 2011;58:1001-7.
- 4122 19. Wing LM, Reid CM, Ryan P, Beilin LJ, Brown MA, Jennings GL, Johnston CI, McNeil JJ, Macdonald  
4123 GJ, Marley JE, Morgan TO, West MJ; Second Australian National Blood Pressure Study Group. A  
4124 comparison of outcomes with angiotensin-converting--enzyme inhibitors and diuretics for  
4125 hypertension in the elderly. *N Engl J Med* 2003;348:583-92.
- 4126 20. ALLHAT Collaborative Research Group. Major outcomes in high-risk hypertensive patients  
4127 randomized to angiotensin-converting enzyme inhibitor or calcium channel blocker vs diuretic:

- 4129 The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA.  
4130 2002;288:2981-97.
- 4131 21. Roush GC, Holford TR, Guddati AK. Chlorthalidone compared with hydrochlorothiazide in reducing  
4132 cardiovascular events: systematic review and network meta-analyses. Hypertension  
4133 2012;59:1110-7.
- 4134 22. Carter BL, Ernst ME, Cohen JD. Hydrochlorothiazide versus chlorthalidone: evidence supporting  
4135 their interchangeability. Hypertension 2004;43:4-9.
- 4136 23. Ernst ME, Carter BL, Goerdts CJ, Steffensmeier JJ, Phillips BB, Zimmerman MB, Bergus GR.  
4137 Comparative antihypertensive effects of hydrochlorothiazide and chlorthalidone on ambulatory  
4138 and office blood pressure. Hypertension 2006;47:352-8.
- 4139 24. Kwon BJ, Jang SW, Choi KY, Kim DB, Cho EJ, Ihm SH, Youn HJ, Kim JH. Comparison of the efficacy  
4140 between hydrochlorothiazide and chlorthalidone on central aortic pressure when added on to  
4141 candesartan in treatment-naïve patients of hypertension. Hypertens Res. 2013;36:79-84.
- 4142 25. [https://vaww.cmopnational.va.gov/cmop/PBM/Clinical Guidance/Archived Criteria, Guidelines  
4143 and Reviews/Clinical Recommendations \(Archive\)/Thiazides in Hypertension, Review of Recent  
4144 Evidence \(Archived Dec 2014\).doc](https://vaww.cmopnational.va.gov/cmop/PBM/Clinical%20Guidance/Archived%20Criteria,%20Guidelines%20and%20Reviews/Clinical%20Recommendations%20(Archive)/Thiazides%20in%20Hypertension,%20Review%20of%20Recent%20Evidence%20(Archived%20Dec%202014).doc)
- 4145 26. Ernst ME, Carter BL, Zheng S, Grimm RH Jr. Meta-analysis of dose-response characteristics of  
4146 hydrochlorothiazide and chlorthalidone: effects on systolic blood pressure and potassium. Am J  
4147 Hypertens 2010;23:440-6.
- 4148 27. Peterzan MA, Hardy R, Chaturvedi N, Hughes AD. Meta-analysis of dose-response relationships for  
4149 hydrochlorothiazide, chlorthalidone, and bendroflumethiazide on blood pressure, serum  
4150 potassium, and urate. Hypertension 2012;59:1104-9.
- 4151 28. Lund BC, Ernst ME. The comparative effectiveness of hydrochlorothiazide and chlorthalidone in an  
4152 observational cohort of veterans. J Clin Hypertens (Greenwich). 2012 Sep;14(9):623-9.
- 4153 29. Dhalla IA, Gomes T, Yao Z, Nagge J, Persaud N, Hellings C, Mamdani MM, Juurlink DN.  
4154 Chlorthalidone versus hydrochlorothiazide for the treatment of hypertension in older adults: a  
4155 population-based cohort study. Ann Intern Med 2013;158:447-55.
- 4156 30. Bakris GL, Sica D, White WB, Cushman WC, Weber MA, Handley A, Song E, Kupfer S.  
4157 Antihypertensive efficacy of hydrochlorothiazide vs chlorthalidone combined with azilsartan  
4158 medoxomil. Am J Med. 2012;125:1229.e1-1229.e10.
- 4159 31. Cushman WC, Bakris GL, White WB, Weber MA, Sica D, Roberts A, Lloyd E, Kupfer S. Azilsartan  
4160 medoxomil plus chlorthalidone reduces blood pressure more effectively than olmesartan plus  
4161 hydrochlorothiazide in stage 2 systolic hypertension. Hypertension. 2012;60:310-8.

- 4166 32. Ernst ME, Moser M. Use of diuretics in patients with hypertension. *N Engl J Med*. 2009 Nov  
4167 26;361(22):2153-64.
- 4168 33. Dolan E, Stanton A, Thijs L, Hinedi K, Atkins N, McClory S, Den Hond E, McCormack P, Staessen JA,  
4169 O'Brien E. Superiority of ambulatory over clinic blood pressure measurement in predicting  
4170 mortality: the Dublin outcome study. *Hypertension*. 2005 Jul;46(1):156-61.
- 4171 34. Fagard RH, Celis H, Thijs L, Staessen JA, Clement DL, De Buyzere ML, De Bacquer DA. Daytime and  
4172 nighttime blood pressure as predictors of death and cause-specific cardiovascular events in  
4173 hypertension. *Hypertension*. 2008 Jan;51(1):55-61.
- 4174 35. Woodman R, Brown C, Lockette W. Chlorthalidone decreases platelet aggregation and vascular  
4175 permeability and promotes angiogenesis. *Hypertension*. 2010 Sep;56(3):463-70.
- 4176 36. Kurtz TW. Chlorthalidone: don't call it "thiazide-like" anymore. *Hypertension* 2010;56:335-7.
- 4177 37. Rodenburg EM, Hoorn EJ, Ruiter R, Lous JJ, Hofman A, Uitterlinden AG, Stricker BH, Visser LE.  
4178 Thiazide-Associated Hyponatremia: A Population-Based Study. *Am J Kidney Dis*. 2013 Apr 18.  
4179 [Epub ahead of print]
- 4180 38. Alderman MH, Piller LB, Ford CE, et al; Antihypertensive and Lipid-Lowering Treatment to Prevent  
4181 Heart Attack Trial Collaborative Research Group. Clinical significance of incident hypokalemia and  
4182 hyperkalemia in treated hypertensive patients in the antihypertensive and lipid-lowering  
4183 treatment to prevent heart attack trial. *Hypertension*. 2012;59(5):926-33.
- 4184 39. Barzilay JI, Davis BR, Cutler JA, Pressel SL, Whelton PK, Basile J, Margolis KL, Ong ST, Sadler LS,  
4185 Summerson J; ALLHAT Collaborative Research Group. Fasting glucose levels and incident diabetes  
4186 mellitus in older nondiabetic adults randomized to receive 3 different classes of antihypertensive  
4187 treatment: a report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart  
4188 Attack Trial (ALLHAT). *Arch Intern Med*. 2006 Nov 13;166(20):2191-201.
- 4189 40. Barzilay JI, Davis BR, Pressel SL, Cutler JA, Einhorn PT, Black HR, Cushman WC, Ford CE, Margolis  
4190 KL, Moloo J, Oparil S, Piller LB, Simmons DL, Sweeney ME, Whelton PK, Wong ND, Wright JT Jr;  
4191 ALLHAT Collaborative Research Group. Long-term effects of incident diabetes mellitus on  
4192 cardiovascular outcomes in people treated for hypertension: the ALLHAT Diabetes Extension  
4193 Study. *Circ Cardiovasc Qual Outcomes*. 2012 Mar 1;5(2):153-62.
- 4194 41. McAdams DeMarco MA, Maynard JW, Baer AN, Gelber AC, Young JH, Alonso A, Coresh J. Diuretic  
4195 use, increased serum urate levels, and risk of incident gout in a population-based study of adults  
4196 with hypertension: the Atherosclerosis Risk in Communities cohort study. *Arthritis Rheum*. 2012  
4197 Jan;64(1):121-9.
- 4198 42. Siegel D, Hulley SB, Black DM, Cheitlin MD, Sebastian A, Seeley DG, Hearst N, Fine R. Diuretics,  
4199 serum and intracellular electrolyte levels, and ventricular arrhythmias in hypertensive men. *JAMA*  
4200 1992;267:1083-9.

