SodiUm SeleniTe Administration IN Cardiac Surgery (SUSTAIN CSX – Trial). A Multicentre Randomized Controlled Trial of High Dose Sodium-selenite Administration in High Risk Cardiac Surgical Patients

NCT Number: 02002247

Version: 27-May 2021

Statistical Analysis Plan for: The SUSTAIN-CSX Trial

1 Administrative Information

1.1 SAP Summary Table

TRIAL FULL TITLE	SodiUm SeleniTe Adminstration IN Cardiac Surgery (SUSTAIN CSX®-trial). A multicenter, randomized controlled trial of high dose sodium-selenite administration in high risk cardiac surgical patients
TRIAL REGISTRATION	https://clinicaltrials.gov/ct2/show/NCT02002247
PROTOCOL PUBLICATION	NONE
CURRENT PROTOCOL DATE	2018-08-01
TRIAL PRINCIPAL INVESTIGATOR	Daren K. Heyland
TRIAL SENIOR STATISTICIAN	Andrew G. Day
TRIAL COORDINATOR	John Clarke
STATISTICIAN(S) PERFORMING ANALYSIS	Xuran Jiang and Andrew G. Day
SAP AUTHOR(s)	Andrew G. Day, Xuran Jiang and John Clarke
SAP DATE	2021-05-27
SAP STATUS	Version 1.- Finalized and approved.
SAP REVISION HISTORY	None yet
STATUS OF TRIAL AT TIME OF SAP FINALIZATION OF V1.0	Enrollment completed. Blinded data cleaning completed. No by arm outcome results generated yet.

1.2 Signatures

I have read and approve the enclosed SAP dated 2021-05-27 for the Sustain CSX trial.

Senior Statistician & SAP Author

Name: Andrew G. Day

Signature: _____

Date: _____

Statistician Performing Analysis (other than senior statistician):

Name: Xuran Jiang

Signature: _____

Date: _____

Trial Co-ordinator

Name: John Clarke

Signature: _____

Date: _____

Principal Investigator

Name: Daren K. Heyland

Signature: _____

Date: _____

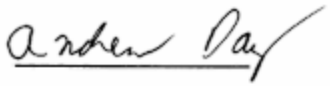
Statistical Analysis Plan SUSTAIN CSX Trial Clinical Evaluation Research Unit

1.2 Signatures

I have read and approve the enclosed SAP dated 2021-05-27 for the Sustain CSX trial.

Senior Statistician & SAP Author

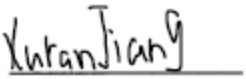
Name: Andrew G. Day

Signature: 

Date: May 27, 2021

Statistician Performing Analysis (other than senior statistician):

Name: Xuran Jiang

Signature: 

Date: 27/05/21

Trial Co-ordinator

Name: John Clarke

Signature: 

Date: May 27th, 2021

Principal Investigator

Name: Daren K. Heyland

Signature: 

Date: May 27/21

1.3 Purpose, usage, and target audience of this document

This document provides a detail description of the analysis plan for the SUSTAIN CSX trial. This document is meant to be used in conjunction with the study protocol. This document does not subsume the protocol, but several elements of the protocol, such as the sample size justification are reproduced herein for completeness. This document has the following purposes:

1. Provides a written agreement between the principle investigator, sponsor, lead study statistician and data analysts regarding exactly what analysis will be performed.
2. Provides a record of the analysis plan specified prior to examining any outcomes by arm.
3. Provide clear specifications for the analyst(s) performing the data filtering/transformation, variable derivations, statistical analyses and report generation.

This document follows the guidance published in JAMA by Gamble et al (2017) and referenced at https://www.equator-network.org/reporting-guidelines/guidelines-for-the-content-of-statistical-analysis-plans-in-clinical-trials/ [1] The SAP checklist is completed in Appendix A.

1.4 SAP Contributors and Signatories

4. Andrew Day drafted the SAP, Xuran Jiang contributed details regarding the definition of several outcomes, John Clarke added details regarding the trial operation and data management, and Daren Heyland helped interpret the protocol and prioritize outcomes, analyses, and validation. All authors provided critical review and editing to all parts of the SAP. The finalized version of the SAP was approved and signed off by all authors.

2 Contents

3 Introduction to Study

3.1 Background and Rationale

Copied from https://clinicaltrials.gov/ct2/show/NCT02002247

Over a million patients undergo open heart surgery annually and this number is likely to accelerate as the population ages and the prevalence of diabetes and cardiovascular disease continue to increase. Unfortunately, death, organ failure, and other serious complications are all too frequent following open heart surgery, especially in some high-risk patient populations.

