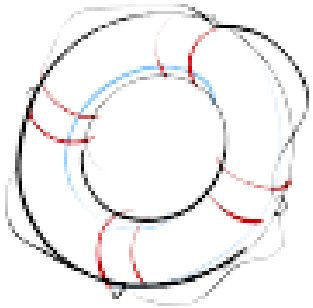
VA COOPERATIVE STUDY # 578 PREVENTION OF SERIOUS ADVERSE EVENTS FOLLOWING ANGIOGRAPHY (PRESERVE)



Statistical Analysis Plan v2.0

Effective 08/26/2016

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A DEPARTMENT OF VETERANS AFFAIRS COOPERATIVE STUDY

MAVERIC Study Specific Documents	DATE OF ISSUE	DOCUMENT DESCRIPTION
		This document describes the statistical analysis plan for the CSP578 randomized clinical trial.

AUTHOR: Soe Soe Thwin, MS, PhD **SUBMITTED BY:** Soe Soe Thwin, MS, PhD

DOCUMENT/RECORD HISTORY:

DATE	VERSION	RECORD HISTORY
09/13/2013	1.0	Initial Version
08/26/2016	2.0	Revised Version (Summary of revisions included)

AUTHORIZATION SIGNATURES

NAME	FUNCTION TITLE	SIGNATURE	DATE
Steven Weisbord MD, MSc	Study Chairman		8/30/16
Paul Palevsky, MD	Study Chairman		8/30/2016
James Kaufman, MD, MPH	Study Director		
Soe Soe Thwin, MS, PhD	Study Biostatistician		
Ryan Ferguson , MPH, ScD	Acting Center Director		

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James Kaufman, MD, MPH	Study Director	James Kaufman	8/29/16
Soe Soe Thwin, MS, PhD	Study Biostatistician	Soe Soe Thwin	8/29/2016
Ryan Ferguson , MPH, ScD	Acting Center Director 9/6/16	Ryan Ferguson	9-6-16

List of Revisions

(1) Section 3.4 - Algorithm to compute adherence for oral medication

% Adherence for oral medication is based on total #capsules only, and therefore removed section using #dose

(2) Section 3.4 - Algorithm to compute adherence for IV medication

% Adherence will be based on recommended ranges of
Pre - Volume of 3 to 12 ml/kg
Intra- Rate of 1 to 1.5 ml/kg/hour
Post- Volume of 6-12 ml/kg

% Adherence will be computed as a range from % of lower limit to % of upper limit.

Per protocol subject if 80-120% for pre- procedure and intra-procedure at minimum.

Pre-Procedure		Intra-procedure		Post-procedure	
Volume (mL/kg)	% Dose Given	Rate (mL/kg/Hr)	% Dose Given	Volume (ml/kg)	% Dose Given
1	33.3%	0.5		1	16.7%
2	66.7%	0.6		2	33.3%
3	100%	0.7		3	50%
4	100%	0.8		4	66.7%
5	100%	0.9		5	83.3%
6	100%	1.0	100%	6	100%
7	100%	1.1	100%	7	100%
8	100%	1.2	100%	8	100%
9	100%	1.3	100%	9	100%
10	100%	1.4	100%	10	100%
11	100%	1.5	100%	11	100%

12	100%	1.6	107%	12	100%
13	108.3%	1.7		13	108.3%
14	116.7%	1.8		14	116.7%
15	125%	1.9		15	125%

(3) Day-90 blood sample now allowed to be collected within Angio+90+6month window.

(4) Day-90 blood sample not necessary if pt is already on dialysis at day-90.

(5) DMC Shell tables are updated often, and therefore reside on Sharepoint independent of the Statistical Analysis Plan, link provided.

Abbreviations

CRF	Case Report Forms
SAP	Statistical Analysis Plan
CSP	Cooperative Studies Programs
Bicarb	IV isotonic sodium bicarbonate
Saline	IV isotonic saline
NAC	N-acetylcysteine
VHA	Veterans Health Administration
MAKE-D	major adverse kidney events and death
CIAKI	contrast induced acute kidney injury
ESRD	end stage renal disease
CKD	chronic kidney disease
eGFR	estimated glomerular filtration rate
SCr	Serum Creatinine
DMC	Data Monitoring Committee
CDW	VHA Corporate Data Warehouse

1. Introduction

This document outlines the statistical methods for the analysis of data collected in the Department of Veterans Affairs Cooperative Studies Programs (CSP) study #578 entitled "Prevention of Serious Adverse Events Following Angiography". The purpose of this document is to provide guidelines from which the analysis will proceed. Deviations from these guidelines will be documented and filed electronically in the study central file Sharepoint site.

