Statistical Analysis Plan (SAP)

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Note: inspiration to write this SAP came from the SAP template provided by **TransCelerate** [1] as well as recommendations from Gamble et al. [6], Stevens et al. [11] and Evans and Ting [1].

[1] Available via: https://www.transceleratebiopharmainc.com/assets/clinical-content-reuse-solutions/

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2 List of Abbreviations

- SAP: Statistical analysis plan
- BALI: Balloon lithoplasty
- PCI: Percutaneous coronary intervention
- OCT: Optical Coherence Tomography
- MLA: minimal lumen area
- IVL: intravascular lithoplasty
- MSA: minimal stent area

3 Introduction

This document is the Statistical Analysis Plan (SAP) for a randomized (1:1), superiority, clinical trial comparing the use of balloon intravascular lithoplasty (IVL) to the current conventional techniques of routine lesion preparation before implantation of newest-generation drug-eluting stents in severely calcified coronary lesions. The protocol for this trial been registered at ClinicalTrials.gov. Version 5.3 of the protocol was used to make this SAP.

3.1 Objectives, Endpoints, and Estimands

3.1.1 Primary

The primary objective is to show that the use of balloon lithoplasty for routine lesion preparation is superior to the current conventional techniques used for routine lesion preparation before implantation of newest-generation drug-eluting stents in severely calcified coronary lesions. The primary outcome is a composite of measures indicating procedural failure and 1-year target vessel failure. Specifically, the two intervention being compared are:

- Routine lesion preparation with balloon intravascular lithoplasty (IVL) with or without the use of rotational atherectomy at the operators discretion, and
- Routine lesion preparation with conventional techniques using conventional balloons, modified balloons, or high-pressure balloons with or without the use of rotational atherectomy at the operators discretion

prior to implantation of newest-generation drug-eluting stents in severely calcified coronary lesions. After the procedure, patients are followed for one year to determine the primary composite endpoint. The primary composite endpoint is determined by the following:

- Failed or no stent delivery determined by the angiographic core laboratory.

  Failed or no stent delivery is defined as failure to deliver and deploy 1 or more coronary stents to cover the intended length of the intended target lesion.

- OCT-assessed residual area stenosis $\geq$20%.

  Residual area stenosis is defined as 1 -[in-stent minimal lumen area (MLA) / reference lumen area]. Residual area stenosis will be determined primarily by OCT, or, if necessary, by quantitative coronary angiography, as defined in the OCT and quantitative coronary angiography definitions section of the protocol. The use of angiography is a form of imputation and we will investigate the impact of this in Section 7.1.2.

- Target vessel failure within one year.

  Defined as cardiac death, target vessel-related myocardial infarction, or clinically driven target vessel revascularization.

  - Cardiac death is defined as death due to coronary heart disease, sudden cardiac death, heart failure including cardiogenic shock, and death related to the cardiac procedure within 28 days from the procedure. If death is not clearly attributable to other non-cardiac causes, it is adjudicated as cardiac.
  - Target vessel myocardial infarction is defined as myocardial infarction according to the 4th Universal definition of Myocardial Infarction or peri-procedural myocardial infarction within 48 hours. Peri-procedural myocardial infarction is defined according to ARC-2 criteria: Troponin elevation of 35 times the 99th URL (or CK-MB elevation of $>$5 times the 99th URL) and either: ST-segment changes, new pathological Q waves, angiographic evidence of a flow limiting complication (loss of patency of a side branch, persistent slow-flow or no-reflow, or embolization), imaging evidence of new loss of viable myocardium, or new wall motion abnormality within 48 hours after the PCI. In patients with elevated biomarkers prior to the procedure, the post-procedure troponin must rise by $>$20% and still be $>$35 times the 99th percentile URL. MIs will default to target vessel-related MIs unless there is other proof of definite attribution to a non-target vessel.
  - Clinically-driven target vessel revascularization is defined as coronary artery bypass grafting or PCI of index vessel performed due to symptoms or signs of ischemia.