- 4202 43. Mount DB, et al. Clinical manifestations and treatment of hypokalemia. UpToDate. Accessed July  
4203 2013.
- 4204
- 4205 44. Roush GC, Buddharaju V, Ernst ME, Holford TR. Chlorthalidone: Mechanisms of Action and Effect  
4206 on Cardiovascular Events. *Curr Hypertens Rep.* 2013 Jul 10. [Epub ahead of print]
- 4207
- 4208 45. Rahman M, Pressel S, Davis BR, et al. Renal outcomes in high-risk hypertensive patients treated  
4209 with an angiotensin-converting enzyme inhibitor or a calcium channel blocker vs a diuretic: a  
4210 report from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial  
(ALLHAT). *Arch Intern Med.* 2005 Apr 25;165(8):936-46.
- 4211
- 4212 46. Rahman M, Ford CE, Cutler JA, et al; ALLHAT Collaborative Research Group. Long-term renal and  
4213 cardiovascular outcomes in Antihypertensive and Lipid-Lowering Treatment to Prevent Heart  
4214 Attack Trial (ALLHAT) participants by baseline estimated GFR. *Clin J Am Soc Nephrol.* 2012  
Jun;7(6):989-1002.
- 4215
- 4216 47. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic  
4217 hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). SHEP  
Cooperative Research Group. *JAMA* 1991;265:3255-64.
- 4218
- 4219 48. Hueskes BA, Roovers EA, Mantel-Teeuwisse AK, Janssens HJ, van de Lisdonk EH, Janssen M. Use of  
4220 diuretics and the risk of gouty arthritis: a systematic review. *Semin Arthritis Rheum.* 2012  
Jun;41(6):879-89.
- 4221
- 4222 49. Mortality findings for stepped-care and referred-care participants in the hypertension detection  
4223 and follow-up program, stratified by other risk factors. The Hypertension Detection and Follow-up  
4224 Program Cooperative Research Group. *Prev Med* 1985;14:312-35.
- 4225
- 4226 50. Wilson L, Nair KV, Saseen JJ. Comparison of New-Onset Gout in Adults Prescribed Chlorthalidone  
4227 vs Hydrochlorothiazide for Hypertension. *J Clin Hypertens.* 2014 Sep 25. doi: 10.1111/jch.12413.  
4228 [Epub ahead of print]
- 4229
- 4230 51. Khosla N, Chua DY, Elliott WJ, Bakris GL. Are chlorthalidone and hydrochlorothiazide equivalent  
4231 blood-pressure-lowering medications? *J Clin Hypertens* 2005;7:354-6.
- 4232
- 4233 52. Matthews KA, Brenner MJ, Brenner AC. Evaluation of the Efficacy and Safety of a  
4234 Hydrochlorothiazide to Chlorthalidone Medication Change in Veterans With Hypertension. *Clin  
4235 Ther.* 2013 Aug 28.[Epub ahead of print]
- 4236
- 4237 53. van Blijderveen JC, Straus SM, Rodenburg EM, Zietse R, Stricker BH, Sturkenboom MC, Verhamme  
4238 KM. Risk of hyponatremia with diuretics: chlorthalidone versus hydrochlorothiazide. *Am J Med*  
2014;127:763-71.
- 4239
- 4240 54. Roush GC, Buddharaju V, Ernst ME. Is chlorthalidone better than hydrochlorothiazide in reducing  
4241 cardiovascular events in hypertensives? *Curr Opin Cardiol* 2013;28:426-32.
- 4242
- 4243

- 4244 55. Dhalla IA, Mamdani MM, Juurlink DN. Chlorthalidone versus hydrochlorothiazide. *Ann Intern Med*.  
4245 2013;158:923-4.
- 4246 56. Einhorn PT, Cushman WC, Whelton PK; ALLHAT Collaborative Research Group. Chlorthalidone  
4247 versus hydrochlorothiazide. *Ann Intern Med* 2013;158:922-3.
- 4248 57. Asche C, Yang J, Yu S, Hagan M. A profiling of hypertension patients treated with chlorthalidone or  
4249 hydrochlorothiazide. *Value Health*. 2013 May;16(3):A295.
- 4250 58. Krause T, Lovibond K, Caulfield M, McCormack T, Williams B; Guideline Development Group.  
4251 Management of hypertension: summary of NICE guidance. *BMJ* 2011;343:d4891.
- 4252 59. Mancia G, Fagard R, Narkiewicz K, et al; Task Force Members. 2013 ESH/ESC Guidelines for the  
4253 management of arterial hypertension: the Task Force for the management of arterial hypertension  
4254 of the European Society of Hypertension (ESH) and of the European Society of Cardiology (ESC). *J*  
4255 *Hypertens* 2013;31:1281-357.
- 4256 60. Floyd JS, Psaty BM. Observational Comparative Effectiveness Studies of Drug Therapies: High-  
4257 Quality Answers or Important Clinical Questions? Comment on "Comparative Effectiveness of 2  $\beta$ -  
4258 Blockers in Hypertensive Patients". *Arch Intern Med* 2012;172:1412-4.
- 4259 61. Lauer MS, D'Agostino RB. The randomized registry trial — the next disruptive technology in clinical  
4260 research? *N Engl J Med* 2013; 369:1579-1581.
- 4261 62. Jansen JP, Fleurence R, Devine B, Itzler R, Barrett A, Hawkins N, Lee K, Boersma C, Annemans L,  
4262 Cappelleri JC. Interpreting indirect treatment comparisons and network meta-analysis for health-  
4263 care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good  
4264 Research Practices: part 1. *Value Health* 2011;14:417-28.
- 4265 63. Pletcher MJ, Lo B, Grady D. Informed consent in randomized quality improvement trials: a critical  
4266 barrier for learning health systems. *JAMA Intern Med* 2014;174:668-70.
- 4267 64. Peto R, Collins R, Gray R. Large-scale randomized evidence: large, simple trials and overviews of  
4268 trials. *J Clin Epidemiol*. 1995 Jan;48(1):23-40.
- 4269 65. Vickers AJ, Scardino PT. The clinically-integrated randomized trial: proposed novel method for  
4270 conducting large trials at low cost. *Trials*. 2009;10:14.
- 4271 66. van Staa TP, Goldacre B, Gulliford M, Cassell J, Pirmohamed M, Taweel A, Delaney B, Smeeth L.  
4272 Pragmatic randomised trials using routine electronic health records: putting them to the test. *BMJ*.  
4273 2012 Feb 7;344:e55.
- 4274 67. Fiore LD, Brophy M, Ferguson RE, D'Avolio L, Hermos JA, Lew RA, Doros G, Conrad CH, O'Neil JA Jr,  
4275 Sabin TP, Kaufman J, Swartz SL, Lawler E, Liang MH, Gaziano JM, Lavori PW. A point-of-care clinical  
4276 trial comparing insulin administered using a sliding scale versus a weight-based regimen. *Clin*  
4277 *Trials*. 2011;8:183-95.

