# STATISTICAL ANALYSIS PLAN for NLAST

Administrative information:

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|---|---|
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| | | 5.1.3.2 (new)<br><br>Table: Summary of objectives and outcomes | New secondary outcome: Late complications, from 30 days until 2 years follow-up<br><br>Updated | |

## SIGNATURE PAGE

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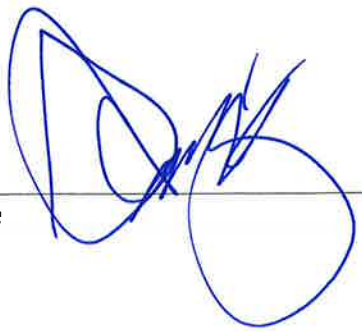

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# 1 Introduction

## 1.1 Background and rationale

International guidelines for the treatment of aortoiliac occlusive disease (AIOD) recommend open surgery for the treatment of Trans-Atlantic Inter-Society Consensus (TASC) II type D lesions. Aortobifemoral bypass has been one of the surgical options for the treatment of the patients with these lesions. Laparoscopic aortobifemoral bypass technique was introduced in 1993 by Dion YM with the promise of achieving the same excellent long-time patency of the open aortobifemoral bypass, but with the additional advantages of a minimally invasive procedure, e.g., lesser post operative pain, lesser complications, shorter recovery, and better cosmetic result.

Although, several retrospective and prospective cohort studies have been published, to address the feasibility of the laparoscopic aortobifemoral bypass, no randomized trial has been reported to this date, for the treatment of TASC II type D lesions.

Norwegian Laparoscopic Aortic Surgery Trial (NLAST) is a randomized, multi-center study, designed to compare laparoscopic aortobifemoral bypass with the open aortobifemoral bypass for the treatment of TASC II type D lesions.

## 1.2 Trial objectives

### 1.2.1 Primary objective

The primary objective of this study is to assess if laparoscopic aortobifemoral bypass (ABFB) is superior to conventional open ABFB with regard to complications in patients with symptomatic AIOD with TASC II type D lesions.

### 1.2.2 Secondary objectives

The secondary objectives of this study are:

- To assess if laparoscopic ABFB is superior to open ABFB with regard to all-cause mortality
- To assess if laparoscopic ABFB is superior to open ABFB with regard to the patency of bypass
- To assess if laparoscopic ABFB is superior to open ABFB with regard to procedure-related events and measurements

### 1.2.3 Explorative objective

To describe details of the complications for laparoscopic and open ABFB.

# 2 Trial methods

## 2.1 Trial design

The NLAST study is designed as a randomized, non-blinded, controlled, parallel-group, multicenter, single-country, superiority study. The study was carried out in three hospitals in Norway: Oslo University Hospital, Østfold Hospital Trust, and Hospital of Southern Norway. Treatment allocation is a 1:1 ratio. Patients are randomized to either laparoscopic ABFB or open ABFB treatment. The

patients have been followed up for morbidity, reoperations, and mortality for up to 10 years after operation.

## 2.2 Randomization

Eligible patients are allocated in a 1:1 ratio between laparoscopic ABFB and open ABFB, using a computer randomization procedure stratified by study center. The randomization is blocked within each stratum.

## 2.3 Sample size

The original sample size calculation was based on an allocation ratio of 2:1, with the open surgery group being twice the size of the laparoscopic surgery group. Under the assumption of a rate of systemic and local complications of 47% in the open surgery group (Bruls et al., 2012; Kazmi SSH 2015 (unpublished in 2013)) and 15% in the laparoscopic surgery group (a relative reduction of 0.315) during a mean follow-up time of 2.9 years, 70 patients in the open surgery group and 35 patients in the laparoscopic group would provide 90% power with a type I error rate of 5%. To account for loss of information due to drop-outs, the sample size was increased by 20%, such that the total number of patients to include was 126.

Before the study started, the allocation rate was changed to 1:1, providing 97% power with 126 patients and no information loss, and 91% power with 126 patients and 20% information loss.

The sample size calculations were based on a Pearson chi-squared test with continuity correction for two independent probabilities.

## 2.4 Statistical framework

### 2.4.1 Hypothesis test

This trial is designed to establish superiority of laparoscopic ABFB to open ABFB treatment with regard to complications in patients with symptomatic aorto-iliac occlusive disease (AIOD) with Trans-Atlantic Inter-Society Consensus (TASC) II type D lesions.

