ST. OLAVS HOSPITAL
TRONDHEIM UNIVERSITY HOSPITAL

Norwegian Air Ambulance Foundation

Statistical analysis plan

The REBOARREST trial

A randomised trial on resuscitative endovascular balloon occlusion of the aorta in non-traumatic out of hospital cardiac arrest

The Universal Trial Number (UTN) WHO: U1111-1253-0322

Sponsor: Clinic of Cardiology, St. Olavs University Hospital

Funder: Norwegian Air Ambulance Foundation

Chief Investigator: Dr. Andreas Jørstad Krüger, MD, PhD

Project Manager: Dr. Jostein Rødseth Brede, MD, PhD

Statistical analysis plan version 1.0 Date: June 2023

This document is written based on information from the study protocol version 1.3, dated 14.06.2021.

Revision history

Version number Date	Description

1 CONTACT DETAILS

Chief Investigator

Name	Andreas Jørstad Krüger
Professional position	MD, PhD, Consultant Anaesthesiologist
Address	Luftambulansebasen Trondheim, Vestre Rosten 114, 7075 Trondheim, Norway.
E-mail address	Andreas.kruger@ntnu.no
Phone number	+47 908 62 586

Study statistician

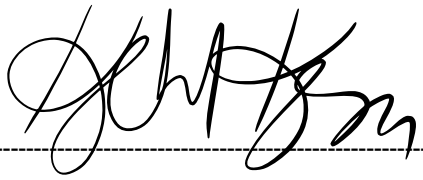
Name	Kjetil Thorsen
Professional position	PhD, Department of Research, Norwegian Air Ambulance Foundation, Oslo, Norway.
E-mail address	Kjetil.thorsen@norskluftambulanse.no
Phone number	+47 980 35 175

2 SIGNATURES

Statistician signatory approval

I hereby declare that I will conduct the statistical analysis in compliance with the protocol and the applicable regulatory requirements:

Name: Kjetil Thorsen



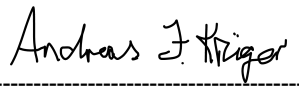
---------- 01.06.2023

Statistician signature Date

Chief Investigator signatory approval

I hereby declare that I will conduct the study in compliance with the protocol and the applicable regulatory requirements. This document contains confidential and proprietary information and may not be copied or reproduced in whole or part without the written permission of sponsor.

Name: Andreas Jørstad Krüger



---------- Trondheim 01.08.2024

Chief Investigator signature Date

Other signatures

I hereby declare that this statistical analysis plan is in compliance with the protocol and the applicable regulatory requirements and study documents:

Name	Role	Signature	Date
Bjørn Hoftun Farbu	SAP author		01.06.2023
Tom Ivar Lund Nilsen	DMC statistician		01.06.2023

3 ABBREVIATIONS

ACLS	Advanced Cardiovascular Life Support
CPR	Cardiopulmonary Resuscitation
CRF	Case Report Form
EtCO2	End Tidal CO2
IPD	Important Protocol Deviation
ITT	Intention-to-treat
LVEF	Left Ventricular Ejection Fraction
mRS	Modified Rankin Scale
NID	Not Important Deviation
OHCA	Out of Hospital Cardiac Arrest
PD	Protocol Deviation
PI	Principal Investigator
REBOA	Resuscitative Endovascular Balloon Occlusion of the Aorta
ROSC	Return of Spontaneous Circulation
SAE	Serious Adverse Event
SD	Standard deviation

4 INTRODUCTION

This Statistical Analysis Plan follows the "Guidelines for the Content of Statistical Analysis Plans in Clinical Trials" published by Gamble, complying with the ICH E9 guideline [1]. Background, rationale and objectives for this trial are thoroughly described in the protocol and are here referred briefly.

4.1 Background

Out-of-hospital cardiac arrest (OHCA) carries a low survival rate with a reported 30-day survival rate of 14% in Norway [2]. Cardiopulmonary resuscitation (CPR) prolongs the time prior to hypoxic irreversible damage, by delivery of partially oxygenated blood to vital organs [3]. The treatment of out-of-hospital cardiac arrest is advanced cardiovascular life support (ACLS) as stated in the guidelines from the Norwegian Resuscitation Council [4] and the European Resuscitation Guidelines [5].

Resuscitative endovascular balloon occlusion of the aorta (REBOA) is a technique used to provide occlusion of the aorta by inflation of an intra-aortic balloon. Thoracic aortic occlusion provides a redistribution of the cardiac output to organs proximal to the occlusion through reduction of vascular volume where generated cardiac output is distributed. Preclinical studies demonstrate that REBOA during cardiopulmonary resuscitation provide both increased coronary artery blood flow and perfusion pressure and increased rates of return of spontaneous circulation (ROSC) [6-13]. A pilot trial demonstrated that pre-hospital REBOA procedure during resuscitation is feasible and did not negatively influence the quality of the ACLS [14].

4.2 Rationale

The purpose of the study is to assess the efficacy of REBOA as an adjunct treatment to ACLS in non-traumatic out-of-hospital cardiac arrest.

4.3 Objectives

The primary objective is to assess the efficacy of REBOA as an adjunct treatment to ACLS versus ACLS only on sustained ROSC (≥20 minutes) in patients with non-traumatic out-of-hospital cardiac arrest. Secondary objectives of this trial are to assess the difference in 30-day survival with good neurological status, left ventricular ejection fraction (LVEF) upon hospital admission, and adverse events between the intervention and control group, and to describe the hemodynamic physiology of aortic occlusion during ACLS in the intervention group.