Accordingly, the primary estimand is described by the following attributes:

- Population: Adults with severely calcified coronary lesions with indication for PCI, the specific population is defined by the inclusion and exclusion criteria as given in Section 4.
- Endpoint: is a composite of procedural failure and within 1-year target vessel failure.
- Treatment: The interventions are conventional lesion preparation and preparation including balloon lithoplasty prior to implantation of newest-generation drug-eluting stents
- Intercurrent events:
  - Failure to obtain all information needed to evaluate the primary composite endpoint for reasons other than death from a cause not included in the primary endpoint, i.e. reason other than cardiac death. This will be addressed in the "Sensitivity Analyses for missingness" in Section 7.1.2.
- Population-level summary: Difference in 1-year risk of composite endpoint of procedural failure and within 1-year target vessel failure.

Remark: The justification for the "Intercurrent Events" is that we wish to report the difference in the risk of the primary endpoint comparing the two interventions in a world where people may die of other causes within the year, thus non-cardiac death is not an intercurrent event. The estimand of interest is made clear by the population of interest being among all patients and not just those that do not die from other causes.

We recognize that by ignoring non-cardiac death, we allow for the possibility that an intervention that kills people in some unexpected way would be considered superior by our primary estimand. Thus, as outlined in Section 7.1.1, we will never report the findings of the primary analysis without also reporting a comparison of the incidence of non-cardiac death between the intervention arms.

Correspondingly, the primary clinical question of interest is:

"What are the risks of the composite endpoint among patients randomized to receive IVL for lesion preparation before implantation of newest-generation drug-eluting stents in a severely calcified coronary lesion, and how does this risk compare to using the current conventional techniques of lesion preparation, regardless of actual use of balloon lithoplasty, additional interventions performed during initial PCI or additional treatments during the one-year after procedure, or other changes in status of patients not included in the endpoint of interest?"

3.1.2 Key Secondary Endpoints

Safety Endpoints

1. major adverse cardiac events and its components within one year:
   - -1a Cardiac death at or before one year after the index procedure
   - -1b Any myocardial infarction at or before one year after the index procedure
   - -1c Stroke at or before one year after the index procedure
2. In-hospital procedure events
   - -2a Periprocedural myocardial infarction
   - -2b Coronary dissection (flow-limiting or beyond intended by lesion preparation)
   - -2c Coronary perforation/rupture

Efficacy Endpoints

1. Components of the primary composite endpoint:
   - -3a Failed or no stent delivery
   - -3b Residual area stenosis $\geq$ 20% (OCT-assessed) after PCI
   - -3c Target vessel failure at 1 year
2. Components of target vessel failure at 1 year:
   - -4a Cardiac death
   - -4b Target vessel-related myocardial infarction
   - -4c Clinically driven target vessel revascularization.
3. OCT endpoints

-5a Stent expansion at index procedure, MSA divided by the average reference area.

-5b In-stent late lumen loss up to 1 year, which is the decrease in MLA area from the index procedure.

Correspondingly, the secondary objectives are to estimate the risks for each of the secondary outcomes if they are binary, and some comparison of those risks by arm, or to estimate the average values of continuous measures and some comparison of those average values by arm. The clinical questions of interest are:

Safety:
"What are the risks of any major adverse cardiac event overall and via the pathways of cardiac death, any myocardial infarction or stroke within one year among patients randomized to receive IVL for lesion preparation before implantation of newest-generation drug-eluting stents in a severely calcified coronary lesion, and how does this risk compare to using the current conventional techniques of lesion preparation, regardless of actual use of balloon lithoplasty, additional interventions performed during initial PCI or additional treatments during the one-year after procedure, or other changes in status of patients not included in the endpoint of interest?"

"What are the risks of any in-hospital procedure event overall and via the pathways of periprocedural myocardial infarction, coronary dissection being beyond intended by lesion preparation or coronary perforation/rupture among patients randomized to receive IVL for lesion preparation before implantation of newest-generation drug-eluting stents in severely calcified coronary lesion, and how does this risk compare to using the current conventional techniques of lesion preparation, regardless of actual use of balloon lithoplasty, additional intervention performed during initial PCI or additional treatments during the one-year after procedure, or other changes in status of patients not included in the endpoint of interest?"