Selenium is a trace element that is important for many of the body's regulatory and metabolic functions especially during times of stress. International members of the study team have shown in a non-randomized study that high dose selenium supplementation was associated with improved clinical outcomes compared to a historical control group. The next step in this program of research is to conduct a randomized trial.

3.2 Overall Aim

The aim of this trial is to investigate the effects of perioperative high dose selenium supplementation in high-risk cardiac surgical patients undergoing complicated open heart surgery. If the hypothesis is proven true, and this simple, inexpensive nutrient reduces complications and improves recovery of patients undergoing cardiac surgery, there is the potential to dramatically change clinical practice and improve health outcomes.

3.3 Study Hypotheses

Perioperative high dose selenium supplementation in high-risk cardiac surgical patients undergoing complicated open heart surgery will led to better outcomes including lower mortality and fewer days requiring life sustaining therapies.

4 Study Methods

4.1 Trial Design

A randomized, placebo-controlled, double-blind, multicentre definitive trial of 1400 patients across 20 sites in Germany and Canada, which will include the pilot study patients. An industry partner (Biosyn) will provide the product and some additional support for the European sites. Patients will be randomized to receive either a daily perioperative high-dose selenium or placebo until postoperative day 10 (maximum) or upon earlier discharge from ICU.

4.2 Randomization

Randomization description copied from published protocol.

At each participating center the local coordinating investigator will screen daily all cardiac surgical patients scheduled to undergo cardiac surgery in the near future or on the next day. A screening

log will be kept at each site to determine the number of patients meeting the inclusion criteria, those truly eligible patients, those who consent and are randomized and reasons why potentially eligible patients did not get enrolled. Following a full explanation of the nature and purpose of the study, a written informed consent will be obtained from the patients participating in the study. At the time of enrolment into the study, patients will be randomized to receive either selenium or a matching placebo similar in appearance, consistency, volume, and smell so as to blind patients, investigators and health care practitioners as to the nature of the study medication. Patients will be consecutively randomized by a web-based randomization system (concealed and blinded) developed by the Clinical Evaluation Research Unit at the Kingston Health Sciences Centre and randomization will be stratified according to centre. Randomization will be based on the method of permutated blocks of undisclosed random size stratified by centre.

4.3 Sample Size Considerations

Sample size copied from published protocol.

The distribution of the control arm was calculated based on a database of patients that underwent cardiac surgery during a 12 month follow up at Aachen University (n = 1127) and would met the inclusion criteria of the current study (n = 170). In our dataset, the mean (SD) POD free days was 23.2 (9.2); 4% of the patients died, 6% survived on life-sustaining therapy with 0 POD free days. We checked these numbers with data from the University of Ottawa Heart Institute (Canada), and numbers are consistent with the 4% 30-day mortality rate and the 6% not yet free from life-sustaining therapy by 30 days. We used simulation to estimate the power of applying the Wilcoxon rank-sum test to our primary outcome of PODs free days. The intervention arm was then generated by multiplying the control arm daily rate of liberation from life sustaining therapies by a fixed factor (hazard ratio) but assuming the same 4% mortality rate. The mean days on life-sustaining therapy was then subtracted from 30 to obtain the free days. 10.000 samples were simulated so the power estimate has more than a 95% chance of being accurate to within 1%. Based on the simulation, we would require 700 patients per arm to achieve 90% power at a two-sided alpha=0.05 if the intervention caused as 20% relative increase in the daily rate of liberation from life-sustaining therapy but no change in mortality compared to the control arm. Based on our Aachen data, such an effect size would result in an earlier liberation of life-sustaining therapies and mean increase of 1.5 POD free days (from 23.2 to 24.7 days). We believe such an effect size is plausible and is in line with minimally clinically important differences accepted in other recent major trials in the ICU setting.2

4.4 Framework

This is a confirmatory (i.e. hypothesis testing) superiority RCT comparing the efficacy and safety of perioperative high dose selenium supplementation to placebo in high-risk cardiac surgical patients undergoing complicated open heart surgery.

4.5 Interim Analysis

None

4.6 Timing of Final Analysis

All outcomes will be analyzed once all data is collected and cleaned and after finalization of the analysis plan.

4.7 Timing of outcome assessments

Most outcome assessments were measured in hospital up to 30 days or at 6 months. The timing of each outcome is described with the outcome in section 6.1.