4.4 Statistical hypothesis

Null hypothesis H_0: There is no difference in the proportion of patients with sustained ROSC between the intervention group (advanced cardiovascular life support + REBOA) and the control group (advanced cardiovascular life support only).

Alternative hypothesis H_A: There is a difference in the proportion of patients with sustained ROSC between the intervention group (advanced cardiovascular life support + REBOA) and the control group (advanced cardiovascular life support only).

5 STUDY METHODS

5.1 Trial design

This is a randomised, parallel group, multi-centre, phase II clinical trial designed to assess the efficacy and hemodynamic effects of REBOA in study subjects suffering from non-traumatic OHCA. Patients are randomised in

a 1:1 ratio to either ACLS according to national guidelines or ACLS according to national guidelines plus REBOA. A group sequential design with adaptive sample size modification is further chosen to allow for the possibility of stopping the trial early due to significant differences in benefit or harm in the primary endpoint or in the proportion of patients with 30-day survival between the intervention and control group, and to re-estimate sample size at the interim analyses to obtain the desired statistical power.

5.2 Eligibility criteria

5.2.1 INCLUSION CRITERIA

The subject must meet all the following criteria to be included in the trial:

- Estimated age between 18 and 80 years
- Out-of-hospital cardiac arrest
- Non-traumatic cardiac arrest
- Less than 10 minutes from debut of arrest to start of basic or advanced cardiac life support
- ACLS is established and can be continued

5.2.2 EXCLUSION CRITERIA

Fulfilling one criterion excludes the subject from being included in the trial:

- Traumatic cardiac arrest, including strangulation, electrocution and patients rescued from avalanches
- Accidental hypothermia with temperature < 32 ^{0}C
- Suspected cerebral haemorrhage as aetiology of the arrest
- Suspected non-traumatic haemorrhage as aetiology of the arrest
- Pregnancy, obvious or suspected
- Patient included to the study site's e-CPR (Extracorporeal Cardiopulmonary Resuscitation) protocol
- Other factors as decided by the treatment team (environmental factors, safety factors and others)

5.3 Randomisation and blinding

A permuted block randomisation method stratified by site will be used to allocate eligible patients to either the intervention group or the control group. Blocks will be of variable size unknown to investigators and physicians. Randomisation will be as sealed envelopes to be selected on scene if the patient is eligible for randomisation. Each site will have envelopes available in the intervention kit (one in each helicopter and/or rapid response car).

Randomisation allocation and production of envelopes will be performed by KlinForsk, Clinical Research Unit, Central Norway. The random allocation sequence is generated by KlinForsk using a Microsoft Access data base. No investigator has access to the allocation sequence.

Due to the nature of the intervention, neither the treating physician nor any other health personnel will be blinded to the intervention. Patients will however remain unconscious from randomisation until occurrence of the primary end point. The treating physician will be the assessor of the primary outcome. Because of the invasive intervention, investigators will be aware of treatment allocation in agreement with monitor in order to closely follow up adverse events and protocol adherence. The statistician performing the final analysis will be blinded to group allocation.

5.4 Trial intervention

Patients randomised to REBOA will have a REBOA catheter inserted through an introducer in either right or left femoral artery during ongoing CPR. When the balloon is in the thoracic aorta (zone 1), it will be inflated to (near) aortic occlusion. In the feasibility study average procedural time was 12 minutes [14]. The balloon will remain inflated until ROSC. When ROSC is deemed to have occurred, the balloon will be deflated over 30 seconds. If the patient re-arrest, the balloon is inflated again.

5.5 Sample size

At the time of protocol writing, no other prospective study other than the pilot study [14] was known to us. This pilot study was without a control group, the number of patients was only 10, with 60% obtaining ROSC and with one survivor after 30 days. We still lack prospective data as a basis for an exact estimation of sample size for a conclusive trial design. Patients who are eligible for a REBOA procedure are defined by the inclusion and exclusion criteria, the duration of the dispatch and necessary procedure duration. Patients who could have been eligible for REBOA in Norway are described in detail in a needs assessment for REBOA in non-traumatic OHCA [15]. The reported rate of ROSC in this cohort was 18% [15].

Thus, we will assume that the proportion obtaining sustained ROSC in the control group is 18%. Further, we define a clinically relevant effect to be twice this proportion in the intervention group (i.e. 36%). With 80 % power and a two-sided significance level of 0.05, the sample size needed to demonstrate a doubling in the proportion obtaining ROSC, from 18 % to 36 %, is 94 patients in each group [16]. To allow for repeated testing of the primary end point in the interim analyses and a potential withdrawal/loss to follow-up rate of around 3 %, we choose to include 100 patients in each group, 200 in total.

5.6 Interim analyses and stopping guidance

The analysis schedule is outlined in Table 1, with three interim analyses after 30, 60 and 90 patients are included in both the intervention and the control group. No specific time schedule for interim analyses is set. All interim analyses will be conducted by the data monitoring committee (DMC). The results will only be communicated to the DMC members, unless the DMC recommends the sponsor to terminate the trial or have other important concerns regarding the conduct of the trial. DMC may contact the study statistician in case of technical issues and clarifications.