Efficacy:
"What are the risks of failed or no stent delivery, OCT-assessed residual area stenosis $\geq$20% or target vessel failure within one year among patients randomized to receive IVL for lesion preparation before implantation of newest-generation drug-eluting stents in severely calcified coronary lesion, and how does this risk compare to using the current conventional techniques of lesion preparation, regardless of actual use of balloon lithoplasty, additional intervention performed during initial PCI or additional treatments during the one-year after procedure, or other changes in status of patients not included in the endpoint of interest?"

"What are the risks of target vessel failure within one year via the pathways of cardiac death that is possibly related to target vessel failure, target vessel-related myocardial infraction, or clinically driven target vessel revascularization within a year of index procedure among patients randomized to receive IVL for lesion preparation before implantation of newest-generation drug-eluting stents in severely calcified coronary lesion, and how does this risk compare to using the current conventional techniques of lesion preparation, regardless of actual use of balloon lithoplasty, additional intervention performed during initial PCI or additional treatments during the one-year after procedure, or other changes in status of patients not included in the endpoint of interest?"

"What is the average stent expansion among patients having IVL for lesion preparation at index procedure and how does this stent expansion compare to using the current conventional techniques

of lesion preparation, regardless of actual use of balloon lithoplasty?"

"What is the average in-stent late lumen loss among patients undergoing IVL for lesion preparation at index procedure and how does this in-stent late lumen loss compare to using the current conventional techniques of balloon lesion preparation,regardless of actual use of balloon lithoplasty, additional intervention performed during initial PCI or additional treatments during the one-year after procedure, or other changes in status of patients not included in the endpoint of interest?

3.1.3 Exploratory

There are several exploratory endpoints:

- Procedural endpoints
  - Complications (many)
  - Procedure details (durations/doses etc)
  - Procedure cost
- OCT endpoints at index procedure
  - Stent malapposition
  - Calcium disruption
- OCT endpoints at 1 year
  - In-segment late lumen loss
  - In-segment re-stenosis
  - Stent malapposition
- Symptom status at 1 year

Here, we do not specify a hypothesis, as we will also not report p-values from any exploratory analysis.

4 Population

Inclusion criteria

- Age $\geq$18 years and $<$90 years
- Stable coronary heart disease or non-ST elevation acute coronary syndrome
- PCI planned in a severely calcified, non-occluded, de-novo lesion in a native vessel.
- Functional evidence of ischemia (non-invasive stress test or fractional flow reserve) in the target vessel territory or stenosis $\geq$90% by visual estimate
- Target vessel reference diameter visually estimated at 2.5-4 mm on angiography with ability to pass a 0.014" guidewire across lesion

- Ability to tolerate dual antiplatelet therapy
- Informed consent

Exclusion criteria

- Study lesion is unprotected left main
- Chronic total occlusion of study lesion
- Severely calcified bifurcated lesion with expected need to use two-stent technique
- Coronary artery dissection of study lesion
- ST-segment elevation acute myocardial infarction within 72 hours
- Planned later revascularization in non-study lesions (other lesions in need of revascularization must be treated before treatment of the study lesion, either staged or during the study procedure)
- Planned cardiovascular interventions within 30 days after study intervention
- Clinical instability including decompensated heart disease
- Life expectancy of less than 1 year
- Active peptic ulcer or upper gastrointestinal bleeding with 6 months
- Ongoing systemic infection
- Pregnant or nursing
- Left ventricular ejection fraction $< 35\%$
- Renal function with eGFR < 30 mL/min

4.1 Study Design

This is a two-arm, randomized (1:1), parallel, multinational open-label but assessor-blinded superiority clinical trial. The assessment of the primary outcome is blinded. Patients are booked for clinical follow-up 12 months after the procedure. At the clinical follow-up clinical events relevant to the primary endpoint are recorded prior to coronary angiography. OCT is performed again at this time (prior to any additional intervention, if conducted), and the results are available to the operator. As the clinical follow-up occurs prior to the coronary angiography, events triggered by coronary angiography are not part of the primary endpoint at one year.