5 Statistical Principals

5.1 Confidence intervals and P-values

95% confidence will be presented for selected key outcomes. P-values will be two-sided without adjustment for multiplicity. However, interpretation of secondary outcomes will consider the multiplicity of tests. There is one pre-specified primary test of efficacy. $P<0.05$ will be considered statistically significant.

5.2 Analysis populations

The primary analysis will be a modified intention-to-treat including all patients to the arm they were randomized regardless of study compliance except we will exclude randomized patients who became ineligible due to not undergoing the planned surgery AND did not receive any study medication. In addition, for key efficacy outcomes, we plan a per-protocol analysis that further excludes patients who stayed less than 24 hours in the ICU or experienced an IP-related protocol violation.

5.3 Eligibility Criteria:

Published at https://clinicaltrials.gov/ct2/show/NCT02002247#eligibility.

5.4 Screening, recruitment, patient flow/follow-up

A CONSORT style flow diagram will present the numbers of patients screened and all reasons excluded prior to randomization. The table will also include the number randomized to each arm and the number used in the primary analysis in each arm with reasons for the exclusion of randomized patients.

5.5 Baseline Characteristics

Baseline characteristics will be described by arm and overall using descriptive statistics only. Categorical variables will be described as counts (%). Continuous variables will be described as mean±SD (min to

max) and/or median [Q1 to Q3]. Separate tables will be generated for pre-operative, intra-operative, and post-operative characteristics.

The following baseline patient characteristics will be described: Age, sex, ethnicity, height, weight, BMI, Unplanned weight loss in the last 3 months, Food intake in the week prior to ICU admission, Baseline SOFA, Charlson Comorbidity Index, Functional Comorbidity Index, Patients without angina however had CCS data entered, CCS Grading(among patients with angina), NYHA Classification, EuroSCORE II classification, Manuscript classification, Duration of the surgical procedure (hours), Duration of cardiopulmonary bypass (hours), Duration of aortic clamping (hours), Baseline SF-36 (all 8 domains and 2 summary scales), Baseline Barthel ADL index, Baseline Frailty Scale, Euroscore II (%), Euroscore II (%), time from hospital admission to randomization and additional variables as explicated in the analytic dictionary.

6 Analysis

6.1 Outcome Definitions

6.1.1 Primary Outcome:

Number of days alive and free of life sustaining therapy (i.e. PODS free) in the first 30 days after the day of surgery. PFDs do not include day of surgery or days prior to surgery. Randomization is always prior to surgery and usually occurs on day of surgery, but for some patients randomization occurred prior to the day of surgery. Life sustaining therapy includes any use of the following for any duration of time on the given day: mechanical ventilation, vasopressor therapy, mechanical circulatory support, continuous renal replacement therapy, or intermittent hemodialysis. Patients who die in the first 30 days after day of surgery will be assigned 0 PODS free days.

(1) **Mechanical ventilation**: Mechanical ventilation via an endotracheal tube or tracheostomy tube OR use of non-invasive mechanical ventilation (CPAP or BiPAP) will count as mechanical ventilation unless the patient routinely uses these modalities at home. A patient will be considered liberated from mechanical ventilation at the time of extubation if they remain off mechanical ventilation at least 48 hours. However, if patients are re-intubated within 48 hours, then the intervening time will not be considered free days.

(2) **Vasopressor therapy**: days with more than 2 hours of any dose of norepinephrine, epinephrine, vasopressin, Dobutamine, Milrinone or Levosimendan and >5 ug/kg/min of dopamine, or > 50 ug/minute of phenylephrine, will not be considered free days. The 48-hour rule does not apply to vasopressor therapy or renal replacement therapy.

(3) **Mechanical circulatory support**: Use of Intra-Aortic Balloon Pump (IABP) or Extra Membrane Oxygenation (ECMO) or any Left Ventricular Assist Device (LVAD, like Impella or TandemHeart, etc.) for any duration will be considered to receive Mechanical Circulatory Support on that calendar day. As with mechanical ventilation, days will not be considered free if mechanically circulatory support is re-initiated within 48 hours, but days free in the first 48 hours will count if mechanical circulatory support is re-initiated on or after 48 hours.

(4) **Renal replacement therapy**: if the calendar day is on or between the start and stop date of any renal replacement therapy then the day is not a free day.

6.1.2 Secondary Outcomes:

1. 30-Day Mortality [Time Frame: 30 days]

   Count and percentage of patients who died within 30 days from surgery.