The following documents were used in preparation of this statistical analysis plan (SAP):

- Clinical Study Protocol CSP #578
- Case Report Forms (CRF) from above entitled Protocol
- Global CSP SOP 2.9: "Developing and Conducting Statistical Analyses
- Local Work Instruction WI 201Statistical Analysis Plan and Biostatistical Research Data Processing Plan Creation and Amendment
- Local Job Aid No. 5: Guide to Writing Statistical Analysis Plans

2. Overview of the Study Design and Objectives

This is a double-blind, randomized clinical trial that will use a 2 x 2 factorial design to assess the effectiveness of IV isotonic Sodium Bicarbonate (Bicarb) compared to IV isotonic saline (Saline) and the efficacy of orally administered N-acetylcysteine (NAC) compared to placebo for the prevention of serious, adverse, patient-centered outcomes in high-risk patients undergoing coronary or non-coronary angiography.

A total of 7680 subjects recruited from the 33 Veterans Health Administration (VHA) centers are expected to be randomized equally to each of the 4 groups as shown in Table 1 below. An additional 1000 subjects are expected to be enrolled in the 12 non-VHA sites in Australia to augment the data collected in the US.

Table 1. Intervention Groups

	Bicarb	Saline
NAC	Group1: NAC+Bicarb	Group2: NAC+Saline
Placebo	Group3:Placebo+Bicarb	Group4:Placebo+Saline

Compare NAC vs. Placebo (Groups 1+2 vs. 3+4)

Compare Bicarb vs. Saline (Groups 1+3 vs. 2+4)

The primary objective:

As the primary objective, the trial will test two hypotheses:

(#1) IV isotonic bicarbonate is more effective than saline, and

(#2) NAC is more effective than placebo

in prevention of major adverse kidney events (need for acute dialysis or 50% increase in serum creatinine at 90 days after angiography) and death (MAKE-D) following coronary and non-coronary angiography. This will be accomplished by comparing the incidence of MAKE-D in groups 1 and 3 combined to groups 2 and 4 combined for hypothesis (#1), and by comparing groups 1 and 2 combined to groups 3 and 4 combined for hypothesis (#2). See **3.5.1**.

Secondary Objective:

The trial will also evaluate the effectiveness of the study interventions for the prevention of 5 individual secondary endpoints (section **3.5.2**) by comparing the treatment groups as in the primary objective. The secondary endpoints are:

1)contrast induced acute kidney injury (CIAKI) at day5 after angiography

2)death

3)major adverse kidney endpoints (MAKE)

4)hospitalization with acute coronary syndrome, heart failure, or cerebrovascular accident

5)all-cause hospitalization.

Tertiary Objective:

The trial will explore the effectiveness of the study interventions for the prevention of the following outcomes (see **3.5.3**), within one year following coronary or non-coronary angiography by comparing the treatment groups as in the primary objective. The tertiary endpoints are:

1) development of end stage renal disease (ESRD), and
2) death.

3. Investigational Plan

3.1. Description of the Study Population

Inclusion Criteria: Patients are eligible if, at the time of index angiography, they have underlying chronic kidney disease (CKD) with estimated glomerular filtration rate (eGFR) values calculated using the 4-variable Modification of Diet in Renal Disease (MDRD) formula as described on page 33 of the protocol:

(1) eGFR <60 ml/min/1.73 m2 and a diagnosis of diabetes mellitus, or
(2) eGFR <45 ml/min/1.73 m2 regardless of whether or not they have diabetes mellitus.

Table 2. Exclusion Criteria. Patients are excluded if they satisfy any of these 13 conditions.

(1) <18 years of age		(8) have de-compensated heart failure
(2) pregnant		(9) having an emergent angiogram
(3) unwilling to comply with 4 and 90 day outcome assessment		(10) received iodinated contrast within past 7 days
(4) participating in a clinical trial		(11) received NAC within past 48 hours
(5) received dialysis		(12) have known allergy to NAC
(6) have stage 5 CKD		(13) have known allergy to iodinated contrast
(7) have unstable baseline Serum Creatinine (SCr)		

3.2. Description of the Intervention Strategy

Eligible patients who consent to participate will be randomized prior to angiography to receive one of 4 regimens: 1) NAC and Bicarb, 2) NAC and Saline, 3) Placebo and Bicarb, or 4)Placebo and Saline. Study drug administration schedule is outlined in Table 3.

Table 3. Study Drug Administration Schedule.