5 Multiplicity Adjustment

No multiple testing correction will be used, as formal hypothesis testing will be performed only for the primary endpoint/estimand described in Section 3.1.1, for the null hypothesis defined in Section 7.1.1.

Reporting for other endpoints/estimands will either be limited to point estimates of effects with 95% (two-sided) confidence intervals, or p-values will be noted explicitly as secondary. The widths of the intervals will not be adjusted for multiplicity; therefore, it will not be possible to use them in place of formal hypothesis testing. This is in line with current recommendations [8].

6 Analysis Sets

- The **"Main analysis set A"** consists of all randomized participants who have a complete measure of the primary composite endpoint. This will exclude three groups of patients: patients who withdraw consent prior to 1 year and explicitly do not wish to participate in the 1-year clinical follow-up data collection, patients that are deemed to be lost to follow-up by the Clinical Endpoint Adjudication Board (see section 4.3 of protocol version 5.3), and patients who lack baseline OCT or Quantitative coronary angiography.

- The **"Sensitivity analysis set or Main analysis B"** consists of all randomized participants.

- **Secondary Safety endpoint analysis set 1, 1a, 1b, 1c**: consists of all randomized participants who have a measure of in-hospital and 1 year major adverse cardiac events for set 1, all randomized participants who have a measure of Cardiac death at or before one year after the index procedure, 1a, all randomized participants who have a measure of any myocardial infarction at or before one year after the index procedure, 1b, and all randomized participants who have a measure of stroke at or before one year after the index procedure, 1c.

- **Secondary Safety endpoint analysis set 2, 2a, 2b, 2c**: consists of all randomized participants who have a measure of in-hospital procedure events overall, 2, of periprocedural myocardial infarction, 2a, coronary dissection (beyond intended by lesion preparation), 2b, and coronary perforation/rupture, 2c. As it is very likely that all randomized participants will have measures of these events or be followed to know that the event did not occur, all of these groups may be the same as "Sensitivity analysis set or Main analysis B"

7 Statistical Analyses

7.1 Primary Endpoint Analysis

7.1.1 Main Analytical Approach

For this analysis, we will use the "Main analysis set A" detailed in Section 6. We will estimate the primary estimand, that is, the risk ratio π_1/π_0, as the empirical (i.e. observed) proportion of participants with the composite endpoint within 12 months after index PCI. An appropriate two-sided 95% confidence interval and matching p-value for the null hypothesis: $H0 : \pi_1/\pi_0 = 1$ will be computed.

We will use the function `uncondExact2x2` of the `R` package `exact2x2`; see [2] for the mathematical details and Appendix 9.2 for the specific `R` code that we will use. If the p-value is ≤ 0.05 and the risk ratio is < 1 for the composite primary endpoint then we will consider this evidence of the superiority of balloon lithoplasty preparation of lesions in comparison to current conventional techniques to reduce the risk of the composite endpoint. If the p-value is ≤ 0.05 and the risk ratio is > 1, we will consider this evidence of harm of balloon lithoplasty preparation of lesions in comparison to current conventional techniques, i.e. it increases the risk of the composite endpoint.

Using dataset "Main analysis set B" detailed in Section 6, we will, in addition, estimate the difference in risk $\pi_1 - \pi_0$ of all mortality that is not cardiac death within at least 12 months; the competing risk of the composite endpoint. An appropriate exact two-sided 95% confidence interval for the parameter $\pi_1 - \pi_0$ will be computed. This will be reported regardless of the result of the above analysis. We will again use the function `uncondExact2x2` of the `R` package `exact2x2`; see

[2] for the mathematical details and Appendix 9.2 for the specific R code that we will use. The primary composite endpoint results will never be presented without the results for all other causes of mortality unless there are no other deaths in the full trial.

In addition, regardless of the results, we will report the estimates of the arm-specific risk of the composite endpoint and the risk of mortality that is not cardiac death within one year (i.e. the empirical proportions) together with exact binomial two-sided 95% confidence intervals (computed using the `binom.test()` function of R).