2. Hospital Acquired Infections [Time Frame: hospitalization]

   Count and percentage of patients with definite or probable infections will be reported.
   To be evaluated up to hospital discharge.

3. Perioperative hemodynamic profile [Time Frame: post anesthetic induction, upon ICU admission and at change of nursing shift on the morning of the first postoperative day and subsequent days in the ICU]

   This includes: Heart Rate, systemic and pulmonary blood pressures, central venous pressure, cardiac output, and mixed venous blood oxygen saturation level (SvO2).

4. Cardiovascular Complications [Time Frame: hospitalization]

   This includes: clinically significant atrial fibrillation (>1 hour), myocardial injury≥72 hours after surgery, stroke after surgery, cardiac arrest. To be assessed up to hospital discharge.

5. Duration of Mechanical Ventilation [Time Frame: hospitalization]

   Duration of mechanical ventilation will be calculated from time of admission to ICU until time of discontinuation. All times of endotracheal extubation and any subsequent re-intubation/re-extubations or tracheostomy will be recorded. A patient will be considered liberated from mechanical ventilation at the time of liberation if they subsequently remain off mechanical ventilation for at least 48 hours i.e. for a patient who is removed from mechanical ventilation and reintubated 30 hours later, the intervening days from extubation to re-intubation will be considered to represent ongoing need for life support. Use of non-invasive mechanical ventilation (CPAP or BiPAP) will count as mechanical ventilation unless the patient routinely uses these modalities at home.

To be assessed up to hospital discharge.

6. Incidence of post-operative delirium [Time Frame: hospitalization]

   CAM-ICU score was assessed upon admission to ICU post-operatively (not pre-operatively, may be same day as surgery or the next day) and will be reported daily while in ICU.

   The CAM (Confusion Assessment Method for the Intensive Care Unit) has four features. Delirium is diagnosed when both Feature 1 and 2 are positive, along with either Feature 3 or Feature 4

   Feature 1. Acute Onset of Mental Status Changes or Fluctuating Course.
   - Is there evidence of an acute change in mental status from the baseline?
   - Did the (abnormal) behavior fluctuate during the past 24 hours, that is, ten to come and go or increase and decrease in severity?

   Feature 2. Inattention
   - Did the patient have difficulty focusing attention?
   - Is there a reduced ability to maintain and shift attention?

   Feature 3. Disorganized Thinking
   - Was the patient's thinking disorganized or incoherent, such as rambling or irrelevant conversation, unclear or illogical flow of ideas, or unpredictable switching from subject to subject?
   - Was the patient able to follow questions and commands throughout the assessment?

   Feature 4. Altered Level of Consciousness
   - Any level of consciousness other than 'alert'.
   - Alert-normal, spontaneous fully aware of environment and interacts appropriately.
   - Vigilant-hyperalert
   - Lethargic-drowsy but easily aroused, unaware of some elements in the environment, or not spontaneously interacting appropriately with the interviewer; becomes fully aware and appropriately interactive when prodded minimally
   - Stupor-difficult to arouse, unaware of some or all elements in the environment, or not spontaneously interacting with the interviewer; becomes incompletely aware and inappropriately interactive when prodded strongly
   - Coma – unarousable, unaware of all elements in the environment, with no spontaneous interaction or awareness of the interviewer, so that the interview is difficult or impossible event with maximal prodding

7. ICU Length of stay [Time Frame: ICU stay]

   ICU length of stay is calculated from time of ICU admission to time and date of actual discharge.

   To be assessed up to ICU discharge.

8. Hospital Re-admission Rates [Time Frame: 6-months]

   To be assessed up to 6-months post-surgery. Count and proportion of patients who were admitted to hospital more than once.

9. Hospital Length of stay [Time Frame: hospitalization]

   Hospital length of stay will be calculated from the date of index surgical procedure to time and date of discharge from hospital.

   To be assessed up to hospital discharge.

10. 6-Month Survival [Time Frame: 6-months]

    Kaplan-Meir curves of and hazard ratio of survival over 6 months starting with day of surgery.

11. Quality of Life [Time Frame: day 30, 3-months and 6-months]

    The SF-36 physical and mental summary scales will be analyzed separately.

    Barthel Index of Activities of Daily Living Total Score

    Frailty Scale

12. Return to work [Time Frame: 6-months]

    Assessed using a questionnaire to determine the patient's ability to return to their pre-operative working capabilities. To be assessed up to 6 months post-surgery.

