# CSP597: Diuretic Comparison Project (DCP)

# Statistical Analysis Plan (SAP)

# V1.1

October 27, 2022

NCT02185417

| MAVERIC Study Specific Documents | DATE OF ISSUE | DOCUMENT DESCRIPTION |
|---|---|---|
| | 10/27/2022 | This document describes the statistical analysis plan for the CSP597. |
| **AUTHORS:** Robert Lew, PhD<br>Sarah Leatherman, PhD<br>Cynthia Hau, MPH | | **SUBITTED BY:**<br>CSP597 Biostatistician |

**DOCUMENTS/ RECORD HISTORY:**

| DATE | VERSION | RECORD HISTORY |
|---|---|---|
| 12/14/2016 | Initial Version for review at DMC meeting | |
| 8/29/2017 | Version 1.0 | Finalized comments generated after DMC meeting |
| 10/17/2022 | Version 1.1 | Minor modification to calculation of medication possession ratio and average daily dose per discussion with CSP597 study committees on 9/8/2022<br><br>Added competing risks analysis for secondary and safety outcomes<br><br>Minor revision to the description of study overview to match language with study protocol |

**AUTHORIZATION SIGNATURE**

| NAME | FUNCTION TITLE | SIGNATURE | DATE |
|---|---|---|---|
| **Robert Lew, PhD** | **Biostatistician** | ROBERT LEW Digitally signed by ROBERT LEW Date: 2022.10.27 12:33:34 -04'00' | |

# Table of Contents

# Abbreviations

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

# 1. Introduction

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

## 1.1 Overview of the Study Design and Objectives

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

This study aims to enroll 13,500 patients (up to 13,700 patients) over 3 years. Based on the feasibility analysis, we anticipate this can be accomplished by randomizing an average of 270 patients from 50 Veterans Affairs (VA) medical centers. The participants will be randomized with equal probability into one of the treatment arms. Based on time of enrollment, participants can be followed for a maximum of 4.5 years. Assuming a uniform rate of enrollment over time (90 patients per medical center each year), the average follow-up time will be approximately 3 years among all participants.

# 2. Investigational Plan

## 2.1 Description of the Study Population

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

### 2.1.1 Inclusion Criteria

Patients who meet the following criteria are considered eligible:

I. Over 65 years of age

II. Receiving hydrochlorothiazide from the VA pharmacy at a daily dose of 25 or 50 mg

III. Have a most recent systolic blood pressure (SBP) ≥120 mmHg, with no SBP <120 mmHg recorded in CPRS over the past 90 days

### 2.1.2 Exclusion Criteria

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

I. Impaired decision-making capacity rendering the patient unable to provide informed consent. (Indicated in medical chart or determined by the primary care provider (PCP))

II. Death expected within 6 months (inferred by PCP permission to randomize)

III. Potassium <3.1 or <3.5 (if on digoxin) meq/L over the past 90 days

IV. Sodium <130 meq/L over the past 90 days

V. Enrolled in Medicare Part C (extracted from administrative data or obtained from patients through consent phone call)

## 2.2 Description of the Intervention Strategy

### 2.2.1 Randomization

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

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

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

### 2.2.2 Study Intervention

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

### 2.2.3 Follow-Up Assessment

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

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

# 3. Statistical Methods

## 3.1 Primary Data Analysis

### 3.1.1 Primary Objective

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

### 3.1.2 Primary Endpoint

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

### 3.1.3 Primary Hypothesis

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

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

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

In theory, if the primary events occurred as projected, the relative percent change will be 17.5% ((578 – 477)/ 578 *100%). The hazard ratio (chlorthalidone hazard rate/ hydrochlorothiazide hazard rate) will be approximately 0.81, which will be midway between the odds ratio of 0.80 (11.1(100 –13.5)/13.5(100 – 11.1)) and the risk ratio of 0.82 (11.1/13.5).

### 3.1.4 Statistical Methods for Primary Data Analysis

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

proportional hazards assumption. The final study results will present both unadjusted and adjusted hazard rates and corresponding hazard ratios with 95% confidence intervals.