- The primary null hypothesis is that laparoscopic ABFB is not superior to open ABFB with regard to the proportion of patients with systemic and local complications during an average follow-up of at least 2.9 years
- The alternative hypothesis corresponding to the primary null hypothesis is that either laparoscopic ABFB is superior to open ABFB or open ABFB is superior to laparoscopic ABFB with regard to the proportion of patients with systemic and local complications

There is only one identified primary analysis in this trial. All other efficacy analyses will be regarded as supportive or exploratory.

### 2.4.2 Decision rule

This trial is designed to address a single primary outcome.

Superiority of laparoscopic surgery over open surgery is claimed if the primary null hypothesis is rejected on the significance level (alpha) of 0.05 (two-sided) and the estimated difference (laparoscopic minus open surgery) between probabilities of complications (see Section 5.2) is less than 0.

Superiority of open surgery over laparoscopic surgery is claimed if the primary null hypothesis is rejected on the significance level (alpha) of 0.05 (two-sided) and the estimated difference (laparoscopic minus open surgery) between probabilities of complications (see Section 5.2) is greater than 0.

## 2.5 Statistical interim analyses and stopping guidance

There will be no interim analysis in this trial.

There is no Data Monitoring Committee in this trial. The Steering Committee has the responsibility to ensure that the trial is conducted according to the principles in the Declaration of Helsinki and the good clinical practice guidelines, and thereby the overall safety and wellbeing of the recruited patients.

## 2.6 Timing of final analysis

The main analysis is planned when all patients have been followed for at least 1 year and on average more than 2.9 years, all data for all conducted patients visits have been entered, verified and validated and the primary database has been locked.

## 2.7 Timing of outcome assessments

| Visit Label | Target Day/Month |
|---|---|
| Screening (visit 1) | Day -1 (Randomization at out-patient clinic) |
| Baseline/operation (visit 2) | Day 0 |
| 30 days (visit 3) | Day 30 |
| 3 months (visit 4) | Day 90 |
| 6 months (visit 5) | Day 182 |
| 1 year (visit 6) | Month 12 |
| 2 years (visit 7) | Month 24 |
| 5 years (visit 8) | Month 60 |
| 10 years (visit 9) | Month 120 |

# 3 Statistical principles

## 3.1 Confidence intervals and P-values

All calculated P-values will be two-sided and compared to a 5% significance level. If a P-value is less than 0.05, the corresponding treatment group difference will be denoted as statistically significant. All efficacy estimates will be presented with two-sided 95% confidence intervals. As there is only one primary null hypothesis to be tested in this trial, there will be no adjustments for multiplicity.

## 3.2 Protocol deviations

The following are major protocol deviations regarded to affect the efficacy of the intervention:

- Entering the trial when the eligibility criteria should have prevented trial entry

- Conversion from laparoscopic to open surgery

The number (and percentage) of patients with major and minor protocol deviations will be summarized by treatment group with details of type of deviation provided. The patients that are included in the full analysis set (see section 3.3) will be used as the denominator to calculate the percentages. No formal statistical testing will be undertaken.

### 3.3 Analysis populations

The Enrolled set will include all patients who have provided informed consent and have been included into the study data base.

The Full Analysis Set (FAS) will be defined as all patients randomly assigned to a treatment group and having carried out the 30-day post-operative assessment. The FAS is the practical implementation of the intention to treat (ITT) strategy.

The Per Protocol Analysis Set (PPS) will include all randomized patients meeting the study eligibility criteria and with no major protocol deviations affecting the treatment efficacy.

## 4 Trial population

### 4.1 Screening data, eligibility and recruitment

A CONSORT flow diagram will be used to summarize the number of patients who were:

- eligible and randomized
- received the randomized allocation
- did not receive the randomized allocation*
- lost to follow-up*
- randomized and included in the primary analysis
- randomized and excluded from the primary analysis*

*reasons will be provided.

### 4.2 Withdrawal/follow-up

The status of eligible and randomized patients at trial end will be tabulated by treatment group according to

- completed intervention as randomized
- completed assessments at each study visit
- withdrew consent
- lost to follow-up

### 4.3 Baseline patient characteristics

The patient demographics and baseline characteristics to be summarized include age in years, gender, smoking status, CRP, creatinine, diagnosis specific disease activity measures, diabetes mellitus, COPD, CHD, Fontaine classification, ASA score, walking distance, AAI right and left, rest pain, run-off score right and left limb, renal disease, hyperlipidemia, TASC type Cerebrovascular disease, previous PTA, previous vascular surgery.