- 4279 68. D'Avolio L, Ferguson R, Goryachev S, Woods P, Sabin T, O'Neil J, Conrad C, Gillon J, Escalera J,  
4280 Brophy M, Lavori P, Fiore L. Implementation of the Department of Veterans Affairs' first point-of-  
4281 care clinical trial. *J Am Med Inform Assoc*. 2012 Jun 1;19(e1):e170-e176. Epub 2012 Feb 24.
- 4282 69. IOM Roundtable on Evidence-Based Medicine. Appendix A. Learning what works best: the nation's  
4283 need for evidence on comparative effectiveness in health care: an issue overview. In: *Learning*  
4284 *What Works: Infrastructure Required for Comparative Effectiveness Research: Workshop*  
4285 *Summary*. Institute of Medicine (US) Roundtable on Value & Science-Driven Health Care.  
4286 Washington (DC): National Academies Press (US); 2011.  
4287 <http://www.ncbi.nlm.nih.gov/books/NBK64784/>
- 4288 70. Eapen ZJ, Lauer MS, Temple RJ. The imperative of overcoming barriers to the conduct of large,  
4289 simple trials. *JAMA* 2014;311:1397-8.
- 4290 71. Smith DH, Neutel JM, Lacourcière Y, Kempthorne-Rawson J. Prospective, randomized, open-label,  
4291 blinded-endpoint (PROBE) designed trials yield the same results as double-blind, placebo-  
4292 controlled trials with respect to ABPM measurements. *J Hypertens*. 2003 Jul;21(7):1291-8.
- 4293 72. Kerr EA, Lucatoro MA, Holleman R, Hogan MM, Klamerus ML, Hofer TP; VA Diabetes Quality  
4294 Enhancement Research Initiative (QUERI) Workgroup on Clinical Action Measures. Monitoring  
4295 performance for blood pressure management among patients with diabetes mellitus: too much of  
4296 a good thing? *Arch Intern Med*. 2012;172:938-45.
- 4297 73. Berry SD, Kiel DP. Treating hypertension in the elderly: should the risk of falls be part of the  
4298 equation? *JAMA Intern Med* 2014;174:596-7.
- 4299 74. Nord J, Stults B, Rose R, Underwood AE, Williams T, West G, Huhtala T, Milne CK. Optimizing office  
4300 blood pressure measurement at a VAMC. *Fed Pract* 2012;29(5):35-39.
- 4301 75. Kim JW, Bosworth HB, Voils CI, Olsen M, Dudley T, Gribbin M, Adams M, Oddone EZ. How well do  
4302 clinic-based blood pressure measurements agree with the mercury standard? *J Gen Intern Med*  
4303 2005;20:647-9.
- 4304 76. Freeman MK, White W, Iranikhah M. Tablet splitting: a review of the clinical and economic  
4305 outcomes and patient acceptance. *Consult Pharm* 2012;27:421-30.
- 4306 77. Kalsbeek WD, Botman SL, Massey JT, Liu PW. Cost-Efficiency and the Number of Allowable Call  
4307 Attempts in the National Health Interview Survey. *Journal of Official Statistics* 1994;10(2): 133–52
- 4308 78. Hörngren J, Lundquist P, Westling S. Effects of number of call attempts on nonresponse rates and  
4309 nonresponse bias – result from some case studies at Statistics Sweden. *Statistics Canada's*  
4310 *International Symposium Series: Proceedings*, 2009.  
4311 <http://www.statcan.gc.ca/pub/11-522-x/2008000/article/10999-eng.pdf>  
4312  
4313  
4314

- 4317 79. Fowler FJ, Jr., Gallagher PM, Stringfellow VL, Zaslavsky AM, Thompson JW, Cleary PD. Using  
4318 telephone interviews to reduce nonresponse bias to mail surveys of health plan members. *Med*  
4319 *Care*. 2002;40:190-200.
- 4320 80. Fu SS, van Ryn M, Burgess DJ, Nelson D, Clothier B, Thomas JL, Nyman JA, Joseph AM. Proactive  
4321 tobacco treatment for low income smokers: study protocol of a randomized controlled trial. *BMC*  
4322 *Public Health* 2014;14:337.
- 4323 81. Koepsell T, McGuire V, Longstreth W, Nelson L, Belle G. Randomized trial of leaving messages on  
4324 telephone answering machines for control recruitment in an epidemiologic study. *Am J Epidemiol*.  
4325 1996;144:704-706.
- 4326 82. Andrade SE, Kahler KH, Frech F, Chan KA. Methods for evaluation of medication adherence and  
4327 persistence using automated databases. *Pharmacoepidemiol Drug Saf*. 2006;15:565-74.
- 4328 83. Sacco RL, Kasner SE, Broderick JP, Caplan LR, Connors JJ, Culebras A, Elkind MSV, George MG,  
4329 Hamdan AD, Higashida RT, Hoh BL, Janis LS, Kase CS, Kleindorfer DO, Lee J-M, Moseley ME,  
4330 Peterson ED, Turan TN, Valderrama AL, Vinters HV. An updated definition of stroke for the 21<sup>st</sup>  
4331 century: a statement for healthcare professionals from the American Heart Association/American  
4332 Stroke Association. *Stroke*. 2013; 44:2064-2089.
- 4333 84. Thygesen K, Alpert JS, Jaffe AS, Simoons ML, Chaitman BR, White HD; Joint ESC/ACCF/AHA/WHF  
4334 Task Force for the Universal Definition of Myocardial Infarction, et al. Third universal definition of  
4335 myocardial infarction. *Circulation*. 2012;126:2020-35.
- 4336 85. Braunwald E, Domanski MJ, Fowler SE, et al; PEACE Trial Investigators. Angiotensin-converting-  
4337 enzyme inhibition in stable coronary artery disease. *N Engl J Med* 2004;351:2058-68.
- 4338 86. Morrow DA, Braunwald E, Bonaca MP, et al; TRA 2P–TIMI 50 Steering Committee and  
4339 Investigators. Vorapaxar in the secondary prevention of atherothrombotic events. *N Engl J Med*  
4340 2012;366:1404-13.
- 4341 87. Tricoci P, Huang Z, Held C, et al; TRACER Investigators. Thrombin-receptor antagonist vorapaxar in  
4342 acute coronary syndromes. *N Engl J Med* 2012;366:20-33.
- 4343 88. White WB, Bakris GL, Bergenstal RM, Cannon CP, Cushman WC, et al. EXamination of  
4344 cArdiovascular outcoMes with alogliptIN versus standard of carE in patients with type 2 diabetes  
4345 mellitus and acute coronary syndrome (EXAMINE): a cardiovascular safety study of the dipeptidyl  
4346 peptidase 4 inhibitor alogliptin in patients with type 2 diabetes with acute coronary syndrome. *Am*  
4347 *Heart J* 2011;162:620-6.
- 4348 89. Einhorn PT, Davis BR, Massie BM, Cushman WC, Piller LB, Simpson LM, Levy D, Nwachuku CE,  
4349 Black HR; ALLHAT Collaborative Research Group. The Antihypertensive and Lipid Lowering  
4350 Treatment to Prevent Heart Attack Trial (ALLHAT) Heart Failure Validation Study: diagnosis and  
4351 prognosis. *Am Heart J*. 2007 Jan;153(1):42-53.