13. 6-minute walking test [Time Frame: hospital discharge]

    This was done in a sub-study of pre specified patients.

    In the 6-minute walking distance (6MWD) was performed at hospital discharge and at 3 months. The analysis of the 6MWD is based on rank order where patient who died prior to testing are assigned the lowest rank, people who were unable due to illness or physical limitation were assigned a value of zero and people who did the test are ranked according to their distance walked. Patients not doing the test for other reasons (missed due to RC unavailable or unaware, missed due to hospital discharge, did not return to clinic, patient refused but able, or COVID-19 reasons) were excluded from the analysis. “Other” will be blindly adjudicated to determine difference from unable or otherwise missing.

6.1.3 Additional Outcomes:

1. Laboratory outcomes [Time Frame: hospital discharge]

   Values above or below certain thresholds, depending on the variable will be reported as an ‘ever’ event, per patient, per group based on establish clinical standards.

2. Days alive post hospital discharge (DAPHD6M) [Time Frame: 182 days]

This is number of days in the first 182 days post-surgery date where patients were alive and discharged from the hospital. Patients who die within 182 days can still have >0 DAPHD6M if they were alive for some days after hospital discharge. A patient who is discharged on day X (where X<182) and dies on day X+2 would be considered to have 1 DAPHD6M, because the date of discharge and the date of death are not counted as free days, but there is otherwise no minimum amount of survival required.

6.1.4 Remaining study variables:

The study analytic dictionary contains a complete list of study variables with information including their label, their REDCap location (or identified as derived), their valid values or allowable range, and the variables scale (binary, nominal, ordinal, continuous or special) which is used to determine how they will be analyzed. The complete stats report will contain the following sections reported mostly in tabular form:

1 Baseline Demographics (Pre-Procedure)
2 Baseline Demographics (Intra-operative)
3 Baseline Demographics (Immediate Post-operative)
4: Compliance with Study Investigational Product
5: Protocol Violations
6: SAEs
7: Treatment period assessment:
8: Standard Nutrition Practices
9: Events of Interest
10: Primary outcome
11: Secondary Outcomes
12: Additional Outcomes

6.1.5 Cost Utility Analysis:

A cost utility analysis will be performed if the results of this study show clear benefit of sodium-selenite administration compared to placebo. The cost effectiveness of sodium-selenite administration compared to placebo will be assessed in terms of the incremental cost per quality adjusted life year (QALY) gained from the perspective of health care system. Analysis will incorporate data on resource use and patients utility values up to 6 months post sodium-selenite administration given the assumption that no long term differences in outcome are expected. Resource use will be assessed by data collected at the follow up interviews. Utility values would be derived from SF-36 using the algorithm proposed by Brazier et al. QALYs will be estimated for each patient within the clinical trial using the total area under the curve method. The incremental cost and QALY will be estimated using a regression analysis approach. Uncertainty in the analysis will be addressed by estimating 95% CIs using a non-parametric bootstrapping method. Further details of the cost utility analysis, should it be indicated, will be detailed in a separate document.

6.2 Analysis Methods

6.2.1 Primary outcome

To test the between arm difference of PODS free days (PFDs) we will use the van Elteren test which is a stratified version of the Wilcoxon rank-sum test where the ranking is done within site to control for heterogeneity in PFDs between sites. This is a slight deviation from the original protocol which planned to use the un-stratified Wilcoxon rank-sum test. The daily proportion of patients alive and free of life sustaining therapy by arm over the first 30 days will be reported in a table or graphically. In this table or figure we will also report the daily usage rates of each specific life sustaining therapy. The key summary measure for the effect size of PFDs will be a within site concordance index (c-index). The within site c-index estimates the probability that a patient in the intervention arm will have more PFDs than a patient in the control arm from the same site. The within site c-index can range from 0 to 1, where 1 indicates that within each site every patient in the intervention arm has more PFDs than any patient in the control arm, 0 is the converse, and 0.5 would indicate no difference between arms. The within site c-index will be defined as follows: 1) within each site, compare every patient in the intervention arm to every patient in the control arm, so for example if a site had 10 patient in the intervention arm and 12 patents in the control arm there would be 120 comparisons, 2) assign each comparison a value if 1 the intervention arm patient has more PFDs, 0 if the control arm patient has more PFDS and 0.5 if both arms have the same PFDs; 3) calculate the average of within site c-indexes weighting each site proportionally to the square root of the number of comparisons within the site. We will then obtain the 2.5^{th} and 97.5^{th} percentile of 10, 000 bootstrap samples to estimate the 95% confidence intervals of the within site c-index.