Note that the above statistical analyses will ignore that the randomization was stratified by site. This is usually not recommended, as this usually leads to a decrease in power as stratification variables are percision variables [3, 7]. However, our context is very specific, as we expect for there to be a low number of composite endpoint events, at least in the IVL arm. This has two important consequences. First, the loss of power is expected to be negligible. Second, ensuring proper type-I error control using a "covariate-adjusted" alternative approach is difficult using standard software. Additionally, the impact of not adjusting will be investigated as part of the Sensitivity Analyses.

7.1.2 Sensitivity Analyses

For missingness The main analysis is based on the "Main analysis set A", which does not include patients for whom the primary endpoint is missing. This choice may be anti-conservative if the reason for drop-out was related to the outcome and differed between arms. For this reason, we will use the causal bounds from Gabriel et al. [5] for the effect given in equation 2 and the best-case/worst-case bounds equation 3 of the same paper if there are any missing composite outcome values based on "Main analysis set B" detailed in Section 6. If there is additional noncompliance, we will use the equivalent bounds for the per-protocol effect, as this can sometimes give large intervals. Given the conservative nature of the bounds, we will not further place confidence intervals on them unless it is deemed necessary for publication, in which case exact confidence intervals will be used.
For mechanistic imputation The composite outcome may have some form of "mechanistic" imputation, i.e. residual area stenosis $>$20% is determined by direct measurement (OCT) of, if necessary, by quantitcative coronary angiography. Values indicating residual area stenosis $>$20% from OCT or angiography are considered reliable, however, particularly with quantitative coronary angiography, missing OCT analysis due to poor image quality or failure to obtain OCT is possible and may be related to residual area stenosis. Thus, we will impute all "mechanistic" imputed residual area stenosis that were found to be $<$20% to be $>$20% to determine the impact that missed OCT analyses could cause. Additionally, all patients without true measure of no event, that were adjudicated to have no event for the primary analysis, will instead be imputed to have an event and the impact of the adjudication will be determined by rerunning the primary analysis.

As part of the sensitivity analysis, we will adjust individually and collectively, if possible, for several variables known to be strongly predictive of the composite outcome but not used as stratifying variables for randomization. Thus, if by chance they are imbalanced in randomization, adjustment for them may reduce the effect of interest. In each regression, we will also adjust for site, with an indicator for each site that has at least three events and combining sites that are geographically close as needed when less than three events have occurred within a site. This will provide the correct standard error estimates since the randomization was stratified by site. For this reason, the results may be more significant or significant when the primary analysis is not, regardless of the results of the sensitivity analysis adjusting for site; this analysis will not replace the primary analysis in the publication as it does not strongly control the type I error rate. The additional variables include:

- Presentation (acute vs. chronic)
- Prior revascularization
- Diabetes mellitus
- LAD vs non-LAD

Logistic regression, including both main effects and interactions with treatment assignment, will be considered whenever possible; we will obtain marginal risk ratios via standardization (g-computation). Example code is provided in the code section 9.2. If this is not possible, i.e. the method will not converge due to the lack of events, we will run a main effect only model.

7.2 Additional Analysis

In addition to the primary analysis based on the risk ratio of the composite primary endpoint and the risk difference of non-cardiac deaths, we will display cause specific cumulative incidence using time to the composite endpoint. If there is not competing risk of non-cardiac death, these will instead be the kaplan-meier curves.

7.3 Secondary Endpoints Analyses

For binary secondary safety endpoints we will use chi-squared tests, as we are more concerned with type II errors, i.e. not observing a true safety signal over making a type I error. Just as with the primary composite endpoint, we will never report findings for the secondary endpoints without the competing risk of death not included in the endpoint. For continuous outcomes we will use linear regression adjusting for site.

We will use the datasets numbered in the same manner as the safety outcome as detailed in Section 6 for each of the secondary safety analyses, as follows: The justification for this is that unlike efficacy secondary analysis that we would like to be comparable to the primary results and using the same dataset, for safety we will use all available data.