4353 90. Go AS, Mozaffarian D, Roger VL, et al; AHA Statistics Committee and Stroke Statistics  
4354 Subcommittee. Heart disease and stroke statistics--2013 update: a report from the American  
4355 Heart Association. *Circulation* 2013;127:e6-e245.

4356 91. Kannel WB. Blood pressure as a cardiovascular risk factor: prevention and treatment. *JAMA*  
4357 1996;275:1571-6.

4358 92. Roger VL, Weston SA, Redfield MM, Hellermann-Homan JP, Killian J, Yawn BP, Jacobsen SJ. Trends  
4359 in heart failure incidence and survival in a community based population. *JAMA* 2004;292:344-50.

4360 93. Hicks KA, Hung HMJ, Mahaffey KW, et al. Standardized definitions for cardiovascular and stroke  
4361 end point events in clinical trials. FDA draft report, 2012.

4362 94. Ron E, Carter R, Jablon S, Mabuchi K. Agreement between death certificate and autopsy diagnoses  
4363 among atomic bomb survivors. *Epidemiology*. 1994 Jan;5(1):48-56.

4364 95. Sesso HD, Gaziano JM, Glynn RJ, Buring JE. Value of an Endpoints Committee versus the use of  
4365 nosologists for validating cause of death. *Contemp Clin Trials*.2006 Aug;27(4): 333-9.

4366 96. German RR, Fink AK, Heron M, et al. The accuracy of cancer mortality statistics based on death  
4367 certificates in the United States. *Cancer epidemiology* 2011;35(2):126-31.

4368 97. Prieto-Merino D, Smeeth L, Staa TP, Roberts I. Dangers of non-specific composite outcome  
4369 measures in clinical trials. *BMJ* 2013;347:f6782.

4370 98. McKee PA, Castelli WP, McNamara PM, Kannel WB. The natural history of congestive heart failure:  
4371 the Framingham study. *N Engl J Med*. 1971;285:1441-6.

4372 99. Sohn MW, Arnold N, Maynard C, Hynes DM. Accuracy and completeness of mortality data in the  
4373 Department of Veterans Affairs. *Popul Health Metr*. 2006 Apr 10;4:2.

4374 100. Fletcher RD, Amdur RL, Kolodner R, McManus C, Jones R, Faselis C, Kokkinos P, Singh S,  
4375 Papademetriou V. Blood pressure control among US veterans: a large multiyear analysis of blood  
4376 pressure data from the Veterans Administration health data repository. *Circulation*  
4377 2012;125:2462-8.

4378 101. ACCORD Study Group, Cushman WC, Evans GW, Byington RP, et al. Effects of intensive blood-  
4379 pressure control in type 2 diabetes mellitus. *N Engl J Med*. 2010;362:1575-85(+ online  
4380 supplement).

4381 102. Jennison, C and Turnbull, B. Group Sequential Methods with Applications to Clinical Trials. Boca  
4382 Raton, FL: Chapman & Hall/CRC Interdisciplinary Statistics, 2000.

4383 103. Daniels MJ and Hogan JW. Missing Data in Longitudinal Studies: Strategies for Bayesian Modeling  
4384 and Sensitivity Analysis. Boca Raton, FL: Chapman and Hall/CRC, 2008.

4385  
4386  
4387  
4388

4389 104. Beyersmann J, Allignol A, and Schumacher M. Competing Risks and Multistate Models with R.  
4390 New York, NY: Springer, 2012.

4391 105. <http://answers.hhs.gov/ohrp/questions/7276>

4392 106. Morris MC; Nelson RM. Randomized, controlled trials as minimal risk: An ethical analysis. Crit Care  
4393 Med 2007; 35:940–4.

4394 107. Nelson K, Garcia RE, Brown J, Mangione CM, Louis TA, Keeler E, Cretin S. Do patient consent  
4395 procedures affect participation rates in health services research? Med Care 2002;40:283-8.  
4396

4397 108. Cann CI, Rothman KJ. IRBs and epidemiologic research: how inappropriate restrictions hamper  
4398 studies. IRB 1984;6(4):5-7.  
4399

4400 109. Armstrong D, Kline-Rogers E, Jani SM, Goldman EB, Fang J, Mukherjee D, Nallamotheu BK, Eagle KA.  
4401 Potential impact of the HIPAA privacy rule on data collection in a registry of patients with acute  
4402 coronary syndrome. Arch Intern Med 2005;165:1125-9.  
4403

4404 110. Kaiser J. Patient privacy. Rule to protect records may doom long-term heart study. Science  
4405 2006;311:1547-8.  
4406

4407 111. Ellickson PL, Hawes JA. An assessment of active versus passive methods for obtaining parental  
4408 consent. Eval Rev 1989;13:45-55.  
4409  
4410  
4411  
4412  
4413  
4414  
4415  
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4417  
4418  
4419  
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| Version | Effective Date   | Description of Changes  |
|---------|------------------|---|
| 2.2     | March 16, 2016   | <ul style="list-style-type: none"> <li>Removal of reference to the 'ART Database' for identification of allergic reactions (p. 28, 53). The study will collect all data from the Corporate Data Warehouse (CDW) and Electronic Medical Record (EMR); ART is a specific VistA package that will not be used</li> <li>Removal of "(2 weeks)" from sentence on p. 33. This protocol indicates monthly data pulls elsewhere, thus we removed the reference to "2 weeks" for consistency</li> <li>Clarified CPRS tools used for randomization (order vs. progress note). CPRS changes allow for improved communication with PCPs and consistency between randomization arms.</li> <li>Added language for ICD-10 codes</li> </ul> |
| 2.3     | July 07, 2016    | <ul style="list-style-type: none"> <li>Revised references on p29 to fix typos.</li> <li>Removed Appendix D. CPRS Screens v2.1 from protocol</li> <li>Clarified voicemail procedures. The voicemail procedures were amended to allow callers to leave a voicemail after a caller returns a previous voicemail to ensure good customer service.</li> </ul>  |
| 2.4     | January 05, 2017 | <ul style="list-style-type: none"> <li>Edited opt-out language to remove references to opt-out card and to explain new voicemail box phone tree system</li> <li>Fixed typo on p.36 about Type I errors</li> <li>Clarified consent procedures, allowing research staff to contact, consent, and withdraw patients on follow-up calls that originated with the Call Center</li> <li>Added a pre-eligibility check prior to sending randomization view alerts to providers</li> <li>Removed vascular access for dialysis from the definition of renal failure</li> <li>Redefined the definition of stroke from WHO definition to AHA definition</li> </ul>   |
| 2.5     | May 08, 2017     | <ul style="list-style-type: none"> <li>Clarified language on external mail contractor</li> </ul>  |
| 2.6     | June 28, 2017    | <ul style="list-style-type: none"> <li>Removed reference to health factors which are not being utilized</li> <li>Updated definition of urgent coronary revascularization to include unstable angina</li> <li>Added definition of unstable angina</li> <li>Clarified 'Ascertainment of Outcome Data' section to reflect the current process being utilized</li> <li>Removed specific outcome definition from protocol to be an appendix (Outcome Definitions)</li> <li>Updated source for vital status and cause of death data</li> <li>Clarified 'Data Management and Data Security Plans' section to better describe security protocols and data access</li> </ul>   |