6.2.2 Secondary outcomes

Secondary binary outcomes such as cardiovascular complications, postoperative delirium, re-admissions, hospital-acquired infections and 30-day mortality will be compared between groups by a logistic mixed effects model with site included as a random effect.[1] Odds ratios with 95% confidence intervals will be reported.

Six-month mortality will be described by group using Kaplan-Meier curves. Survival will be compared by a hazard ratio with 95% confidence intervals and corresponding Wald test. Estimates will be derived from the Cox proportional hazards model with a random frailty for site. If the proportional hazards assumption is clearly and meaningfully violated, we will report a smoothed time dependent hazard ratio over time. However, the aforementioned overall Wald test will remain the primary test of statistical significance. Patients will be censored at the earliest of 183 days post randomization or last known follow-up.

Length of ICU and hospital stay will be summarized by arm using the quartiles of time to live discharge estimated from the subdistribution cumulative incidence function (CIF) where death is treated as a competing risk precluding the possibility of discharge. The between arm difference in time to live discharge will be tested using the Wald test from the Cox proportional hazards model with site as a random frailty to account for potential between site heterogeneity. Patients who die prior to discharge will be censored after the end of the follow-up period to account for the competing risk of death. This will yield virtually the same results as the Fine and Gray approach treating death as a competing risk precluding discharge, except we will have incorporated ICU as a random effect. This outcome is also known as time-to-discharge-alive (TTDA).

The SF-36, Barthel Index and frailty scale will be collected at baseline. At 30 days, 3 months and 6 months after surgery, we will repeat the Barthel Index and SF-36 and collect return to work data. The SF-36 physical and mental summary scales and the Barthel index will be treated as continuous variables and analyzed using a linear mixed effects model for longitudinal data. In order to include all patients

with a baseline assessment regardless of follow-up, we will use constrained longitudinal data analysis where the independent dummy variable indicating treatment arm (1-treatment or 0-control) will be set so to 0 at baseline for both arms but 1 post baseline for the intervention arm.[2, 3] This model will include site as a random effect and will allow for unstructured within patient correlation as estimated by restricted maximum likelihood. The focus of these secondary analyses will be primarily descriptive as these outcomes are limited to survivors and no imputation for decedents is planned. Thus, these outcomes will not be informative of treatment efficacy if they are in the opposite direction from survival. The between group difference in the change from baseline to the various follow-up time points will be described as expected means with 95% confidence intervals.

6.2.3 Additional outcomes:

Days alive and home in 6 months will be analyzed using the same approach as PFDs.

Variables collected but not specifically listed above will be described by arm at each time they were collected using counts and percentages for categorical variables and medians and quartiles or means and standard deviations for continuous variables. Post baseline differences in these variables will be tested using the Cochran-Mantel-Haenszel test stratified by site for the categorical variables and the van Elteren test stratified by site for continuous variables. Analysis of these variables will be considered exploratory so no adjustment for multiplicity will be applied to p-values, but multiplicity of tests will be considered in when interpreting these results.

Study reporting will be in accordance with the CONSORT statement.[4]

6.2.4 Adjustment for covariates

Analysis involving hypothesis testing or creation of confidence intervals will control for site which was the sole stratification factor at randomization. No other covariates will be controlled for.

6.2.5 Assumption checking

The analysis of the primary outcome is non-parametric so no assumptions will be checked. The proportional hazards assumption of 6-month survival will be assessed graphically.

6.2.6 Subgroup analysis

A priori, we expect that there may be a heterogeneity of treatment effect amongst different patient populations. For example, older, sicker patients with less reserve may benefit the most from selenium supplementation. Thus, we plan to do a subgroup analysis comparing the treatment effect in older patients vs. younger patients (based on median age of 70), patients who are frail (Clinical Frailty Scale ≥ 4)[5] vs. those who are not, patients who are at nutrition risk (positive features of reduced oral intake or recent weight loss) vs. those that are not, in patients that undergo combined procedures (CABG+ value(s) and CABG plus 'other') vs. those that do not have combined procedures, patients who underwent urgent survey vs. those who underwent elective surgery, patients with moderate-severe baseline chronic kidney disease vs. those that do not, patients with a low ejection fraction (EF <39%) vs. those with EF 40 or greater, and patients with a higher vs lower Euroscore (based on the median score)