Patient demographics and baseline characteristics will be summarized by randomized treatment arm and overall using descriptive statistics (N, mean, standard deviation, median, 25/75 percentiles) for continuous variables, and number and percentages of patients for categorical variables. There will be no statistical analysis of treatment difference. Any clinical important imbalance between the treatment groups will be noted.

# 5 Analysis

## 5.1 Outcome definitions

### 5.1.1 General definitions and derived variables

#### *5.1.1.1 Complications*

Complications include local, systemic, and vascular complications which arose under or after the operative procedure. They are classified according to Clavien-Dindo scale of surgical complications. Further complications include pneumonia, local infection, local fluid leakage, heart attack, cerebral insult, ileus, vascular graft infection, and patency if stenosis or occlusion of the graft.

#### *5.1.1.2 Patency*

Patency is a categorical variable with four outcomes:

- 1 = Primary patency: open
- 2 = Assisted primary patency: patency preserved with minor reintervention
- 3 = Secondary patency: patency obtained by restoration after occlusion
- 4 = Occluded

Patency is measured for the left and right limbs separately (Limb-based)

#### *5.1.1.3 Re-operations*

Re-operations within 30 days of surgery, for bleeding or other surgical complications.

### 5.1.2 Primary outcome definition: Complications during follow-up ≥ 2.9 years

The primary outcome is the occurrence of complications (see definition in Section 5.1.1.1) during an average follow-up of at least 2.9 years after surgery. The primary outcome is dichotomous (yes/no).

### 5.1.3 Secondary outcomes definitions

#### *5.1.3.1 Post-operational complications within 30 days*

Post-operative complications within 30 days is a dichotomous variable (yes/no).

#### *5.1.3.2 Late complications, from 30 days until end of follow-up*

Late complications is a dichotomous variable (yes/no).

#### *5.1.3.3 Time to complications up to 10 years after surgery*

Time to complications up to 10 years after surgery is the time from operation until the first visit where the patient has recorded a complication (see definition of visits in Section 2.7). If a patient does not experience a complication, the observation is censored at the patient's last visit. This outcome is a time to event outcome, and the outcome is interval-censored.

#### *5.1.3.4 Time to mortality*

Time to all-cause mortality is defined as the time from operation until the patient's date of death. Patients who do not die are censored at their last visit. This is a time to event outcome.

#### *5.1.3.5 Patency at 30 days (left limb and right limb)*

Patency at the 30 days visit is an ordered categorical outcome with four categories (see Section 5.1.1.2). There are two outcomes: one for the left limb and one for the right limb.

#### *5.1.3.6 Patency at 12 months (left limb and right limb)*

Patency at the 12 months visit is an ordered categorical outcome with four categories (see Section 5.1.1.2). Patency at the 30 days visit will be used for patients with no 12 months visit. There are two outcomes: one for the left limb and one for the right limb.

#### *5.1.3.7 Patency up to 10 years after surgery (left limb and right limb)*

Patency up to 10 years after surgery is defined as the patency at each patient's last visit. This is an ordered categorical outcome with four categories. There are two outcomes: one for the left limb and one for the right limb.

#### *5.1.3.8 Duration of operation*

Duration of operation is defined as the time measured in minutes from incision until the closure of the operative wound. This is regarded as a continuous outcome.

#### *5.1.3.9 Length of hospital stay*

Length of hospital stay is defined as the number of days from the patient was admitted to the hospital to the patient was discharged from the hospital. This is regarded as a continuous outcome.

#### *5.1.3.10 Operative blood loss*

Operative blood loss is defined as blood loss measured in ml during the surgery. This is regarded as a continuous outcome.

#### *5.1.3.11 Postoperative rest pain*

Rest pain is a dichotomous variable (yes/no) measured post-operative.

#### *5.1.3.12 Re-operations within 30 days*

Re-operations (see Section 5.1.1.5) within 30 days is a dichotomous variable (yes/no).

#### *5.1.3.13 Time to re-operations up to 10 years after surgery*

Time to re-operations up to 10 years after surgery is the time from operation until the first visit where the patient has recorded a re-operation for a vascular patology in the Y graft, and or infra inguinal arteries. If a patient does not have a re-operation, the observation is censored at the patient's last visit. This outcome is a time to event outcome, and the outcome is interval-censored.