Time	IV	ORAL
Immediately prior to the angiographic procedure	3 to12 ml/kg of the IV isotonic study crystalloid solution (Bicarb or saline) infused over a minimum of 1 hour and maximum of 12 hours at an infusion rate of not less than 1 mL/kg per hour and not more than 3 mL/kg per hour	NAC or Placebo in an oral dose of 1200 mg (4 capsules) administered within 1 hour preceding the procedure
During the procedure	IV isotonic study crystalloid solution infused at a rate of 1 to 1.5mL/kg per hour	None
Following the procedure	6 to 12 mL/kg of the IV isotonic study crystalloid solution infused over a minimum of 4 hours and maximum of 12 hours at an infusion rate of not less than 1 mL/kg per hour and not more than 1.5 mL/kg per hour	NAC or Placebo in an oral dose of 1200 mg (4 capsules) administered within 1 hour following the procedure
Day 1 through 4 post procedure	None	NAC or Placebo administered in an oral dose of 1200 mg (4 capsules) twice daily

3.3. Definition of Intention to Treat Sample

All consented and randomized subjects will be accounted for and reported in the CONSORT diagram for the study, however, only those randomized subjects who initiated either IV or oral intervention (i.e., did not drop out or withdraw prior to start of the allocated intervention), will be considered as an intention to treat (ITT) subject to be included in the Data Monitoring Committee (DMC) reports and primary efficacy analysis.

An analytic sample file consisting of only the “ITT” subjects as defined above will be created and maintained throughout the study. This file will be called the “CSP578_ITT” file.

3.4. Definition of per-Protocol sample

Adherence to allocated intervention according to the protocol, as outlined in Table 3, will be ascertained for randomized subjects for identification of “per-Protocol” sub-group. Percent adherence will be determined for IV fluid and oral interventions separately.

Oral medication adherence will be computed by capsule count only as follows:

$$\% \text{ adherence} = \frac{Total\#capsulesTaken}{40} \times 100\%$$

Those who had (>=80% and <=120%) adherence by the capsule count will be considered as adherent to the protocol.

IV fluid adherence will be based on the recommended ranges for each period (pre-procedure, intra-procedure, and post-procedure) described in Table 3.

Pre – procedure: Volume of 3 to 12 ml/kg
Intra – procedure: Rate of 1 to 1.5 ml/kg/hour
Post – procedure: Volume of 6 to12 ml/kg

% adherence will be computed as a range from % of lower limit to % of upper limit outlined in Table 4.

Table 4. IV fluid adherence table

Pre-Procedure		Intra-procedure		Post-procedure	
Volume (mL/kg)	% Dose Given	Rate (mL/kg/Hr)	% Dose Given	Volume (ml/kg)	% Dose Given
1	33.3%	0.5	50%	1	16.7%
2	66.7%	0.6	60%	2	33.3%
3	100%	0.7	70%	3	50%
4	100%	0.8	80%	4	66.7%
5	100%	0.9	90%	5	83.3%
6	100%	1.0	100%	6	100%
7	100%	1.1	100%	7	100%
8	100%	1.2	100%	8	100%
9	100%	1.3	100%	9	100%
10	100%	1.4	100%	10	100%
11	100%	1.5	100%	11	100%

12	100%	1.6	106.7%	12	100%
13	108.3%	1.7	113.3%	13	108.3%
14	116.7%	1.8	120%	14	116.7%
15	125%	1.9	126.7%	15	125%

Those who had (>=80% and <=120%) adherence for, at minimum, the pre-procedure and intra procedure periods will be considered as adherent to the protocol.

Those who are adherent to the protocol for both oral study medication and IV study fluid will be included in the “per-Protocol” analytic sub-sample.

3.5. Description of the Efficacy Endpoints

3.5.1. Primary Endpoints

The primary endpoint for the study is the composite end-point assessed at 90 days post index angiographic procedure and is comprised of the 3 events described below. Those subjects with at least one of these 3 events will be considered to have the primary study endpoint.

(1) Death from all causes to be verified by medical record and/or vital status registry documentation such as the VA Beneficiary Identification and Records Locator System, the National Center for Health Statistics National Death Index database, the Social Security Administration’s Death Master File.

(2) Acute dialysis defined as the initiation of any modality of renal replacement therapy, which includes intermittent hemodialysis, peritoneal dialysis, continuous renal replacement therapy, or prolonged intermittent renal replacement therapy.

(3) Persistent decline in kidney function defined as ≥50% increase in SCr at 90 days post procedure relative to baseline SCr collected pre-Angiography procedure, and derived as follows.

(SCrday90 / Scr pre-procedure)*100% ≥150%

Both the initial 90 day specimen and the confirmatory sample processed at the Central Lab must establish a ≥50% increase in SCr to qualify as an endpoint event.