The treatment effect on between-group risk differences for sustained ROSC (i.e, primary endpoint) and 30-day survival with good neurologic outcome will be assessed for both benefit and harm. The DMC will consider to recommend stopping the trial if there is a difference in the primary endpoint or 30-day survival between the groups, with a significance level following the O´Brien-Fleming approach (Table 1) [17, 18]. The interim analyses will be conducted using logistic regression adjusted for study site. In case of convergence issues of the logistic regression model due to few included patients at some centers, centers within the same country may be collapsed to improve model specification.

From the second interim analysis, the DMC will conduct a sample size re-estimation, based on the assumption that the current difference between the two groups in the primary endpoint persists. The sample size will be estimated

as described above, but without adjusting for repeated testing or withdrawal/loss to follow-up. If the sample size needed to identify a statistically significant difference (with 80% power and a significance level of 0.05) is more than three times the planned sample size, the DMC will consider recommending the sponsor to stop the trial due to futility.

At the last interim analysis, the DMC will re-estimate the sample size if the difference in the primary endpoint is non-significant. If the estimated sample size needed to identify a statistically significant difference between the groups is above 200 in total, but equal to or less than 300 (with 80% power and a significance level of 0.05), the final sample size will be modified and the DMC will consider to recommend the sponsor to continue the trial until the modified sample size is reached. If an increase in sample size is warranted, the conditional power at this stage will be estimated, and if it falls in the "promising zone" according to Mehta, the final nalysis will be performed as planned [19]. If the conditional power is in the "unfavorable zone", we will apply the test procedure described by Lehmacher in the final analysis in order to keep our planned significance level [20].

Table 1. Interim analyses

Analysis	Type	Number of participants in each group	Total number of participants	Assessment	Significance level *
1	Interim	30	60	Primary endpoint and 30-day survival with good neurological outcome	0.0001
2	Interim	60	120	Primary endpoint, 30-day survival with good neurological outcome, and futility	0.004
3	Interim	90	180	Primary endpoint, 30-day survival with good neurological outcome and futility/extention	0.019
4	Final	100-150	200-300	All endpoints**	0.043

*Significance levels are according to the O´Brien-Fleming approach.
**The results may be published before all patients have reached one year post inclusion.

6 STATISTICAL PRINCIPLES

6.1 Confidence intervals and p-values

All applicable statistical tests will be two-sided with a 5 % significance level. To account for repeated testing of the primary endpoint in the interim analyses, a significance level following the O´Brien-Fleming approach will be used.

Other p-values will not be adjusted for multiple comparisons. Precision of the estimated effects of the intervention will be assessed by a 95% confidence interval.

6.2 Adherence and protocol deviations

The intervention can be aborted after randomisation for numerous reasons not defined as protocol deviations, i.e. patient achieving ROSC before balloon occlusion, resuscitation efforts are abandoned or technical reasons concerning the procedure. Adherence to the intervention will be presented as patients randomised to REBOA, with patients not achieving aortic occlusion listed with numbers and reasons. Important and not important protocol deviations will be summarised with number (and percentages) by treatment group with details of type of deviation provided. The patients that are included in the full analysis set will be used as the denominator to calculate the percentages. No formal statistical testing will be conducted for this purpose.

Protocol Deviation (PD): any change, divergence or departure from the study design or procedures defined in the protocol.
Important Protocol Deviation (IPD): A PD that may significantly impact the completeness, accuracy, and/or reliability of the study data or that may significantly affect a subject's rights, safety, or well-being.
Not Important Deviation (NID): A PD that is unlikely to have a significant effect on the rights, safety, or well-being of subjects and/or the quality or integrity of data.

IPDs for The REBOARREST Trial are:

- Subjects entered into the study even though they did not meet the entry criteria.
- Subjects randomized to the control group received the intervention and vice versa.
- Failure to collect data necessary to interpret the primary endpoint and/or the secondary endpoint "*30-day survival rate with good neurologic status defined as modified Rankin scale (mRs) score 0-3*".
- Important risks identified in the risk evaluation as not acceptable:
  - Venous placement of the REBOA catheter
  - Any study procedure resulted in a negative influence of the resuscitation quality to the degree that it probably affected the subject's safety

6.3 Analysis populations

We define the following populations for this trial:

- **Full analysis set (FAS):** Following the Intention-to-treat (ITT) principle participants will be analysed according to the treatment they were randomised to receive, irrespective of compliance with the protocol. All patients in the REBOA group will be included in regardless of actual occlusion of the aorta. Patients whose consent are not obtained, or withdrawn, will be excluded.

- **Per protocol set (PPS):** The per-protocol set will consist of subjects without important protocol deviations and, among subjects randomised to the intervention group, only those who actually received aortic occlusion. Reasons for not achieving aortic occlusion in the intervention group will be provided (see section 6.2).

7 TRIAL POPULATION

7.1 Screening data

The following summaries will be presented for all screened patients:

Enrolment: the number of days recruiting, the number of patients screened, the number of patients recruited, the number of patients recruited per month, the number of screened patients not recruited, and the reason for non-recruitment. This summary will be provided as overall numbers and by study centre.

7.2 Eligibility

The number of ineligible patients randomised, if any, will be reported, with reasons for ineligibility.

7.3 Recruitment

A Consolidated Standards Of Reporting Trials (CONSORT) flow diagram [21] will be used to summarise the number of patients who were:

- Assessed for eligibility at screening
    - Eligible at screening
    - Ineligible at screening*
    - Eligible and randomised
    - Eligible but not randomised*
    - Received the randomised allocation
    - Did not receive the randomised allocation*
    - Lost to follow-up*
    - Randomised and included in the primary analysis
    - Randomised and excluded from the primary analysis*

*reasons will be provided.