Safety endpoints

1. In-hospital and 1 year major adverse cardiac events and its components:

   -1a Cardiac death at or before one year after the index procedure

   -1b Any myocardial infarction at or before one year after the index procedure

   -1c Stroke at or before one year after the index procedure

2. In-hospital procedure events

   -2a Periprocedural myocardial infarction

   -2b Coronary dissection (beyond intended by lesion preparation)

   -2c Coronary perforation/rupture

For binary efficacy endpoints we will use the same exact testing as for the primary composite end point for binary outcomes and site adjusted linear regression for continuous outcomes. For all secondary efficacy analyses we will use the "Main analysis set A" detailed in Section 6, to make the results comparable and on the same set as the primary.

Efficacy endpoints

1. Components of the primary composite endpoint:

   -3a Failed or no stent delivery

   -3b Residual area stenosis $\geq 20\%$

   -3c Target vessel failure within one year

2. Components of target vessel failure at or before 1 year:

   -4a Cardiac death.

   -4b Target vessel-related myocardial infarction

   -4c Clinically driven target vessel revascularization.

3. OCT endpoints

   -5a Stent expansion at index procedure, MSA divided by the average reference area.

   -5b In-stent late lumen loss up to 1 year, which is the decrease in MLA area from the index procedure

7.3.1 Secondary Safety Sensitivity Analyses

Just as in the main analysis, if there are missing values in any of the safety datasets, 1, 1a, 1b, 1c, 2, 2a, 2b, or 2c, we will report the best/worst case bounds Gabriel et al. [5]. There will be no additional sensitivity analysis for the secondary efficacy endpoints.

7.3.2 Additional Survival Analysis

For all binary event endpoints among the secondary endpoint in addition to the risk ratio of the endpoint and the risk difference of death from a cause not including in that particular event, we will display cause specific cumulative incidence using time to the endpoint. If there is not competing risks, these will instead be the kaplan-meier curves.

7.4 Exploratory Endpoints Analysis

For binary exploratory endpoints we will use the same exact testing as for the primary composite end point for binary outcomes and site adjusted linear regression for continuous outcomes. Multiple datasets will be considered, with the default data set being "Main analysis set A", whenever possible. As some of the exploratory endpoints may have more missingness than the primary composite, when this is not possible the largest possible dataset will always be used.

There are several exploratory endpoints:

- Procedural endpoints
  - Complications (many)
  - Procedure details (durations/doses etc)
  - Procedure cost
- OCT endpoints at index procedure

  - Stent expansion
  - Stent malapposition
  - Calcium disruption

- OCT endpoints at 1 year
  - In-stent late lumen loss
  - In-segment late lumen loss
  - In-segment re-stenosis
  - Stent malapposition
  - Quantification of neointima

- Symptom status at 1 year

7.4.1 Subgroup Analyses

Prespecified subgroup analysis of the primary composite endpoints in patients with 4 points on the OCT calcium score defined by Fujino et al. [4]. In order to have 4 points the patient must have presence of all 3 criteria: maximum calcium angle >180 degrees, maximum calcium thickness of > 0.5mm, and calcium length > 5.0mm. Consequently, we exclude the patients who

- do not have any OCT during index admission
- patients who have less than 4 points on the score

Within this subgroup we will perform the primary analysis and any secondary analyses that are possibly given the subgroup. If the subgroup is small and events become rare, we will use exact methods to avoid type I error rate inflation.

7.4.2 Timing of Follow-up Visits

Descriptive statistics, per arm, will be presented for the time from randomization to the "12-month" follow-up visit (which will possible be slightly less or more than 12 months for all patients). Median, minimum, maximum, first and third quartiles will be reported. An exploratory analysis of time to the ''12-month" visit will be preformed to ensure that there is no significant difference in timing by arm.

7.4.3 Recruitment

Recruitment of the patients will be summarized via descriptive statistics. Especially, start and end dates of recruitment will be presented as well as a flowchart, inspired by the CONSORT guidelines and template [10].

7.4.4 Descriptive Statistics of Baseline Characteristics

Baseline characteristics will be descriptively summarized, within each of these four groups: randomized each arm within the main analysis set A and each arm among any patients that do not complete follow-up The list of baseline variables to be summarized includes the variables outlined in Table 1.