Please note:

1. **90 day blood sample is allowed to be collected within 6month window starting 90 days post index angiographic procedure.**
2. **90 day blood sample is not necessary if pt is already on dialysis at day 90 post index angiographic procedure.**

3.5.2. Secondary Endpoints

The secondary endpoints except for CIAKI for the study are assessed at 90 days post index procedure and they include the following individual outcomes:

(1) CIAKI defined by an increase in SCr of ≥0.5 mg/dL and/or ≥25% increase at 96 hours following contrast administration, derived as follows.

(SCr96Hours / Scr pre-procedure)*100% ≥125%

(2) Death from all causes to be verified by medical record and/or vital status registry documentation such as the VA Beneficiary Identification and Records Locator System, the National Center for Health Statistics National Death Index database, the Social Security Administration's Death master File.

(3) MAKE defined by (a) initiation of any modality of renal replacement therapy, which include intermittent hemodialysis, peritoneal dialysis, continuous renal replacement therapy, or prolonged intermittent renal replacement therapy, or (b) persistent decline in kidney function as defined in **3.5.1**.

(4) Hospitalization with acute coronary syndrome, heart failure, or cerebrovascular accident within 90 days following the index angiographic procedure. These outcomes will be defined as a primary or secondary discharge diagnosis of acute coronary syndrome (i.e., STEMI, NSTEMI, unstable angina), heart failure, or cerebrovascular accident documented in the VA electronic medical record or the hospital discharge summary obtained for non-VA hospitalizations. Note: This will include the occurrence of any of these events during the index hospitalization.

(5) All-cause re-hospitalization within 90 days of the index angiographic procedure assessed as episodes of re-hospitalization, days of hospitalization (inclusive of the index hospitalization), and hospital free days (alive and not in the hospital) through day 90.

3.5.3. Tertiary Endpoints

The tertiary endpoints for the study are assessed at one year post index procedure. The following endpoints will be obtained from study data and from registry documentation specified below.

1) Development of ESRD defined by the requirement for chronic dialysis for >3 months based on documentation in the United States Renal Data System database,

2) Death from all causes to be verified by medical record and/or vital status registry documentation such as the VA Beneficiary Identification and Records Locator System, the National Center for Health Statistics National Death Index database, the Social Security Administration's Death Master File.

3.6. Description of Baseline Data

Demographic details (e.g., age, sex, race, ethnicity, marital status, military service), medical history (e.g., co-morbidities, smoking history), and baseline labs will be evaluated overall, by intervention group, by country (Australia or USA), and by enrollment site.

3.7. Description of Procedure Related Data

Angiographic procedure related details (e.g., type of procedure, inpatient/outpatient status, type and volume of dye administered), study interventions received prior to and during procedure, and information on additional therapy, if any, required during the procedure will be evaluated overall and by intervention group.

3.8. Description of Follow-up Assessment Data

Details on additional angiography procedure, therapies other than angiography, if any, clinical events such as hospital re-admissions, initiation of dialysis, and death within 90 days post index procedure will be evaluated overall and by intervention group.

3.9. Safety Data

The safety information to be collected for this study include the description of the event, distinction between serious and non-serious adverse event, severity and expectedness of the event, relatedness to the study intervention, and outcome of the event. In addition, data on all events will be classified using the Medical Dictionary for Regulatory Activities (MedDRA) (Version 9.0) coding dictionary.

Safety data will be collected for all consented subjects from the date the consent was signed up to 35 days post index angiography procedure for non-serious adverse events, and up to 90 days post index angiography procedure for serious adverse events. If the subject terminates from the study prior to 90 days post index procedure, collection of safety data will cease on termination date.

For reporting to the DMC and inclusion in the final report safety data will be aggregated for the ITT sample only as described in **3.3**. Data will be summarized as follows.

- Frequency and percentages of all non-serious and serious adverse events overall and by intervention group
- Frequency and percentages of all unique subjects with non-serious and serious adverse events overall and by intervention group
- Rates of non-serious and serious adverse events overall, by intervention group, and by center, calculated as # events/ person-time in years

- Tabulation of event type, MEDRA classification, severity, expectedness, relatedness and outcome of all events overall and by intervention group
- Overall hospitalization, dialysis, and mortality rate at 90 days and 1year overall and by intervention group

4. Sample Size and Power

With a total sample of 7680 subjects equally allocated to each of 4 treatment arms, CSP 587 is powered to detect at least a 25% reduction in the 90-day incidence of MAKE-D for each intervention. Expected event rates used in sample size estimation to achieve 90% statistical power for hypothesis testing are given in Table 4 below. Justification for selecting these rates to estimate sample size and power are provided in the protocol.