7.4 Withdrawal/Follow-up – level of withdrawal

The level of consent withdrawal will be tabulated (classified as “consent to continue follow-up and data collection” or “no further follow-up or data collection”).

Timing of withdrawal/lost to follow-up data will be presented as a table with numbers and reasons for withdrawal and/or exclusion from analysis given at each stage (primary hospital admission, 30 days, 1 year) and summarized by treatment arm.

7.5 Baseline patient characteristics

Patients will be described with respect to age, gender, Charlson Comorbidity Index and Utstein template parameters separately for the two groups (Supplementary mock Table 1). Categorical data will be summarized by numbers and percentages. Continuous data will be summarized by mean and standard deviation (SD) if data are normal and median and interquartile range (Q1-Q3) if data are skewed. Tests of statistical significance will not be performed on baseline characteristics.

8 ANALYSIS

8.1 Outcome definitions

8.1.1 THE PRIMARY ENDPOINT

The primary endpoint of this study is return of spontaneous circulation (ROSC) with a duration of at least 20 minutes, i.e. sustained ROSC (dichotomous outcome).

This clinical endpoint is based on the following Utstein definition updated in 2019 [22]: "Sustained ROSC is deemed to have occurred when chest compressions are not required for 20 consecutive minutes and signs of circulation persist." Whether or not a patient has obtained ROSC is a comprehensive clinical assessment performed at regular intervals during the provision of CPR. This assessment is made in patients with an organized rhythm on ECG during pauses in chest compressions. ROSC should be suspected if one or more of the following occur [22]:

- Signs of life, including coughing, movement and/or regular breathing
- Palpable pulses in radial, carotid and/or femoral arteries
- Invasive systolic blood pressure > 50 mmHg

The current 2015 guidelines from the European Resuscitation Council state that a rise in measured end-tidal CO2 values (EtCO2) during CPR is indicative of ROSC [23]. Establishment of REBOA may also give a transient increase in EtCO2 brede. There are no current cut-off values for EtCO2 deemed appropriate to use in this setting to indicate whether ROSC has occurred or not. Any rise in EtCO2 should be clinically assessed in conjunction with other signs of circulation. If the patient has shorter periods of ROSC and do not obtain a persisting circulation, the patient has not met the primary endpoint. In the documentation, 'any ROSC', is stated in these instances.

8.1.2 THE SECONDARY ENDPOINTS

8.1.2.1 30-day survival with good neurologic status

This is a dichotomous outcome. Alive with good neurologic status is defined as modified Rankin Scale (mRS) score 0-3, as compared to death or poor neurologic status (mRS 4-6) (Supplementary table 1). If mRS is not stated in the electronic patient journal, it is scored by the local principal investigator (PI).

8.1.2.2 Difference in end-tidal CO2 measurements in the control group and the intervention group after aortic occlusion

End-tidal carbon dioxide is the partial pressure of carbon dioxide (pCO_2) measured at the end of expiration, and is recommended to monitor during cardiac arrest [24]. Time points of registration are at randomisation and first ROSC in both groups. In the REBOA-group it is also recorded immediately before balloon inflation and 30, 60, 90 and 120 seconds thereafter. In this study several types of end-tidal CO2 monitors are utilized. Values are manually recorded at the including physician´s discretion. We will present data in kPa. (Continuous and longitudinal data)

8.1.2.3 Change in blood pressures after aortic occlusion

This endpoint applies only to patients in the intervention group where the type of catheter have CE/FDA approval for invasive blood pressure measurements. High resolution intra-aortic blood pressure (mmHg) measured at the tip of the catheter, and recorded in the monitor data file, will be utilized.

The mean change in aortic blood pressure from before to after balloon inflation will be evaluated. Blood pressures in compression phase, relaxation phase and mean pressures will be compared. Before inflation is mean values from start of blood pressure recordings to balloon inflation, and after balloon inflation is mean values over the 2 minutes following inflation. (Continuous and longitudinal data)

8.1.2.4 Left ventricular ejection fraction (LVEF)

LVEF is estimated by echocardiography. It is defined by end-systolic blood volume in left cardiac ventricle divided by end-diastolic blood volume in left ventricle and is expressed as a percentage. The value used in the analysis is the first value recorded in the medical record after admission to hospital, and as estimated by the attending physician. The method of estimation (Simpson, "eye-ball", M-mode etc) is at physician´s discretion (continuous data).

8.1.3 EXPLORATORY ENDPOINTS

8.1.3.1 Variable "Any ROSC"

This is the occurrence of any ROSC after randomisation, regardless of duration.

8.1.3.2 Incidence of all adverse events

Adverse events are specified in the protocol and reported in the CRF. They will be classified according to expectedness, seriousness, severity and causality.

8.1.3.3 All-cause mortality one year after randomisation

8.1.3.4 Organ injury and dysfunction

Variables of organ injury and dysfunction are presented in Supplementary mock table 6.

8.2 Analysis methods

8.2.1 PRIMARY ENDPOINT

- Primary analysis

  The event of ROSC with a duration of at least 20 minutes will be analysed using a logistic regression model. The estimated effect of the dichotomous treatment variable will be adjusted for study site (the stratification factor used in the randomisation) [25]. In case of convergence issues of the logistic regression model due to few included patients at some centers, centers within the same country may be collapsed to improve model specification. The primary analysis will be done in the FAS, and this analysis will be the basis for our primary conclusion.