## 3.2 Secondary Data Analysis

### 3.2.1 Secondary Objectives

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

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

I. gender
II. age (dichotomized at the median)
III. baseline SBP (dichotomized at the median)
IV. history of MI or stroke
V. black race vs. not
VI. diabetes vs. not
VII. eGFR <60 mL/min/1.73m$^2$
VIII. good compliance (medication possession ratio ≥ 80%) with hydrochlorothiazide over the year before randomization

### 3.2.2 Secondary Endpoints

Individual components of the primary outcome will be examined:

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

Treatment effects will be evaluated for additional outcomes below:

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

III. "possible vascular deaths" defined as all deaths caused by vascular diseases, diabetes, external causes, and unknown causes

IV. the composite outcome substituting "possible vascular deaths" for non-cancer deaths

V. any revascularization of an artery

VI. erectile dysfunction (ED), defined as first prescription of PDE5 inhibitor or referral for ED

### 3.2.3 Statistical Methods for Secondary Data Analyses

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

## 3.3 Tertiary Data Analysis

### 3.3.1 Tertiary Objective

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

### 3.3.2 Tertiary Endpoints

The expected adverse events of this study are:

I. hospitalization for primary diagnosis of hypokalemia, hyponatremia, or renal failure

II. renal failure, defined as dialysis, vascular access for dialysis, or renal transplant

III. other recorded hypokalemia (<3.5 meq/L) or hyponatremia (<130 meq/L)

IV. new diabetes, defined as first use of medication for diabetes

V. acute gout episodes

VI. new allergic reaction to thiazide-type diuretics

### 3.3.3 Statistical Methods for Tertiary Data Analysis

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

## 3.4 Exploratory Data Analysis

### 3.4.1 Exploratory Objective

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

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

### 3.4.2 Statistical Methods for Exploratory Data Analysis

The per-protocol analysis will be performed following statistical procedures used in the ITT cohort. Other exploratory analyses may be conducted using a generalized estimating equation (GEE) to account for varying time intervals and treatment interruptions, with potential modeling of time-dependent effects of protocol deviations. We may also explore censoring patterns such as models that assume not missing-at-random using a Bayesian approach to the pattern mixture model (Missing Data in Longitudinal Studies Chapman and Hall Boca Raton 2008). In addition, a change in medication may alter the subsequent risk of a cardiovascular event. Therefore, we may add time-dependent covariates to the Cox model, such as binary indicators of medication switching (from chlorthalidone to hydrochlorothiazide, or vice versa). To directly estimate subsequent risk, we may use a multistage model (MSM) to assess the hazard rate of a major cardiovascular event after a switch. 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 may carry out a competing risks analysis to assess the effect of cancer deaths.

In addition, a mixed effects model for repeated measures may be used to test whether: 1) SBP increases/decreases over time among participants receiving chlorthalidone, 2) SBP increases/decreases over time among participants receiving hydrochlorothiazide,

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$^{th}$ 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.

# 5. General Considerations

## 5.1 Definition of Intention to Treat Sample

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

## 5.2 Definition of Per-Protocol Sample

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

$$MPR = \frac{Days\ of\ chlorthalidone\ or\ hydrochlorothiazide\ supply\ between\ the\ date\ of\ randomization\ and\ the\ study\ end\ date}{Days\ between\ randomization\ and\ patient's\ study\ end\ date}$$

$$Overall\ ADD = \frac{Total\ cumulative\ dose\ of\ chlorthalidone\ or\ hydrochlorothiazide}{Days\ between\ randomization\ and\ patient's\ study\ end\ date}$$

$$ADD\ of\ prescribed\ drug = \frac{Total\ cumulative\ dose\ of\ chlorthalidone\ or\ hydrochlorothiazide}{available\ days\ of\ supply}$$

## 5.3 Missing and Miscoded Data

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

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

## 5.4 Baseline Characteristics

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

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

### 5.4.1 Demographics

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

### 5.4.2 Clinical factors

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

## 5.5 Safety Evaluation and Reporting

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

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

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

## 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.

# 6. Data Monitoring Committee Report

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

## 6.1 Analytic Sample for DMC Report

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

## 6.2 Algorithm

Shell tables with annotated algorithms for creating aggregated tables in the DMC report are kept securely on the CSP597 SharePoint site and/or study data storage network. Only authorized study personnel will have access to the secured SharePoint site/data storage network.

## 6.3 Outline of DMC Report

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

### 6.3.1 Section A: Subject Disposition

Table A1. Consort Diagram for CSP 597

Table A2. Enrollment by Sites

Table A3. Protocol Deviation

### 6.3.2 Section B: Baseline and Follow-Up Measures

Table B1. Baseline information

Table B2. Medical History

Table B3. Compliance to study medication

Figure B4. Current prescription status of study medication

Table B5. Systolic blood pressure and other use of antihypertensive Agents

### 6.3.3 Section C: Outcome Measures

Table C1. Occurrence of Study Outcomes

### 6.3.4 Section D: Safety Assessment

Table D1. Expected Safety Events

Table D2. List of Unanticipated Serious Adverse Events