Table 4. Expected 90-day Incidence of MAKE-D Endpoint

	Bicarbonate	Saline	
NAC	5.59%	7.46%	6.52%
Placebo	7.46%	9.95%	8.70%
	6.52%	8.70%	

Overall event rate 7.6%

These estimations assume no interaction between the two active interventions, are adjusted for an O'Brien-Fleming stopping rule with one interim and one final test of hypothesis, and allow for an overall two-sided type I error of 2.5% for each hypothesis being tested. Hence, each of the interim hypothesis for main effect will be tested at p=0.001 level (allowing for 0.1% Type I error), and each of the final hypothesis for main effect will be tested at p=0.024 level (allowing for 2.4% Type I error).

If an attenuation of effect is present due to interaction between Sodium Bicarbonate and NAC, adjustment to the statistical power for 10% to 50% attenuation are given as follows.

Table 5. Statistical Power in the Presence of Effect Attenuation.

% attenuation from interaction between Bicarbonate & NAC	Rate in Bicarbonate/NAC	Rate in treatment (T) group	Rate in control (C) group	% reduction (C-T)/C	Power
No interaction	5.60 %	6.52%	8.7%	25%	90%
10% attenuation	5.78%	6.62%	8.7%	23.9%	87.5%
20% attenuation	5.97%	6.71%	8.7%	22.9%	84%

30% attenuation	6.15%	6.81%	8.7%	21.7%	79.3%
50% attenuation	6.53%	6.99%	8.7%	19.7%	69.4%

Sample recruitment and subsequent event rates will be summarized and presented to the DMC bi-annually as outlined in section **7** below. These reports will be used for monitoring the progress of the study and any modification to the recruitment schedule or the statistical analysis plan will be at the recommendation of the DMC.

5. Statistical Methods

5.1. Handling of Missing Data in Analysis

Up to 3% of subjects have been estimated to drop out prior to end of follow-up before 90 days. Distribution of subjects lost to follow-up and missing data on key variables across the treatment groups will be monitored throughout the study.

Missing endpoint data will not be imputed. All those with missing endpoint data either due to attrition or active withdrawal of consent will be excluded from primary analysis. Those who completed 90 days of follow-up and have initial 90 day blood-draw demonstrating a $\geq$50% increase in serum creatinine but are missing the confirmatory blood draw will not be included in the primary analysis as having met the primary endpoint, however, they will be included in the sensitivity analysis as having met this endpoint data. See section **5.3.5**.

5.2. Univariate and Bivariate Distributions of Baseline, Procedure Related, Safety and Follow-up data

- In general, the number of observations, mean, median, standard deviation, minimum, and maximum will be calculated for continuous variables. The number of decimals places will be to plus two decimal places.
- Frequencies and percentages will be calculated for categorical data.
- 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 4 intervention groups.
- Baseline is defined as the randomization visit.

5.3. Primary Efficacy Analysis

Primary efficacy analysis will include the intention to treat sample as defined in **3.3** and further specified in **5.1** above.

The primary hypotheses will be tested by modeling the binary outcome of presence or absence of MAKE-D event within 90 days post angioplasty procedure. All the proposed tests for the primary analysis are tests of superiority and will be set up as two-sided tests, i.e., study intervention can be better or worse than the control.

Our analytic strategy is to use generalized linear model regression, specifically the GENMOD procedure in the SAS statistical package with a logit link, to model the binary outcome data to estimate the odds of a MAKE-D event at 90 days post angioplasty among those allocated to IV isotonic sodium bicarbonate therapy compared to those allocated to IV isotonic saline, and among those allocated to NAC compared to those allocated to Placebo. Sample SAS code is provided in section **6**.

Analytic reports will provide the proportions, the differences among proportions, the odds ratios, and the 95% confidence interval, Wald chi-square p-value, followed by a report of the results.

5.3.1. Testing for Interaction

A multivariable logistic regression model to be fitted includes two binary predictors with an interaction term, and can be expressed as:

$$\text{Log (Odds (MAKE-D))} = \alpha + \beta_1 X_1 + \beta_2 X_2 + \beta_3 X_1X_2 \qquad \text{(Model 1)}$$

Where X_1 is the indicator for IV intervention (1=Bicarb, 0=Saline), X_2 is the indicator variable for oral intervention (1=NAC, 0=Placebo), and X_1X_2 is the interaction of the two interventions (1=Bicarb and NAC, 0=otherwise).