- Summary measures

  The absolute number of patients with sustained ROSC in the two groups will be presented as numbers and percentages. The primary effect estimate will be the adjusted between-group risk difference, with 95% CI, based on marginal means.

Mock Table 1. Primary Endpoint

	REBOA – group (n1=)	Control – group (n2=)	Unadjusted RD (95 % CI)	Adjusted RD (95 % CI)	p-value
ROSC lasting 20 minutes or more	n/n1 (%)	n/n2 (%)			

REBOA: Resuscitative endovascular balloon occlusion of the aorta, ROSC: Return of spontaneuous circulation, CI: Confidence interval, RD: Risk difference

- Assumption checks and alternative analyses

  As there are no continuous covariates in the logistic regression, there will be no assumption checks performed for the primary analysis.

- Missing data

  We will use complete cases. Randomisation and intervention are performed on scene and the primary endpoint will be determined within the timeframe of prehospital resuscitation. Further, it is not possible to close the electronic CRF before both the randomisation and primary endpoint are registered. Therefore we expect no missing data for variables used in the analysis of the primary outcome.

- Per-protocol analysis

  As stated in the protocol, a per-protocol analysis will be considered if >5 % of the total number of patients randomised to REBOA did not receive aortic occlusion. This is in order to evaluate the efficacy of aortic occlusion in obtaining sustained ROSC, rather than the effectiveness of assigning patients in cardiac arrest to the REBOA procedure. Some patients in the intervention group will achieve ROSC, or possibly be decleared dead, before the procedure is finished and the balloon is inflated. In addition, there might be other known and unknown confounding factors. We will therefore adjust for selection bias by applying the complier average causal effect (CACE) method [26, 27]. Compliers will be patients in the intervention group where the balloon is inflated. We expect few, or none, contaminators (i.e. patients in the control group where a balloon is inflated). The FAS will be the basis for this analysis.

- Sensitivity analyses

  We will adjust the primary analysis by "time to randomisation" and "rhythm at randomisation". If there is enough variation, we will consider to treat the study site as a random effect. Time will be assessed for non-linearity and added as a non-linear effect if appropriate. Missing data, subgroups and other analyses will be assessed in a blinded review after closure of the CRF, but before breaking the blind.

  For the per-protocol analysis we will perform several sensitivity analyses. First, we will analyse the primary endpoint in the PPS, but exclude patients from the control group who achieve sustained ROSC or are decleared dead in the time corresponding to median procedural time. We will apply logistic regression adjusted for time to randomisation, initial rhythm and age, in addition to site, since these variables might affect both the chance of a successful REBOA procedure and the chance of ROSC. Second, we will do a similar analysis without excluding patients in the control group, but rather include patients in the intervention group where the balloon is not inflated *because* they achieve sustained ROSC or are decleared dead. If appropriate, we will perform an instrumental variable analysis as a third sensitivity analysis.

- Subgroup analyses

  To examine possible effect modification, exploratory subgroup analyses will be conducted regardless of whether statistically significant treatment effect on the primary outcome is observed in the overall sample. The subgroups will be tested for interaction as described by Christensen et al. [28]. The seven subgroup variables

are measured at baseline: age (< 65 compared to ≥65), sex (male compared to female), initial rhythm (shockable compared to non-shockable), time from debut of arrest to randomisation (at or above the median compared to below the median), study site (Trondheim compared to other norwegian sites, Denmark and Bologna), type of catheter used (Reboa Medical compared to Prytime), probable cause of arrest (hypoxemia compared to other causes). The results will be presented as a forest plot (Mock table 2). Multiple imputation will be considered.

Mock table 2. Forest plot of treatment effect in subgroups

Subgroup		*Risk difference (95 % CI)*	*p-value for interaction*
Age			
Sex	Male		
	Female		
Initial rhythm	Shockable		
	Non-shockable		
Time from debut of arrest to randomisation			
Study site	Trondheim (N)		
	Other norwegian sites		
	Denmark		
	Bologna (I)		
Type of catheter used	Reboa Medical		
	Prytime		
Probable cause of arrest	Hypoxemia		
	Other		
		Standard ACLS better / REBOA better	

REBOA: Resuscitative endovascular balloon occlusion of the aorta, CI: Confidence interval, ROSC: Return of spontaneous circulation, N: Norway, I: Italy

8.2.2 SECONDARY ENDPOINTS

8.2.2.1 30-day survival with good neurologic status

This dichotomous endpoint will be analysed and presented the same way as the primary endpoint. We will not perform assumption checks or subgroup analyses. We expect little missing data. The endpoint will be analysed in the FAS. A per-protocol analysis and a blinded review similar to the primary endpoint will be considered.

8.2.2.2 Difference in end-tidal CO2 measurements in the control group and the intervention group after aortic occlusion

- Main analysis

  In the intervention group, the mean change in end-tidal CO2 values after balloon inflation (from immediately before inflation to 30, 60, 90 and 120 seconds thereafter) will be modelled applying a linear mixed effect

model, with time treated as a categorical variable [29]. No subgroup analysis will be performed for this endpoint.