|            |                    |  |
|------------|--------------------|--|
|            |                    | <ul style="list-style-type: none"> <li>Added language noting that the DMC can request additional safety data not specified in the protocol</li> <li>Removed language regarding monthly medical record data</li> </ul>  |
| <b>2.7</b> | August 23, 2017    | <ul style="list-style-type: none"> <li>Added language permitting the study team to provide education to sites as well as the site liaison</li> <li>Added a reminder email to providers (See Appendix A.8)</li> </ul>   |
| <b>2.8</b> | October 02, 2017   | <ul style="list-style-type: none"> <li>Added language changing that voicemails will be left on the 1st, 8th and 14th call to Veterans</li> </ul>   |
| <b>2.9</b> | May 01, 2018       | <ul style="list-style-type: none"> <li>Generalized call center language to include trained study staff</li> <li>Added that we will contact pharmacists during site rollout</li> <li>Added the option to call a patient an additional 3 times if they contact the study team after the 15th call</li> <li>Added information on temporary and permanent ineligibility</li> <li>Replaced "encrypted mail" as the method to send secure information to the mail center to "secure method that meets VA requirements"</li> <li>Expanded planned publications section</li> </ul> |
| <b>3.0</b> | July 06, 2018      | <ul style="list-style-type: none"> <li>Changed PI from Dr. Frank Lederle to Dr. Areef Ishani</li> </ul>  |
| <b>3.1</b> | October 23, 2018   | <ul style="list-style-type: none"> <li>Added second testpatient view alert order to request provider participation to providers that have previously declined, to be sent eight weeks after original order</li> </ul>  |
| <b>3.2</b> | November 23, 2018  | <ul style="list-style-type: none"> <li>Removed Canandaigua VAMC as the call center</li> </ul>  |
| <b>3.3</b> | February 13, 2019  | <ul style="list-style-type: none"> <li>Added language about email or texting</li> <li>Replaced reference to CSRD with CSP</li> </ul>   |
| <b>3.4</b> | May 06, 2019       | <ul style="list-style-type: none"> <li>Changed MAVERIC to Boston CSPCC</li> <li>Edited voicemail language to change voicemails to be on a time scale (months) instead of a call scale</li> <li>Added language to potentially resend initial mailing materials (A2) to Veterans after 5 calls</li> </ul>  |
| <b>3.5</b> | June 06, 2019      | <ul style="list-style-type: none"> <li>Added language about Spanish mailings and Spanish speaking callers</li> </ul>   |
| <b>3.6</b> | December 18, 2019  | <ul style="list-style-type: none"> <li>Added an option to use video for site education</li> </ul>  |
| <b>3.7</b> | June 24, 2020      | <ul style="list-style-type: none"> <li>Removed Dr. William Cushman as Co-Chair. Removed him in header line</li> </ul>  |
| <b>3.8</b> | September 03, 2020 | <ul style="list-style-type: none"> <li>Edited language about reaffirmation calls to include all study team members</li> </ul>  |
| <b>3.9</b> | November 25, 2020  | <ul style="list-style-type: none"> <li>Added language about dual enrollment</li> <li>Exchanged CRPS for VA HER</li> <li>Changed language to make temporarily ineligible letters optional</li> </ul>  |
| <b>4.0</b> | March 23, 2021     | <ul style="list-style-type: none"> <li>Updated recruitment number, study timeline, and follow-up duration</li> <li>Added provider survey</li> </ul>  |
| <b>4.1</b> | July 28, 2021      | <ul style="list-style-type: none"> <li>Added end of recruitment letters</li> </ul>   |
| <b>4.2</b> | October 08, 2021   | <ul style="list-style-type: none"> <li>Removed QA component from outcomes</li> <li>Removed email from Appendix 23</li> </ul>   |

|            |                |   |
|------------|----------------|---|
|            |                | <ul style="list-style-type: none"> <li>• Added Appendix 25</li> </ul>   |
| <b>4.3</b> | April 07, 2022 | <ul style="list-style-type: none"> <li>• Updated sample size to the final number of enrolled patients</li> <li>• Added dual enrollment with CSP2005 that has been approved by the Study PIs and Coordinating Centers</li> <li>• Clarified how data may be used for the analysis of secondary and tertiary objectives</li> </ul> |
| <b>4.4</b> | May 09, 2022   | <ul style="list-style-type: none"> <li>• Added dual enrollment with CSP2026 that has been approved by both study PIs and Coordinating Centers</li> </ul>  |

\*Please note that the protocol version initially approved by the VA Central IRB was version 2.1

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|--|---|---|---------------|
| <b>MAVERIC Study<br/>Specific<br/>Documents</b>                              | <b>DATE OF ISSUE</b>                      | <b>DOCUMENT DESCRIPTION</b>   |               |
|  | 8/29/2017                                 | This document describes the statistical analysis plan for the CSP597. |               |
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## Abbreviations

|       |   |
|-------|---|
| ACME  | Automated Classification of Medical Entities    |
| ADD   | Average Daily Dose                              |
| BMI   | Body Mass Index                                 |
| CDW   | Corporate Data Warehouse                        |
| ED    | Erectile Dysfunction                            |
| CMS   |   |
| CPRS  | Centers for Medicare & Medicaid Services        |
| CSP   | Computerized Patient Record System              |
| CSPCC | Cooperative Studies Program                     |
| CV    |   |
| CVD   | Cooperative Studies Program Coordinating Center |
| DCP   | Cardiovascular                                  |
| DMC   | Cardiovascular Disease                          |
| ED    | Diuretic Comparison Project                     |
| eGFR  | Data Monitoring Committee                       |
| EMR   | Erectile Dysfunction                            |
| GEE   |   |
| ICD   | estimated Glomerular Filtration Rate            |
| ITT   | Electronic Medical Record                       |
|       | Generalized Estimating Equation                 |
| MI    | International classification of disease         |
| MPR   | Intention To Treat                              |
| MSM   |   |
| PCP   | myocardial infarction                           |
| POC   | Medication Possession Ratio                     |
| SAP   | Multistage Model                                |
| SBP   |   |
| SOP   | Primary Care Provider                           |
| VA    | Point-Of-Care                                   |
| VHA   | Statistical Analysis Plan                       |
|       | Systolic Blood Pressure                         |
|       | Standard Operating Procedure                    |
|       | Veterans Affairs                                |
|       | Veterans Health Administration                  |

4488

## 1. Introduction

4489 This document outlines the statistical methods for the analysis of the data collected in  
4490 the Department of Veterans Affairs (VA) Cooperative Studies Program (CSP) study #597  
4491 entitled "Diuretic Comparison Project {DCP)". The purpose of this document is to  
4492 provide guidelines from which the analysis will proceed.