The parameter β_1 will estimate the independent effect of Bicarb compared to Saline, the parameter β_2 will estimate the independent effect of NAC compared to Placebo, and the parameter β_3 will estimate the additional effect of both Bicarb and NAC.

Presence of significant interaction between Bicarb and NAC (either beneficial or detrimental) will be tested as follows.

Null	H_0: $\beta_3 = 0$
Alternative	H_a: $\beta_3 <> 0$

If the Wald Chi-square test has $p > 0.05$, then the null hypothesis for interaction cannot be rejected and we will conclude that there is no evidence of significant modification of effect from receiving both Bicarb and NAC.

If the Wald Chi-square test has $p \leq 0.05$, then the null hypothesis for interaction will be rejected and alternative hypothesis accepted to conclude that a significant modification of

effect exists from receiving both Bicarb and NAC. Primary analysis will proceed as described in section **5.3.3**.

5.3.2. Absence of Interaction

In the event of a non-significant interaction term at p=0.05 level, the regression model will be refitted without the interaction term. This multivariable logistic regression model will include two binary predictors, and can be expressed as:

$$\text{Log (Odds (MAKE-D))} = \alpha + \beta_1 X_1 + \beta_2 X_2 \qquad \text{(Model 2)}$$

Where X_1 is the indicator for IV intervention (1=Bicarb, 0=Saline), and X_2 is the indicator variable for oral intervention (1=NAC, 0=Placebo).

The parameter β_1 will estimate the independent effect of Bicarb compared to Saline, and the parameter β_2 will estimate the independent effect of NAC compared to Placebo.

Efficacy of Bicarb relative to Saline will be tested as follows.

Null	H_0: $\beta_1 = 0$
Alternative	H_a: $\beta_1 <> 0$

If the Wald Chi-square test has $p \leq 0.024$, then the null hypothesis will be rejected and alternative hypothesis accepted. If the 95% Confidence Interval of the Odds Ratio does not include 1 and $\beta_1 < 0$, we can conclude that Bicarb is superior to Saline, after adjusting for NAC and Placebo. Conversely, if the 95% Confidence Interval of the Odds Ratio does not include 1 and $\beta_1 > 0$, we can conclude that Bicarb is not superior to Saline, after adjusting for NAC and Placebo.

Similarly, efficacy of NAC relative to Placebo will be tested as follows.

Null	H_0: $\beta_2 = 0$
Alternative	H_a: $\beta_2 <> 0$

If the Wald Chi-square test has $p \leq 0.024$, then the null hypothesis will be rejected and alternative hypothesis accepted. If the 95% Confidence Interval of the Odds Ratio does not include 1 and $\beta_2 < 0$, we can conclude that NAC is superior to Placebo, after adjusting for Bicarb and Saline. Conversely, if the 95% Confidence Interval of the Odds Ratio does not include 1 and $\beta_2 > 0$, we can conclude that NAC is not superior to Saline, after adjusting for Bicarb and Saline.

5.3.3. Presence of Interaction

In the event of a significant interaction at p=.05 level, a stratified analysis will ensue where logistic models with single binary predictors for different levels of X_1 and X_2 will be refitted as follows

In NAC subgroup:	Log (Odds (MAKE-D)) = $\alpha + \beta_{1a} X_1$	(Model 3)
In Placebo subgroup :	Log (Odds (MAKE-D)) = $\alpha + \beta_{1b} X_1$	(Model 4)
In Bicarb subgroup:	Log (Odds (MAKE-D)) = $\alpha + \beta_{2a} X_2$	(Model 5)
In Saline subgroup:	Log (Odds (MAKE-D)) = $\alpha + \beta_{2b} X_2$	(Model 6)

Where X_1 is the indicator for the IV intervention (1=Bicarb, 0=Saline), and X_2 is the indicator variable for the oral intervention (1=NAC, 0=Placebo).

The parameter β_{1a} will estimate the independent effect of Bicarb compared to Saline among those allocated to NAC, β_{1b} will estimate the independent effect of Bicarb compared to Saline among those allocated to Placebo, β_{2a} will estimate the independent effect of NAC compared to Saline among those allocated to Bicarb, and β_{2b} will estimate the independent effect of NAC compared to Placebo among those allocated to Saline.

The efficacy of Bicarb relative to Saline and NAC relative to Placebo will be tested in each of the 4 subgroups at p=0.048 overall.

Based on the parameter estimates, the magnitude and direction of any interaction will be evaluated.