- Summary measures

  The evolution of end-tidal CO2 values after balloon inflation, together with end-tidal CO2 in the two treatment groups at randomisation, will be presented in a figure using descriptive terms. The results from the linear mixed effect model will be presented with estimated coefficients of change ($\beta_{0\text{-}4}$) and 95 % confidence intervals in the supplementary appendix (Supplementary Mock table 2).

- Assumptions

  Measurements between patients are independent, the relationship is linear and the error term and mixed effect are both normal with zero mean and constant variance.

- Missing data

  If missing data, we will remove patients if there is no data before inflation, there is a long time between randomization and inflation, or if 3 or more values are missing after inflation. We will impute the following way:
  1. Missing values before inflation: replaced with values at randomization.
  2. Missing intermediate values after inflation: linear interpolation.
  3. Missing first or last values after inflation: use values at first ROSC after inflation, multiple imputation, k-Nearest Neighbour, or remove.

8.2.2.3 Change in blood pressures after aortic occlusion

- Main analysis

  This applies only to patients in the intervention group where the REBOA-catheter is inserted and have CE/FDA approval for invasive blood pressure measurements. Blood pressures before and after balloon inflation (compression phase, relaxation phase and mean pressures) will be compared by Student´s t-test or Wilcoxon rank sum test. No subgroup analysis will be performed.

- Assumptions

  Measurements are independent and normal distributed.

- Missing data

  Since this is applicable in patients with registered high-resolution invasive blood pressure only, we expect little missing data. If missing, we will use multiple imputation.

8.2.2.4 Left ventricular ejection fraction (LVEF) measured by echocardiography

- Main analysis

  The first obtained LVEF after hospital admission in the two groups will be compared by Student´s t-test or Wilcoxon rank sum test. This analysis will be perfomed in the FAS only. No subgroup analysis will be performed for this endpoint.

- Missing data

  The British Society of Echocardiography defines normal ejection fraction to be ≥55 % [30]. Where LVEF is stated as "normal" in the patient journal, "55 %" will be used.

Mock table 3 – Secondary endpoints

	REBOA – group (n=)	Control – group (n=)	Adjusted RD (95 % CI)	p-value
30-day survival with mRS 0-3	Proportion (%)	Proportion (%)		
LVEF	Mean +/- SD or median (Q1-Q3)	Mean +/- SD or median (Q1-Q3)	NA	

REBOA: Resuscitative endovascular balloon occlusion of the aorta, mRS: Modified Rankin Scale, LVEF: Left ventricular ejection fraction, RD: Risk difference, CI: Confidence interval, SD: Standard deviation, NA: Not applicable.

8.2.3 EXPLORATORY ENDPOINTS

8.2.3.1 Variable "Any ROSC"

The protocol states that the balloon should be deflated over 30 seconds immediately when ROSC is confirmed. It is possible that this deflation make the patient re-arrest. To assess whether aortic occlusion lead to ROSC, but not lasting for 20 minutes and fulfilling the primary endpoint, the dichotomous variable "any ROSC" will be analysed the same way as the secondary endpoint "30-day survival rate with good neurologic status".

In patients in the intervention group who receive aortic occlusion, we will analyse the effect of time to aortic occlusion on any ROSC by logistic regression adjusted for site.

8.2.3.2 Incidence of all adverse events

The number of adverse events will be reported according to severity, by their relationship to the intervention, and presented by treatment group. To avoid dilution of adverse effects in the intention-to-treat population, adverse events related to the procedure will be assessed in patients were the procedure is initiated irrespectively of protocol violations and cross-over. The proportions of patients with adverse events will be compared descriptively across treatments and differences assessed for clinical significance. No formal statistical testing will be undertaken.

8.2.3.3 All cause mortality one year after randomisation

"All cause mortality one year after randomisation" will be analysed by Cox regression and presented as a Kaplan-Meier curve. This variable will be included in the primary publication only if sufficient number of patients have reached one year post-randomisation at submission.

8.2.3.4 Organ injury and dysfunction

The other exploratory endpoints are presented in Supplementary mock table 3. For variables of organ injury and dysfunction, we will present the worst values the first four days. The worst value for the variables is the highest value recorded. Normal distributed data will be presented as mean +- SD, and compared with Student´s t-test. Skewed or ordinal data will be presented as median (Q1-Q3) and compared with Wilcoxon rank sum test.

8.3 Additional analyses

8.3.1 TIME TO AORTIC OCCLUSION

Given the importance of time elapsed from collapse for the chance of achieving ROSC, we will supplement the subgroup analysis "Time to randomisation" with an analysis of "Time to aortic occlusion" among those patients where the balloon is inflated. Thus, we will analyse the effect of time to aortic occlusion on the primary endpoint by logistic regression, stratified by site.

8.3.2 OTHER MANAGEMENT

Other management will be presented in a table with counts and percentages (Supplementary mock table 4). No formal statistical testing will be undertaken.

8.4 Statistical software

The interim analyses will be performed using Stata 17.0 or later versions (StataCorp LCC, Collage Station, TX). For other analyses R statistical software will be used (v.4.2.2 or later versions; R Core Team, 2022).