4493

4494

4495

### 1.1 Overview of the Study Design and Objectives

4497 The present study is an open-label, blinded-endpoint, multicenter, prospective  
4498 randomized two-arm controlled clinical trial. This trial is designed to compare the  
4499 effects of two thiazide-type diuretics, hydrochlorothiazide and chlorthalidone, on  
4500 cardiovascular {CV} events and non-cancer death. A randomized trial comparing the  
4501 effectiveness of the two drugs has never been conducted, primarily for reasons of cost.  
4502 Consequently, a less-expensive study design {termed a "point-of-care {POC}" trial} is  
4503 utilized to answer the question of whether chlorthalidone is more effective than  
4504 hydrochlorothiazide at preventing CV events and non-cancer death among older  
4505 patients with hypertension.

4506

4507 This study aims to enroll 13,500 patients over 3 years at the 50 Veterans Affairs {VA}  
4508 medical centers. The participants will be randomized with equal probability into one of  
4509 the treatment arms. Based on time of enrollment, participants can be followed for a  
4510 maximum of 4.5 years. Assuming a uniform rate of enrollment over time (90 patients  
4511 per medical center each year), the average follow-up time will be approximately 3 years  
4512 among all participants.

4513 **2. Investigational Plan**

4514  
4515 **2.1 Description of the Study Population**

4516 Patients who satisfy the inclusion and exclusion criteria are considered eligible to be  
4517 enrolled in this study.

4518  
4519  
4520 **2.1.1 Inclusion Criteria**

4521 Patients who meet the following criteria are considered eligible:

- 4522
- 4523 I. Over 65 years of age
  - 4524 II. Receiving hydrochlorothiazide from the VA pharmacy at a daily dose of 25 or 50  
4525 mg
  - 4526 III. Have a most recent systolic blood pressure (SBP)  $\geq 120$  mmHg, with no SBP  $< 120$   
4527 mmHg recorded in CPRS over the past 90 days

4528  
4529  
4530 **2.1.2 Exclusion Criteria**

4531 Patients with any of the following conditions are excluded from enrollment:

- 4532
- 4533 I. Impaired decision-making capacity rendering the patient unable to provide  
4534 informed consent. (Indicated in medical chart or determined by the primary  
4535 care provider (PCP))
  - 4536 II. Death expected within 6 months (inferred by PCP permission to randomize)
  - 4537 III. Potassium  $< 3.1$  or  $< 3.5$  (if on digoxin) meq/L over the past 90 days
  - 4538 IV. Sodium  $< 130$  meq/L over the past 90 days
  - 4539 V. Enrolled in Medicare Part C (extracted from administrative data or obtained  
4540 from patients through consent phone call)

4541 **2.2 Description of the Intervention Strategy**

4542  
4543 **2.2.1 Randomization**

4544 Participants will be randomized with a 1:1 allocation ratio to:

- 4545 I. Continue receiving hydrochlorothiazide at current daily dose (25 or 50 mg), or  
4546 II. Switch to chlorthalidone at half dose (12.5 or 25 mg, respectively)

4547  
4548 Both stratification and blocking will be employed to control for potential imbalance in  
4549 randomization. The randomization scheme will be stratified by participating medical  
4550 centers to account for possible regional differences in clinical practice, and the  
4551 treatment allocation will be performed within blocks of size 6.

4552  
4553 **2.2.2 Study Intervention**

4554 We will obtain informed consent from patient for study participation. Prior to the start  
4555 of the intervention, we will obtain approval from his/her associated PCP for randomizing  
4556 the particular patient. Participants of this study will be randomly allocated to either the  
4557 hydrochlorothiazide or chlorthalidone arm. The administration of the allocated  
4558 treatment will be managed by his/her PCP. There are no study-specific clinic visits or  
4559 assessments. During the entire study period, participants will be monitored by their  
4560 health care providers through usual clinical care. Data collection of this study will be  
4561 performed by extracting relevant study data from electronic medical records. A series  
4562 of pre-defined algorithms will be developed to identify study outcomes and safety  
4563 events. The overall compliance of study medications will be determined indirectly using  
4564 medication possession-ratio (MPR) and average daily dose (ADD) based on electronic  
4565 pharmacy records.

4566  
4567 **2.2.3 Follow-Up Assessment**

4568 Participants will be followed passively through the VA electronic medical record (EMR)  
4569 system. The pre-defined extraction algorithms will be performed and collect relevant  
4570 follow-up data from the VHA Corporate Data Warehouse (CDW), Centers for Medicare &  
4571 Medicaid Service (CMS) database, and the National Death Index.

4572  
4573 Assuming a uniform rate of enrollment over time, the first patient entered will have 4.5  
4574 years of follow-up and the last patient entered will have 1.5 years of follow-up, yielding  
4575 an average follow-up time of 3 years on 13,500 subjects.

4576 **3. Statistical Methods**

4577 **3.1 Primary Data Analysis**

4578  
4579 **3.1.1 Primary Objective**

4580 The primary objective is to determine whether chlorthalidone is superior to  
4581 hydrochlorothiazide for the prevention of CV events and non-cancer death over time.

4582  
4583 **3.1.2 Primary Endpoint**

4584 The primary endpoint is time to a composite outcome involving CV events of interest  
4585 and non-cancer death. The CV events of interest are defined as hospitalization for  
4586 stroke, myocardial infarction (MI), urgent coronary revascularization due to unstable  
4587 angina, and acute decompensated heart failure. Time to event will be measured as time  
4588 from study enrollment to the first occurrence of the composite outcome.

4589  
4590  
4591 **3.1.3 Primary Hypothesis**

4592 We posit a 4.5 year event rate of 13.5% in the hydrochlorothiazide arm and a 17.5%  
4593 reduction of CVD events in the chlorthalidone arm to inform our primary hypothesis  
4594 stated below:

4595  
4596  $H_0$ : The 4.5 year event rate will be 13.5% (or 578 primary events) in both treatment arms

4597  $H_1$ : The 4.5 year event rate will be 11.1% (or 477 primary events) in the chlorthalidone arm

4598 In theory, if the primary events occurred as projected, the relative percent change will  
4599 be  $17.5\% \left( \frac{578-477}{578} * 100\% \right)$ . The hazard ratio (chlorthalidone hazard rate/  
4600 hydrochlorothiazide hazard rate) will be approximately 0.81, which will be midway  
4601 between the odds ratio of 0.80 ( $11.1(100-13.5)/13.5(100-11.1)$ ) and the risk ratio of  
4602 0.82 ( $11.1/13.5$ ).

4603  
4604  
4605 **3.1.4 Statistical Methods for Primary Data Analysis**

4606 The effect of treatment on the primary study outcome will be assessed by means of a  
4607 two-sided log-rank test and Cox proportional hazards models based on intention-to-  
4608 treat (ITT) principles. Both unadjusted and adjusted models will be used. The adjusted  
4609 Cox model will account for baseline characteristics such as demographics (e.g., age, sex)  
4610 and clinical factors (e.g., blood pressure, medications, history of disease, and body mass  
4611 index (BMI)). A time-treatment interaction term will also be included to test the  
4612 proportional hazards assumption. The final study results will present both unadjusted

4613 and adjusted hazard rates and corresponding hazard ratios with 95% confidence  
4614 intervals.