and longer vs. shorter CPB (based on median value). In support of these proposed analyses, there is an apparent decline in circulating selenium levels in the elderly in certain populations, which may occur independently of intake.[6,7] Given the potential differences in baseline selenium levels between North Americans and Europeans (due to selenium depletion in the soil in Europe),[8] we plan to compare the effect of selenium in the Canadian vs. German subpopulations. Forest plots will be provided to display the effect measure with 95% CIs within each subgroup and sites. For these subgroup analyses, we plan to examine the primary outcome and select secondary outcomes (TTDA, 6 month survival and DAPHD6M). The effect measure for the primary outcome will be the stratified c-index as described in section 6.2. Statistical tests of interaction between treatment arm and subgroup may be performed if treatment effect appears meaningfully different between subgroups.

6.3 Missing Data

The number of missing items will be presented by arm for each outcome. For the primary outcome, if >5% of patients have missing values then we will perform multiple imputation based on prior daily data and baseline characteristics to use the entire mITT population for the primary analysis of the primary outcome.

6.4 Additional analysis

The database generated from the SUSTAIN CSX trial may be used for additional secondary analyses exploring questions other than assessing the efficacy Sodium Selenite Administration in high-risk cardiac surgical patients undergoing complicated open-heart surgery. Plans for these additional secondary analyses are to be determined and are not part of the primary SUSTAIN CSX analysis.

6.5 Statistical Software

The main analysis was performed using SAS 9.4 TS level 1M2 and SAS/STAT version 14.2 under Windows 7 Professional version 6.1.7601. The independent validation of selected items (see section 8.2) was performed using the same software and operating system except SAS 9.4 was level 1M4.

7 Quality assurance

7.1 Data quality

Data was entered into REDCap by trained local site personal. Each user with access to REDCap had a unique username and password. Access to REDCap was secure and an audit trial was maintained to keep track of the username, time, and values of all data entry and modification. A custom secure randomization module was used to implement the randomization list and maintain concealment of future allocations. A custom query module was used to implement extensive value, range, logical

(including date sequence) data checks. Any violation of the pre-defined data checks triggered data queries that were tracked and required resolution (either correction or acceptance by central staff) prior to data being marked as finalized.

A touch base meeting was conducted with each site after their first patient to address any questions that may have arose in conducting the study and collecting data. Key data items from 2 patients at each site were monitored via source verification once they had randomized 2 patients. After the initial 2 patients were monitored, sites were assessed for risk and follow-up monitoring only conducted when needed. The REDCap database was downloaded and converted into a multi-table analytic SAS database. Some filtering, data transformation, and variable derivation was performed in SAS. Boxplots were generated for all continuous variables and outliers were queried; all outliers were either corrected or verified as correct.

Quality assurance reports were run periodically throughout the trial to assess the completes, timeliness, validity and quality of trial implementation and data capture by site. Issues were flagged and resolved with participating sites in real time.

7.2 Validation of SAS database and analysis

The study PI and study co-ordinary will sense check all results to make sure they are not highly suspicions and that all counts are consistent with the patient flow diagram.

A second statistician who did not perform the primary analysis will independently verify the patient flow counts and re-analyze the following key outcomes: 1) PODS free days, 3) 30-day morality, 6) six-month survival.

8 References

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9 Appendix A: Statistical Analysis Plan (SAP) Checklist v 1.0 2019

Section/Item	Index	Description	Reported on page #
Section 1: Administrative information			
Trial and Trial registration	1a	Descriptive title that matches the protocol, with SAP either as a forerunner or subtitle, and trial acronym (if applicable)	1
	1b	Trial registration number	1
SAP Version	2	SAP version number with dates	1
Protocol Version	3	Reference to version of protocol being used	1
SAP revisions	4a	SAP revision history	1
	4b	Justification for each SAP revision	1
	4c	Timing of SAP revisions in relation to interim analyses, etc.	1
Roles and responsibility	5	Names, affiliations, and roles of SAP contributors	2
Signatures of:	6a	Person writing the SAP	1, 3
	6b	Senior statistician responsible	1
	6c	Chief investigator/clinical lead	1
Section 2: Introduction			
Background and rationale	7	Synopsis of trial background and rationale including a brief description of research question and brief justification for undertaking the trial	6
Objectives	8	Description of specific objectives or hypotheses	6
Section 3: Study Methods			
Trial design	9	Brief description of trial design including type of trial (e.g., parallel group, multi-arm, crossover, factorial) and allocation ratio and may include brief description of interventions	6
Randomization	10	Randomization details, e.g., whether any minimization or stratification	6