9 REFERENCES

1. Gamble, C., et al., *Guidelines for the Content of Statistical Analysis Plans in Clinical Trials.* JAMA, 2017. **318**(23): p. 2337-2343.
2. Tjelmeland, I.B.M., et al., *Norsk hjertestansregister, Et register over gjenopplivningsforsøk i Norge. [Norwegian Cardiac Arrest Registry, a Registry of Resuscitation Attempts in Norway, yearly report 2017].* 2018: p. 71.
3. Hasselqvist-Ax, I., et al., *Early cardiopulmonary resuscitation in out-of-hospital cardiac arrest.* The New England Journal of Medicine, 2015. **372**(24): p. 2307-2315.
4. Norwegian Resuscitation, C., *Norsk Resuscitasjonsråd.* Norsk Resuscitasjonsråd, 2017.
5. Monsieurs, K.G., et al., *European Resuscitation Council Guidelines for Resuscitation 2015.* Resuscitation, 2015. **95**: p. 1-80.
6. Sesma, J., et al., *Effect of Intra-aortic occlusion balloon in external thoracic compressions during CPR in pigs.* The American Journal of Emergency Medicine, 2002. **20**(5): p. 453-462.
7. Nozari, A., S. Rubertsson, and L. Wiklund, *Intra-aortic administration of epinephrine above an aortic balloon occlusion during experimental CPR does not further improve cerebral blood flow and oxygenation.* Resuscitation, 2000. **44**(2): p. 119-127.
8. Nozari, A., S. Rubertsson, and L. Wiklund, *Improved cerebral blood supply and oxygenation by aortic balloon occlusion combined with intra-aortic vasopressin administration during experimental cardiopulmonary resuscitation.* Acta Anaesthesiologica Scandinavica, 2000. **44**(10): p. 1209-1219.
9. Gedeborg, R., S. Rubertsson, and L. Wiklund, *Improved haemodynamics and restoration of spontaneous circulation with constant aortic occlusion during experimental cardiopulmonary resuscitation.* Resuscitation, 1999. **40**(3): p. 171-180.
10. Rubertsson, S., N.G. Bircher, and H. Alexander, *Effects of intra-aortic balloon occlusion on hemodynamics during, and survival after cardiopulmonary resuscitation in dogs.* Crit Care Med, 1997. **25**(6): p. 1003-9.

11. Manning, J.E., et al., *Selective aortic arch perfusion during cardiac arrest: A new resuscitation technique.* Annals of Emergency Medicine, 1992. **21**(9): p. 1058-1065.
12. Barton, C., J.E. Manning, and N. Batson, *Effect of selective aortic arch perfusion on median frequency and peak amplitude of ventricular fibrillation in a canine model.* Annals of Emergency Medicine, 1996. **27**(5): p. 610-616.
13. Paradis, N.A., M.I. Rose, and M.S. Gawryl, *Selective aortic perfusion and oxygenation: An effective adjunct to external chest compression-based cardiopulmonary resuscitation.* Journal of the American College of Cardiology, 1994. **23**(2): p. 497-504.
14. Brede Jostein, R., et al., *Feasibility of Pre-Hospital Resuscitative Endovascular Balloon Occlusion of the Aorta in Non-Traumatic Out-of-Hospital Cardiac Arrest.* Journal of the American Heart Association, 2019. **8**(22): p. e014394.
15. Brede, J.R., J. Kramer-Johansen, and M. Rehn, *A needs assessment of resuscitative endovascular balloon occlusion of the aorta (REBOA) in non-traumatic out-of-hospital cardiac arrest in Norway.* BMC Emergency Medicine, 2020. **20**(1): p. 28.
16. Rosner, B., *Fundamentals of biostatistics, 8 ed*. 2016: Cengage learning.
17. Geller, N.L. and S.J. Pocock, *Interim analyses in randomized clinical trials: ramifications and guidelines for practitioners.* Biometrics, 1987. **43**(1): p. 213-23.
18. O'Brien, P.C. and T.R. Fleming, *A multiple testing procedure for clinical trials.* Biometrics, 1979: p. 549-556.
19. Mehta, C.R. and S.J. Pocock, *Adaptive increase in sample size when interim results are promising: a practical guide with examples.* Stat Med, 2011. **30**(28): p. 3267-84.
20. Lehmacher, W. and G. Wassmer, *Adaptive sample size calculations in group sequential trials.* Biometrics, 1999. **55**(4): p. 1286-90.
21. Schulz, K.F., et al., *CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials.* BMJ (Clinical research ed.), 2010. **340**: p. c332.
22. Nolan, J.P., et al., *Cardiac Arrest and Cardiopulmonary Resuscitation Outcome Reports: Update of the Utstein Resuscitation Registry Template for In-Hospital Cardiac Arrest: A Consensus Report From a Task Force of the International Liaison Committee on Resuscitation (American Heart Association, European Resuscitation Council, Australian and New Zealand Council on Resuscitation, Heart and Stroke Foundation of Canada, InterAmerican Heart Foundation, Resuscitation Council of Southern Africa, Resuscitation Council of Asia).* Circulation, 2019. **140**(18): p. e746-e757.
23. Nolan, J.P., et al., *European Resuscitation Council and European Society of Intensive Care Medicine Guidelines 2021: Post-resuscitation care.* Resuscitation, 2021. **161**: p. 220-269.
24. Soar, J., et al., *European Resuscitation Council Guidelines 2021: Adult advanced life support.* Resuscitation, 2021. **161**: p. 115-151.
25. Kahan, B.C., *Accounting for centre-effects in multicentre trials with a binary outcome – when, why, and how?* BMC Medical Research Methodology, 2014. **14**(1): p. 20.
26. Dunn, G., et al., *Estimating psychological treatment effects from a randomised controlled trial with both non-compliance and loss to follow-up.* The British Journal of Psychiatry, 2003. **183**(4): p. 323-331.
27. Cuzick, J., R. Edwards, and N. Segnan, *Adjusting for non-compliance and contamination in randomized clinical trials.* Stat Med, 1997. **16**(9): p. 1017-29.
28. Christensen, R., M.J.L. Bours, and S.M. Nielsen, *Effect Modifiers and Statistical Tests for Interaction in Randomized Trials.* Journal of Clinical Epidemiology, 2021. **134**: p. 174-177.
29. Fitzmaurice, G.M., N.M. Laird, and J.H. Ware, *Applied longitudinal analysis*. Vol. 998. 2012: John Wiley & Sons.
30. Harkness, A., et al., *Normal Reference Intervals for Cardiac Dimensions and Function for Use in Echocardiographic Practice: A Guideline from the British Society of Echocardiography.* Echo Research & Practice, 2020. **7**(1): p. G1-G18.