## 4615 **3.2 Secondary Data Analysis**

### 4617 **3.2.1 Secondary Objectives**

4618 The secondary objectives are to compare the treatment effects 1) across pre-specified  
4619 subgroups, 2) on individual components of the primary outcomes, and 3) on additional  
4620 outcomes of interest.

4621  
4622 Differential treatment effects will be evaluated in the following baseline characteristics:

- 4623 I. gender
- 4624 II. age (dichotomized at the median)
- 4625 III. baseline SBP (dichotomized at the median)
- 4626 IV. history of MI or stroke
- 4627 V. black race vs. not
- 4628 VI. diabetes vs. not
- 4629 VII. eGFR <60 ml/min/1.73m<sup>2</sup>
- 4630 VIII. good compliance (medication possession ratio 80%) with hydrochlorothiazide  
4631 over the year before randomization

### 4632 **3.2.2 Secondary Endpoints**

4633  
4634 Individual components of the primary outcome will be examined:

- 4635 I. stroke
- 4636 II. **MI**
- 4637 III. urgent coronary revascularization due to unstable angina
- 4638 IV. hospitalization for acute decompensated heart failure
- 4639 V. non-cancer death

4640  
4641 Treatment effects will be evaluated for additional outcomes below:

- 4642 I. all-cause mortality
- 4643 II. the composite outcome substituting all deaths for non-cancer deaths

- 4648 III. "possible vascular deaths" defined as all deaths caused by vascular diseases,  
4649 diabetes, external causes, and unknown causes
- 4650 IV. the composite outcome substituting "possible vascular deaths" for non-cancer  
4651 deaths
- 4652 V. any revascularization of an artery
- 4653 VI. erectile dysfunction (ED), defined as first prescription of PDES inhibitor or  
4654 referral for ED  
4655  
4656

### 4657 **3.2.3 Statistical Methods for Secondary Data Analyses**

4658 Cox regression modeling will be used to explore variation in treatment efficacy across  
4659 the pre-specified subgroups. The components of the primary outcomes will be  
4660 examined individually using log-rank and Cox proportional hazards models. Both  
4661 unadjusted and adjusted analyses will be performed. Covariate adjustment will be  
4662 similar to that used in the primary data analysis.

## 4663 4664 4665 **3.3 Tertiary Data Analysis** 4666

### 4667 4668 **3.3.1 Tertiary Objective**

4669 The tertiary objective is to examine the occurrence of expected adverse events (defined  
4670 as common events related to diuretics), and their associations with the assigned  
4671 treatment regimens.

### 4672 4673 **3.3.2 Tertiary Endpoints**

4674 The expected adverse events of this study are:

- 4675 I. hospitalization for primary diagnosis of hypokalemia, hyponatremia, or renal  
4676 failure  
4677
- 4678 II. renal failure, defined as dialysis, vascular access for dialysis, or renal transplant
- 4679 III. other recorded hypokalemia (<3.5 meq/L) or hyponatremia (<130 meq/L)
- 4680 IV. new diabetes, defined as first use of medication for diabetes
- 4681 V. acute gout episodes
- 4682 VI. new allergic reaction to thiazide-type diuretics

4683 **3.3.3 Statistical Methods for Tertiary Data Analysis**

4684 The expected adverse event will be examined individually using log-rank and Cox  
4685 proportional hazards models. Both unadjusted and adjusted Cox models will be  
4686 performed. The adjustment for baseline covariates will be similar to that used in the  
4687 primary data analysis.

4688 **3.4 Exploratory Data Analysis**

4690 **3.4.1 Exploratory Objective**

4691 The ITT analyses take no account of post-baseline changes in study medications. Thus,  
4692 exploratory analyses may be performed to examine the primary, secondary, and tertiary  
4693 endpoints in a per-protocol subset, which defined as participants who persistently  
4694 receive the allocated medication prescriptions throughout the duration of the study.  
4695

4696 Other exploratory analyses may be performed to evaluate the treatment efficacy with  
4697 considerations of protocol deviations and time-varying repeated measures, as well as  
4698 treatment interruptions due to hospitalization and other clinical factors. We may also  
4699 explore the between-group difference in SBP, which will be measured repeatedly over  
4700 the disease-free intervals (free of component events).  
4701

4702 **3.4.2 Statistical Methods for Exploratory Data Analysis**

4703 The per-protocol analysis will be performed following statistical procedures used in the  
4704 ITT cohort. Other exploratory analyses may be conducted using a generalized  
4705 estimating equation (GEE) to account for varying time intervals and treatment  
4706 interruptions, with potential modeling of time-dependent effects of protocol deviations.  
4707 We may also explore censoring patterns such as models that assume not missing-at-  
4708 random using a Bayesian approach to the pattern mixture model (Missing Data in  
4709 Longitudinal Studies Chapman and Hall Boca Raton 2008). In addition, a change in  
4710 medication may alter the subsequent risk of a cardiovascular event. Therefore, we may  
4711 add time-dependent covariates to the Cox model, such as binary indicators of  
4712 medication switching (from chlorthalidone to hydrochlorothiazide, or vice versa). To  
4713 directly estimate subsequent risk, we may use a multistage model (MSM) to assess the  
4714 hazard rate of a major cardiovascular event after a switch. MSM models extend the  
4715 time-to-first-event models to second, third, and more events. This extension of the Cox  
4716 model allows direct estimation of the hazard rate associated with any transition  
4717 adjusted for previous history and baseline characteristics. Within MSM, we may carry  
4718 out a competing risks analysis to assess the effect of cancer deaths.  
4719

4720 In addition, a mixed effects model for repeated measures may be used to test whether:  
4721



4722  
4723

1) SBP increases/decreases over time among participants receiving chlorthalidone, 2)  
SBP increases/decreases over time among participants receiving hydrochlorothiazide,

4724  
4725  
4726

and 3) SBP is statistically significant different between study arms. The model will allow for irregular time intervals and a random effect will be included for both intercept and linear time.

## 4. Sample Size and Power

The annual primary outcome occurrence rate is projected to be 3% (578 events over 4.5 years) in the hydrochlorothiazide arm. With the goal of enrolling 13,500 patients (6,750 in each study arm for an overall type-I error of 5%), the two-sided test will have a 90% power to detect a 17.5% reduction in CV events among participants receiving chlorthalidone. Thus, this study will have a 90% power to detect a hazard ratio of less than 0.82 or greater than 1.22 in the chlorthalidone arm. However, if the annual occurrence rate is between 2% and 2.5% (rather than the posited 3%), the study will have a power of 75% to 84%.

### 4.1 Interim Analysis

This study will have one interim analysis, which will be performed when the 500<sup>th</sup> primary outcome event occurs (approximately 3.5 years after initiation of enrollment). Assuming a uniform rate of enrollment over time, the first patient entered will potentially have 3.5 years of follow-up and the last patient entered will potentially have 0.5 years of follow-up. Thus, we will have an average follow-up time of approximately 2 years on 13,500 subjects.

Using the O'Brien Fleming procedure, this interim analysis will have a type I error of 0.1%, which negligibly decreases the overall type I error and has virtually no effect on the power to show that chlorthalidone is different from hydrochlorothiazide. Given the potential inflation factor, the increase in sample size of 1.001 will result in 14 more subjects per arm. We will confer with the Data Monitoring Committee (DMC) members and the program leadership for potential stopping guidelines based on findings from the interim analysis.