**Table: Summary of objectives and outcomes**

| Objectives | Outcomes (type) | Analysis method* |
|---|---|---|
| *Primary*<br>Assess if laparoscopic ABFB is superior to open ABFB with regard to complications | *Primary*<br>Complications during follow-up ≥ 2.9 years (dichotomous)<br><br>*Secondary*<br>• Post-operational complications within 30 days (dichotomous)<br>• Late complications, from 30 days until 2 years follow-up (dichotomous)<br>• Time to complications up to 10 years after surgery (time to event; interval-censored) | Newcombe hybrid score<br>Fisher mid-p<br><br><br>Newcombe hybrid score<br><br>Newcombe hybrid score<br><br>Interval-censored Cox |
| *Secondary*<br>Assess if laparoscopic ABFB is superior to open ABFB with regard to mortality | *Secondary*<br>Time mortality up to 10 years after surgery (time to event) | Cox regression |
| *Secondary*<br>Assess if laparoscopic ABFB is superior to open ABFB with regard to the patency of bypass | *Secondary*<br>• Patency at 30 days: left limb<br>• Patency at 30 days: right limb<br>• Patency at 12 months: left limb<br>• Patency at 12 months: right limb<br>• Patency up to 10 years after surgery: left limb<br>• Patency up to 10 years after surgery: right limb<br>(all outcomes: ordered categorical) | Proportional odds model<br>Proportional odds model<br>Proportional odds model<br>Proportional odds model<br>Proportional odds model<br>Proportional odds model |
| *Secondary*<br>Assess if laparoscopic ABFB is superior to open ABFB with regard to procedure-related events and measurements | *Secondary*<br>• Duration of operation (continuous)<br>• Length of hospital stay (continuous)<br>• Operative blood loss (continuous)<br>• Change from preop in postoperative creatinine (continuous)<br>• Postoperative rest pain (dichotomous)<br>• Re-operations within 30 days (dichotomous)<br>• Time to re-operations up to 10 years after surgery (time to event; interval-censored) | Linear regression<br>Linear regression<br>Linear regression<br>Linear regression<br><br>Newcombe hybrid score<br>Newcombe hybrid score<br>Interval-censored Cox |
| *Explorative*<br>Describe details of the complications for laparoscopic and open ABFB | *Explorative*<br>• Complications categorized according to intensity (Clavien-Dindo scale): Grade II, IIIa, IIIb, IVa, IVb<br>• Complications categorized as local, systemic, or related to the vascular graft, pneumonia, heart attack, kidney failure, cerebral ischemia | Descriptive statistics<br><br>Descriptive statistics |

*See Section 5.2 for details

## 5.2 Analysis methods

All analyses will be performed on the full analysis set (see Section 3.3). Additionally, the primary outcome will also be analyzed on the per protocol set.

### 5.2.1 Primary outcome

The primary outcome, complications during follow-up ≥ 2.9 years, will be analyzed with a Newcombe hybrid score confidence interval for the difference between probabilities (Chapter 4 of Fagerland et al., 2017). The observed count and percentage of the outcome in each treatment group and the estimated difference between the probabilities of the outcome with a 95% confidence interval will be reported. We will also report a two-sided *P*-value for the null hypothesis of equal probabilities in the treatment groups, calculated by the Fisher mid-p test (Chapter 4 of Fagerland et al., 2017).

The primary analysis of the primary outcome will be performed on the full analysis set.

As an alternative, supportive analysis, the primary outcome will also be analyzed on the per protocol set.

### 5.2.1 Secondary dichotomous outcomes

Secondary dichotomous outcomes (post-operational complications within 30 days, late complications, postoperative rest pain, re-operations within 30 days) will be analyzed with a Newcombe hybrid score confidence interval for the difference between probabilities (Chapter 4 of Fagerland et al., 2017). The observed count and percentage of the outcome in each treatment group and the estimated difference between the probabilities of the outcome with a 95% confidence interval will be reported.

### 5.2.1 Secondary outcomes with interval-censored survival-time data

Secondary outcomes with interval-censored survival-time data (time to complications up to 10 years after surgery, time to re-operations up to 10 years after surgery) will be analyzed with a Cox proportion hazard regression model for interval-censored survival-time data. The regression model will include treatment (laparoscopic vs open surgery) and study center (stratification factor in the randomization) as independent variables.

The lower endpoint of a patient's interval is defined as the number of days from operation to the patient's last visit (see Section 2.7) without having recorded a complication/re-operation. If a patient recorded a complication/re-operation at the first post-operative visit (visit #3 at 30 days), the lower endpoint is set to 0 days (left-censored observation). The upper endpoint of the interval is defined as the number of days from operation to the first visit wherein the patient recorded a complication/re-operation (interval-censored observation). If a patient did not experience a complication/re-operation, the upper endpoint is set to missing (right-censored observation).