Table 1: Table 1 draft

Age, yrs	mean(SD)
Women	Freq (%)
Acute coronary syndrome	Freq (%)
NYHA >2	Freq (%)
CCS >2	Freq (%)
Ejection fraction	Freq (%)
BMI	kg m-2
Medical history	
Diabetes mellitus	Freq (%)
Hypertension	Freq (%)
Current smoker	Freq (%)
Renal insufficiency	Freq (%)
Myocardial infarction or coronary revascularization	Freq (%)

For continuous variables, we will present median, first and third quartiles and also minimum and maximum. Categorical variables will be summarized by numbers and percentages. Hypothesis tests will not be performed to compare baseline characteristics, but clinical importance of any apparent imbalance will be noted. This is in line with usual recommendations [9].

7.4.5 Descriptive Statistics of Outcomes

Outcomes (primary, secondary and exploritory) will also be descriptively summarized, within relevant subgroups. Similar descriptive statistics as for baseline characteristics will be used. Mean and standard deviation will be presented instead of median, first and third quartiles (or in addition to those) whenever appropriate. For each outcome.

7.4.6 Consort data

Available data about enrollment, protocol adherence and follow-up will be presented in a in a flow diagram, following the CONSORT guidelines [10].

7.5 Changes to Protocol-Planned Analyses

- The power calculations are changed from the protocol as outlined below, the original analysis was planned as a chi-squared test, but the rate of events may be too low for this to have correct type I error rate. Thus, we will use an exact test to strongly control type I error. The new power calculations are given in Section 8, below.

8 Sample Size Determination and Power Calculation

In the protocol, it was stated that to reach 80% power to detect a true difference of 15%, with 25% in the standard of care group and 10% events in the IVL group for a two-sided test with alpha of 0.05, 194 patients total, 97 per arm, are needed when randomized 1:1. However, it was planned to enroll 200 patients to allow for a low level of loss to follow-up.

Instead, when using the intended exact method, we find that 194, 97 per arm, only provides 78% power for the hypothesized true difference in risks. Using the intended enrollment of 100 per arm, we reach the desired 80% power. These power calculations were carried out using the Power2x2 function, as outlined below.

9 Supporting Documentation

9.1 R Code for Power calculations (Primary Estimand Analysis)

```
library(exact2x2)
Power2x2(n1,n2,.1,.25,0.05, pvalFunc=
           function(x1,n1,x2,n2){
             uncondExact2x2(x1,n1,x2,n2,
                            parmtype="ratio", method="FisherAdj", midp=FALSE)$p.value
           }
)
```

9.2 R Code for the Exact Unconditional Test (Primary Estimand Analysis)

```
library(exact2x2)
uncondExact2x2(x1=x1obs,                  # x1obs is the number of events in IVL group
               n1=n1obs,                  # n1obs is the number of patients in IVL group
               x2=x2obs,                  # x2obs is the number of events in SOC group
               n2=n2obs,                  # n2obs is the number of patients in SOC group
parmtype="ratio",                         # estimand is risk ratio
alternative="two.sided",
method="FisherAdj",                       # using Fisher's exact for ordering of the
parameter space
midp=FALSE,                                #midp False so that it is exact in all cases
not just exact on average
conf.level = 0.95,                         # 95% confidence level
conf.int=TRUE)                             # indicating to compute a CI
```

9.3 R Code for Exact 95%-CI for the Difference in Other Mortality Risk

```
library(exact2x2)
uncondExact2x2(x1=x1obs,                  # x1obs is the number of events in IVL group
               n1=n1obs,                  # n1obs is the number of patients in IVL group
               x2=x2obs,                  # x2obs is the number of events in SOC group
               n2=n2obs,                  # n2obs is the number of patients in SOC group
               parmtype="difference",     # estimand is risk difference
               alternative = "two.sided", # two-sided CI wanted
               method="score",            # score statistic ordering is used
               conf.level = 0.95,         # 95% confidence level
```

```
conf.int=TRUE)              # computation of CI wanted
```

References

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