		occurred (including stratifying factors used or the location of that information if it is not held within the SAP)	
Sample size	11	Full sample size calculation or reference to sample size calculation in protocol (instead of replication in SAP)	7
Framework	12	Superiority, equivalence, or noninferiority hypothesis testing framework, including which comparisons will be presented on this basis	7
Statistical interim analysis and stopping guidance	13a	Information on interim analyses specifying what interim analyses will be carried out and listing of time points	8
	13b	Any planned adjustment of the significance level due to interim analysis	NA
	13c	Details of guidelines for stopping the trial early	NA
Timing of final analysis	14	Timing of final analysis, e.g., all outcomes analysed collectively or timing stratified by planned length of follow-up	8
Timing of outcome assessments	15	Time points at which the outcomes are measured including visit "windows"	8
Section 4: Statistical Principals			
Confidence intervals and *P* values	16	Level of statistical significance	8
	17	Description and rationale for any adjustment for multiplicity and, if so, detailing how the type 1 error is to be controlled	8
	18	Confidence intervals to be reported	8
Adherence and Protocol deviations	19a	Definition of adherence to the intervention and how this is assessed including extent of exposure	8
	19b	Description of how adherence to the intervention will be presented	13
	19c	Definition of protocol deviations for the trial	NA
	19d	Description of which protocol deviations will be summarized	NA

Analysis populations	20	Definition of analysis populations, e.g., intention to treat, per protocol, complete case, safety	8
Section 5: Trial Population			
Screening data	21	Reporting of screening data (if collected) to describe representativeness of trial sample	8
Eligibility	22	Summary of eligibility criteria	8
Recruitment	23	Information to be included in the CONSORT flow diagram	8
Withdrawal/ Follow-up	24a	Level of withdrawal, e.g., from intervention and/or from follow-up	8
	24b	Timing of withdrawal/lost to follow-up data	8
	24c	Reasons and details of how withdrawal/lost to follow-up data will be presented	8
Baseline patient characteristics	25a	List of baseline characteristics to be summarized	8-9
	25b	Details of how baseline characteristics will be descriptively summarized	8-9
Section 6: Analysis			
Outcome definitions		List and describe each primary and secondary outcome including details of:	9-13
	26a	Specification of outcomes and timings. If applicable include the order of importance of primary or key secondary end points (e.g., order in which they will be tested)	9-12
	26b	Specific measurement and units (e.g., glucose control, hbA1c [mmol/mol or %])	NA
	26c	Any calculation or transformation used to derive the outcome (e.g., change from baseline, QoL score, Time to event, logarithm, etc.)	9-13
Analysis methods	27a	What analysis method will be used and how the treatment effects will be presented	14-16
	27b	Any adjustment for covariates	15
	27c	Methods used for assumptions to be checked for statistical methods	15
	27d	Details of alternative methods to be used if distributional assumptions do not hold, e.g., normality, proportional hazards, etc.	14 (for 6-month survival)

	27e	Any planned sensitivity analyses for each outcome where applicable	14
	27f	Any planned subgroup analyses for each outcome including how subgroups are defined	15
Missing data	28	Reporting and assumptions/statistical methods to handle missing data (e.g., multiple imputation)	16
Additional analyses	29	Details of any additional statistical analyses required, e.g., complier-average causal effect10 analysis	16
Harms	30	Sufficient detail on summarizing safety data, e.g., information on severity, expectedness, and causality; details of how adverse events are coded or categorized; how adverse event data will be analysed, i.e., grade 3/4 only, incidence case analysis, intervention emergent analysis	NA
Statistical software	31	Details of statistical packages to be used to carry out analyses	16
References	32a	References to be provided for nonstandard statistical methods	17
	32b	Reference to Data Management Plan	16-17
	32c	Reference to the Trial Master File and Statistical Master File	13 (analytic dictionary)
	32d	Reference to other standard operating procedures or documents to be adhered to	16-17

Taken from the paper: Gamble C, Krishan A, Stocken D, Lewis S, Juszczak E, Doré C, et al. Guidelines for the Content of Statistical Analysis Plans in Clinical Trials. JAMA. 2017;318(23):2337-43.

Abbreviations: CONSORT, Consolidated Standards of Reporting Trials; hbA1c, haemoglobin A1c; QoL, quality of life; SAP, statistical analysis plan.