5.3.4. Evaluating Covariate Effects

To explore the possibility of treatment by covariate effects, we will refit the model with a vector of covariates included in the model, expressed as

$$\text{Log (Odds (MAKE-D))} = \alpha + \beta_1 X_1 + \beta_2 X_2 + r[Z] \qquad \text{(Model 7)}$$

Where, [Z] is the vector of factors indicating disease severity, demographic and anthropomorphic measures, and structural factors such as medical site. Factors identified not to be balanced between the intervention groups in section **5.2** will be evaluated.

Additionally, we will explore the effect of including site as a random effect by extending logistic regression to generalized linear models that treat site as a random effect.

5.3.5. Sensitivity Analysis

We will refit Models 1 and 2 to evaluate the odds of the event of interest at 90 days post angioplasty among those allocated to IV isotonic sodium bicarbonate therapy compared to those allocated to IV isotonic saline, and among those allocated to NAC compared to those allocated to Placebo. The primary analysis will be repeated under 5 different scenarios as follows and the results will be displayed in a Forest plot.

(1) On the first "per-Protocol" sample with 80-120% adherence as defined in **3.4** to evaluate efficacy among those adherent to the protocol. Subjects who are over-adherent (>=120%) or have had a non-protocol administration of study medication, particularly IV sodium bicarbonate, will be excluded.

(2) On the second "per-Protocol" sample with >=80% adherence as defined in **3.4** including those subjects who are over-adherent or have had a non-protocol administration of study medication, particularly IV sodium bicarbonate.

(3) On the "ITT" cohort that includes those with the initial 90-day blood sample but are missing the confirmatory sample.

(4) On the "ITT" cohort assuming all those with missing endpoint data had events before 90 days (the worst case scenario), and

(5) On the "ITT" cohort assuming all those with missing endpoint data had no events before 90 days (the best case scenario)

5.4. Secondary Analysis

For each of the five secondary endpoint events listed in **3.5.2** we will follow the same analytic strategy as the primary analysis described in **5.3,** where the odds of having an outcome will be estimated by modeling the outcome as a binary indicator of presence or absence of an event.

We will derive the Odds Ratios (i.e., the odds of the event of interest at 90 days post angioplasty among those allocated to IV isotonic sodium bicarbonate therapy compared to those allocated to IV isotonic saline, and among those allocated to NAC compared to those allocated to Placebo), and test for statistical significance of these odds ratios at p=0.025 level.

5.5. Tertiary Analysis

Data for this exploratory tertiary objective will be accrued from the US Renal Data System Warehouse, NDI database, SSDI database, and the VHA Corporate Data Warehouse (CDW).

For each of the 2 tertiary endpoint events listed in **3.5.3** we will follow the same analytic strategy as the primary and secondary analyses described in 5**.4** above.

5.6. Interim Analysis

This study is expected to enroll 7680 subjects over a 2.5 years (or 30 month) recruitment period. At 18 months, i.e., after 15 months of recruitment plus 3 months of follow-up, approximately half or 3840 subjects are expected to be enrolled with primary endpoint events occurring in roughly 292 subjects (7.6%). Using the O'Brien-Fleming procedure, we will carry out an interim analysis to determine if either intervention shows a substantial beneficial effect.

We will compare the proportion of subjects with a MAKE-D event among those with and without the use of bicarbonate and among those with and without the use of NAC.

We will follow the same analytic strategy as described in **5.3** for primary analysis**,** where the odds of having an outcome will be estimated by modeling the outcome as a binary indicator of presence or absence of the MAKE-D event.

We will derive the Odds Ratios (i.e., the odds of the event of interest at 90 days post angioplasty among those allocated to IV isotonic sodium bicarbonate therapy compared to those allocated to IV isotonic saline, and among those allocated to NAC compared to those allocated to Placebo), and test for statistical significance of these odds ratios at p=0.001 level, assuming no interaction between the active interventions.

If the Wald Chi-square test has $p \leq 0.001$ for regression coefficient β_1 in Model 2, then the null hypothesis of H_0: $\beta_1 = 0$ will be rejected and alternative hypothesis of H_a: $\beta_1 <> 0$ accepted. If the 95% Confidence Interval of the Odds Ratio does not include 1 and $\beta_1 < 0$, we can conclude that Bicarb is superior to Saline. Conversely, if the 95% Confidence Interval of the Odds Ratio does not include 1 and $\beta_1 > 0$, we can conclude that Bicarb is not superior to Saline.

Similarly, if the Wald Chi-square $p \leq 0.001$ for regression coefficient β_2 in Model 2, then the null hypothesis of H_0: $\beta_2 = 0$ will be rejected and alternative hypothesis H_a: $\beta_2 <> 0$ accepted. If the 95% Confidence Interval of the Odds Ratio does not include 1 and $\beta_2 < 0$, we can conclude that NAC is superior to Placebo. Conversely, if 95% Confidence Interval of the

Odds Ratio does not include 1 and $\beta_2 > 0$, we can conclude that NAC is not superior to Saline.