Based on the interval-censored Cox model, the hazard ratio for laparoscopic vs open surgery with a 95% confidence interval will be reported. A plot of the Kaplan-Meier survival curves of the two treatments will be presented.

### 5.2.2 Secondary outcomes with survival-time data

Secondary outcomes with survival-time data (time to all-cause mortality) will be analyzed with a Cox proportional hazard regression model, with treatment (laparoscopic vs open surgery) and study center (stratification factor in the randomization) as independent variables. Based on this model, the hazard ratio and its 95% confidence interval will be reported. A plot of the Kaplan-Meier survival curves of the two treatments will be presented.

### 5.2.3 Secondary ordered categorical outcomes

Secondary ordered categorical outcomes (patency, at different time points) will be analyzed with a proportional odds model (Chapter 6 of Fagerland et al., 2017). The model will include treatment (laparoscopic vs open surgery) and study center (stratification factor in the randomization) as independent variables. The observed number and percentages in each treatment group in each category will be presented together with the odds ratio (for treatment effect in the proportional odds model) and its 95% confidence interval.

#### 5.2.4 Secondary continuous outcomes

Secondary continuous outcomes (duration of operation, length of hospital stay, operative blood loss) will be analyzed with linear regression, with treatment (laparoscopic vs open surgery) and study center (stratification factor in the randomization) as independent variables. The estimated difference in the continuous outcome between laparoscopic and open surgery will be reported as the estimated coefficient for treatment with a 95% confidence interval.

Change from preop in postoperative creatinine will be analyzed with ANCOVA: linear regression with postoperative creatinine as the dependent variable and treatment (laparoscopic vs open surgery), study center (stratification factor in the randomization), and preoperative creatinine as independent variables. The estimated difference in change from preop to postop between laparoscopic and open surgery will be reported as the estimated coefficient for treatment with a 95% confidence interval.

## 5.3 Assumption checks

#### 5.3.1 Newcombe hybrid score interval & Fisher mid-p test

These two methods are robust to small cell counts and sparse data (as opposed to, for instance, the Wald interval and the Pearson chi-squared test), and they are recommended for use in all but the smallest sample-sizes (Chapter 4 of Fagerland et al., 2017).

#### 5.3.2 Cox proportional hazard models

The Cox proportional hazard regression models (both ordinary and interval-censored) assumes that the hazard ratio is constant over time. This will be checked by plotting -log(log(survival)) curves for each treatment against log(analysis time) and assessing if the curves are parallel. If the proportional hazard assumption is deemed to be violated, parametric survival models will be fitted instead. The following survival distributions will be considered: Weibull, exponential, Gompertz, and lognormal. The goodness-of-fit of each model will be assessed with plots of Cox–Snell residuals against the estimated cumulative hazard function of the residuals, and the one with the best fit will be the chosen model.

#### 5.3.1 Proportional odds model

The assumption of proportional odds (for analyzing ordered categorical outcomes) will be tested with the Brant test (Brant, 1990; Chapter 6 of Fagerland et al., 2017).

#### 5.3.2 Linear regression

Approximate normality of the residuals from the linear regression models will be assessed with descriptive statistics (mean, median, standard deviation, skewness coefficient) and histograms. If the assumption of normality is deemed to be violated, median regression with bootstrap confidence intervals will be used instead of linear regression, and medians and differences of medians will be reported instead of means.

## 5.4 Missing data

For the primary outcome and all other time to event outcomes, missing data will be handled by left-, right-, or interval-censoring.

For all other outcomes, we expect less than 10% missing data, and complete case analysis will be performed. In case of an outcome with more than 10% missing data, we will define worst-case and best-case imputation scenarios. For categorical outcomes, best-case will be the category with the most beneficial outcome, and worst-case will be the category with the most disadvantageous outcome. For continuous outcomes, best case (worst case) will be defined as the mean value within the treatment group + one standard deviation in the beneficial (disadvantageous) direction. The analysis of the outcome will then be performed on the three data sets complete case, best-case scenario, and worst-case scenario, and the robustness of the results across the analyses will be discussed.

# 6 Statistical software

All statistical analyses will be done in Stata version 17 (StataCorp LLC, College Station, TX, USA).

# 7 References

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