### 4.2 Futility Analysis

If requested by the DMC, a futility analysis that includes conditional probability estimation will be conducted to determine the probability of observing a significant result assuming the distribution of future event rates from additional data from the second half of the study follow three scenarios. These scenarios are:

- 1) No-change - future event rates are the same as the currently observed event rates,
- 2) Expected - future event rates are as proposed in the protocol, and
- 3) Extreme - all new events at the currently observed event rate are in the control group.

4764 **5. General Considerations**

4765  
4766 **5.1 Definition of Intention to Treat Sample**

4767 All consented and randomized subjects will be accounted for and reported in the  
4768 CONSORT diagram. However, only those consented subjects for whom a randomized  
4769 drug order is entered will be considered as ITT subjects and included in the DMC reports  
4770 and primary efficacy analysis. An analytic sample data file consisting of only the ITT  
4771 subjects will be created and maintained throughout the study period.

4772  
4773  
4774 **5.2 Definition of Per-Protocol Sample**

4775 Participants categorized as protocol compliant will make up the per-protocol subset.  
4776 The overall compliance to the randomly assigned medication will be measured over the  
4777 entire follow-up period using MPR and ADD defined as follows:

4778  
4779 
$$MPR = \frac{\text{Days of chlorthalidone or hydrochlorothiazide supply}}{\text{between the date of randomization and the study end}}$$
  
4780  
4781 
$$\text{date}$$
  
4782 
$$\text{(Total number of days between the first and last refill date)}$$
  
4783 
$$+ \text{days of supply from the last refill}$$

4784  
4785 
$$4788 \text{ Total cumulative dose of chlorthalidone or hydrochlorothiazide}$$
  
4786 
$$4789 \text{ ADD} = \frac{\text{available days of supply}}{\text{-----}}$$

4790  
4791  
4792 **5.3 Missing and Miscoded Data**

4793 A related issue is the possibility that patients who suffer a cardiac or non-cardiac event  
4794 during the study will have the wrong ICD10 code assigned despite review of the  
4795 electronic patient record by cardiologists in our study. If this appears to be a major  
4796 issue we will apply Carroll Ruppert and Stefanski's methods as implemented in the  
4797 r\_langauge package DECON (2013). While this will not correct any errors it will increase  
4798 the standard errors and thereby assess the robustness of our conclusions.

4799  
4800 Changes in medication may also prove to be a major issue of missing data. Subjects in  
4801 this study will not have frequent clinic visits wherein our staff asks them about their  
4802 current medications. Instead we will passively detect changes by review of electronic  
4803 charts including pharmacy data. A systematic change in medication, if not detected,

4804  
4805  
4806

would bias study results. Thus, we will intensively review electronic data for any evidence of such changes. This vigilance is more a matter of study protocol than statistical adjustment.

4807 **5.4 Baseline Characteristics**

4808 With the use of all available data stored in the CDW, baseline measurements will be  
4809 recorded as the closest date before randomization. The baseline measurement will be  
4810 evaluated among the entire study cohort, between study arms, and stratified by  
4811 enrollment sites. The number of observations, mean, median, standard deviation,  
4812 minimum, and maximum will be calculated for continuous variables. The categorical  
4813 results will be reported as frequencies and percentages.

4814  
4815 Distribution of continuous variables and proportions of categorical variables will be  
4816 tabulated by intervention group, and t-test and chi-square tests will be performed to  
4817 evaluate if these variables are balanced across the two intervention groups.

4818  
4819 **5.4.1 Demographics**

4820 Baseline demographics including age, sex, race, ethnicity, marital status, military service,  
4821 height, weight, and BMI will be determined before the start of the study intervention.

4822  
4823 **5.4.2 Clinical factors**

4824 Critical clinical factors such as medical history, comorbidities, medication history, vital  
4825 signs, and key laboratory values will also be extracted.

4826  
4827  
4828 **5.5 Safety Evaluation and Reporting**

4829 The CSPCC staff will collect safety data from the medical record from the time of  
4830 consent through the end of the study period. If the subject withdraws from the study  
4831 prior to study end, collection of safety data will cease on the date of withdrawal.

4832  
4833 Pre-defined safety events of interest will be identified through data extraction from the  
4834 VA CDW and CMS database. In brief, participants' health care providers will identify,  
4835 monitor, and treat (as necessary) adverse events that occur during the course of the  
4836 study. Informatics staff at the MAVERIC CSPCC will extract EMR data routinely with pre-  
4837 defined algorithms including, but not limited to, International Classification of Disease  
4838 (ICD) 10 codes, Current Procedure Terminology (CPT) codes, medication names, and  
4839 laboratory test name with critical values. In addition to data culled from the EMR, the  
4840 trial will allow for spontaneous reporting of events by study participants. There are no  
4841 unanticipated safety events for this study. However, participants will be given a study-  
4842 specific information sheet with relevant contact information for communicating safety  
4843 concerns with the study team.

4844  
4845 All safety data will be reported with aggregated data tables detailing the frequencies of  
4846 these events by treatment arms. The expected adverse events will be reported to in  
4847 the DMC report as secondary and tertiary outcomes.

4848  
4849  
4850  
4851  
4852

## **5.4 Outcome Adjudication**

In cases where the outcome diagnosis is not clear based on the electronic adjudication, we will resort to manual adjudication to determine the validity of the diagnosis. Please refer to the study protocol for more details regarding the process of outcome adjudication.

4853 **6. Data Monitoring Committee Report**

4854 Data and study progress will be monitored by the study executive committee and by the  
4855 DMC. The DMC will review the study progress and safety semi-annually with additional  
4856 meetings and communications as needed.

4857  
4858 **6.1 Analytic Sample for DMC Report**

4860 All subjects randomized more than four weeks prior to the DMC meeting date will be  
4861 included in the analytic cohort for the upcoming DMC report.

4862  
4863 **6.2 Algorithm**

4865 Shell tables with annotated algorithms for creating aggregated tables in the DMC report  
4866 are kept securely on the CSP597 SharePoint site and/or study data storage network.

4867 Only authorized study personnel will have access to the secured SharePoint site/data  
4868 storage network.

4869  
4870 **6.3 Outline of DMC Report**

4872 The DMC report is divided into four sections to cover subject disposition, baseline &  
4873 follow-up Measures, outcome measures, and safety events. Following is the list of  
4874 tables/figures to be included within each of these sections. Revision to this list, if any,  
4875 will be discussed at the first DMC meeting.

4876 **6.3.1 Section A: Subject Disposition**

4877 Table A1. Consort Diagram for CSP597

4878 Table A2. Enrollment by Sites

4880 Table A3. Protocol Deviation

4881  
4882 **6.3.2 Section B: Baseline and Follow-Up Measures**

4883 Table B1. Baseline information

4884 Table B2. Medical History

4886 Table B3. Compliance to study medication

4887 Figure B4. Current prescription status of study medication

4888 Table BS. Systolic blood pressure and other use of antihypertensive Agents



4889 **6.3.3 Section C: Outcome Measures**

4890 Table CI. Occurrence of Study Outcomes

4891

4892

4893 **6.3.4 Section D: Safety Assessment**

4894 Table D1. Expected Safety Events

4895 Table D2. List of Unanticipated Serious Adverse Events

4896