5.6.1. Futility Analysis

If requested by the DMC, a futility analysis that includes conditional power 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 3 scenarios. These assumptions are:

no-change scenario – future event rates are same as currently observed,
expected scenario – future event rates are as proposed in the protocol, and
extreme scenario – all new events at the currently observed rate are in the control group.

6. Sample SAS Code

```
proc genmod;
class outcome Bicarb NAC;
model outcome = Bicarb  NAC/ error=bin link=logit type3;
make 'parmest' out=parmest;
run;

/*to get estimated odds ratios*/
data parmest;
set parmest;
if df gt 0;
OR=exp(estimate);
low_OR=exp(estimate-1.96*stderr);
hi_OR=exp(estimate+1.96*stderr);
run;

proc print data=parmest label noobs;
title 'Estimated Odds Ratios and 95% CIs';
var parm level1 estimate stderr or low_OR hi_OR;
format estimate stderr OR low_OR hi_OR 6.3;
label
parm='Parameter'
level1='Level'
estimate='Beta estimate'
stderr='Standard Error'
OR='Estimated OR'
low_OR='Lower limit 95% CI'
```

hi_OR='Upper limit 95% CI';
run;

7. Data Monitoring Committee Reports

Data and study progress will be monitored by the study executive committee and by the Data Monitoring Committee. The DMC will review the study progress and safety semiannually with additional meetings and communications as needed.

All reports will be generated in conjunction with the Data Management department using SQL and SAS.

Updated Shell tables can be found on Sharepoint using the following link

https://vaww.ord.research.va.gov/CSP/Boston/csp578/centralfile/Data%20Monitoring%20Committee/Forms/AllItems.aspx?RootFolder=%2fCSP%2fBoston%2fcsp578%2fcentralfile%2fData%20Monitoring%20Committee%2f6%2e%20DMC%20Reports%20Shell%20Tables&FolderCTID=&View=%7b2F07C9DC%2d37B3%2d456C%2dAFDC%2d7F19514038EE%7d

7.1. Analytic Sample for DMC Reports

All subjects randomized more than six weeks prior to the DMC meeting date will be included in the analytic cohort for the upcoming DMC report, and all data collected up to four weeks prior to the DMC meeting date will be analyzed. This allows for two weeks lag time for submission of data from sites.

7.2. Outline of DMC Reports

Shell tables with algorithm annotated for creating the table content are provided in section **8** below. The report is divided into four sections to cover subject disposition, baseline assessment, follow-up assessment, and safety assessment. Following is the list of tables to be included within each of these 4 sections. Revision to this list, if any, will be discussed at the first DMC meeting to be held within six months of the initiation of subject enrollment in the VA sites.

7.2.1. Section A: Subject Disposition

Figure A1. CONSORT Diagram for CSP578
Figure A2. Overall Study Enrollment
Figure A3. Enrollment by Site
Table A4. Protocol Deviations
Table A5. Terminations

Table A6. Form Completion, by Form Type
Table A7. Form Completion, by Site

7.2.2. Section B: Baseline Assessment

Table B1. Patient Characteristics
Table B2. Military Service, VA sites only
Table B3. Medical History and Baseline Assessments
Table B4. Baseline Labs
Table B5. Study Procedure - Part I
Table B6. Study Procedure – Part II
Table B7. Study Medication Capsule Administration
Table B8. Study IV Fluid Administration
Table B9. Non-Study Drugs Pre- and Post- Procedure
Table B10. Sample Specimens Collected

7.2.3. Section C: Follow-up Assessment

Table C1. Post Procedure Assessment , Part I
Table C2. Post Procedure Assessment, Part II
Table C3. Study Outcome Events

7.2.4. Section D: Safety Assessment

Table D1. Rates of Non-Serious Adverse Events (NAEs) and Serious Adverse Events (SAEs), by Site
Table D2. Summary of Non-Serious Adverse Events
Table D3. Summary of Serious Adverse Events
Table D4. Non-Serious Adverse Events by System Organ Class and Preferred Term
Table D5. Serious Adverse Events by System Organ Class and Preferred Term

8. References

Proschan MA, Lan KKG, Wittes JT (2006) Statistical Monitoring of Clinical Trials: A Unified Approach. 1st edn. Springer: USA

Jitlal M, Khan I, Lee SM, Hackshaw A (2012) Stopping clinical trials early for futility: retrospective analysis of several randomised clinical studies. British Journal of Cancer (2012) 107, 910–917