10 APPENDIX

Supplementary Table 1. The modified Rankin Scale

Score 0	No symptoms.
Score 1	No significant disability. Able to carry out all usual activities, despite some symptoms.
Score 2	Slight disability. Able to look after own affairs without assistance, but unable to carry out all previous activities.
Score 3	Moderate disability. Requires some help, but able to walk unassisted.
Score 4	Moderately severe disability. Unable to attend to own bodily needs without assistance, and unable to walk unassisted.
Score 5	Severe disability. Requires constant nursing care and attention, bedridden, incontinent.
Score 6	Dead

Supplementary mock table 1. Baseline data for all randomised patients

		REBOA – group (n1=)	Control-group (n2=)
Sex	Male	n/n1 (%)	n/n2 (%)
Age		Mean age in years (SD) Median (Q1-Q3)	
Charlson Comorbidity Index			
Utstein Template			
Suspected aetiology	Cardiac	n/n1 (%)	…
	Hypoxemia	…	
Location	Public indoors		
	Private indoors		
	Outdoors		
	Unknown		
Time to ACLS			
Time to ROSC			
Witnessed cardiac arrest	Health care providers		
	Other bystander		
	Not known		
Bystander CPR			
Shockable rhythm at presentation	VF/VT		
Mechanical chest compressions			
Airway management	Endotracheal intubation		
	Supraglottic airway		

Total dose of adrenaline			…
Mechanical chest compressions		…	n/n2 (%)
Study specific data			
Time to randomisation		Median (Q1-Q3)	Median (Q1-Q3)
REBOA group			
Received aortic occlusion		(yes/no)	NA
Time from collapse to balloon inflation		Median (Q1-Q3)	NA
Procedural time (randomisation to inflation of balloon)		Median (Q1-Q3)	NA
Numbers of cannulation attempts		Median (Q1-Q3)	NA
Admission			
Admitted to hospital	(yes/no)		
At admission	pH	Median (Q1-Q3)	…
	Base deficit	…	
	Lactate		

REBOA: Resuscitative endovascular balloon occlusion of the aorta, SD: Standard deviation, ACLS: Advanced cardiac life support, ROSC: Return of spontaneous circulation, VF: Ventricular fibrillation, VT: Ventricular tachycardia, CPR: Cardiopulmonary resuscitation,

Supplementary Mock table 2. Changes in End-Tidal CO_2, Results From the Linear Mixed Effect Model

	Coef.	Estimate	95 % CI	p - value
Parameters -fixed effects				
Intercept	β_0			
Change at 30 s	β_1			
Change at 60 s	β_2			
Change at 90 s	β_3			
Change at 120 s	β_4			
Parameters -random effects				
Variance random intercepts	$b_{0,1}$			
Variance residual	$\varepsilon_{i,j}$			
Covariance ($b_{0,1}$, $b_{1,j}$)				

Model: $y_{i,j}=\beta_0+\beta_{1\,x}$ time 30 seconds$+\beta_{2\,x}$ time 60 seconds$+\beta_3$ x time 90 seconds$+\beta_4$ x time 120 seconds $+b0,1+ei,j$.
Linear mixed effect model with changes in end-tidal CO_2 (kPa) as dependent variable. The intercept corresponds to the estimated mean value at time of occlusion and the estimated mean changes at 30, 60, 90 and 120 seconds are the added changes to baseline. Estimated with restricted maximum likelihood (unstructured covariance).

Supplementary mock table 3 – Exploratory endpoints

	REBOA – group (n=)	Control – group (n=)	p-value
All cause mortality at one year			

Cerebral injury	NSE
Myocardial injury	Troponin T (Troponin I)
Cardiac failure	NT-Pro-BNP
Kidney failure	KDIGO classification Creatinine
Liver injury	ALAT
Liver failure	INR
Length of stay, ICU	
Length of stay, hospital	

REBOA: Resuscitative endovascular balloon occlusion of the aorta, NSE: Neuron Spesific Enolase, ALAT: Alanine Aminotransferase, INR: International Normalized Ratio, ICU: Intensive Care Unit

Supplementary mock table 4 – Other Management

	REBOA – group (n1=)	Control – group (n2=)
Percutaneous coronary intervention (PCI)	n/n1 (%)	n/n2 (%)
ECMO		
Intraaortic balloon pump (IABP)		
Impella		

REBOA: Resuscitative endovascular balloon occlusion of the aorta, ECMO: Extracorporeal Membrane Oxygenation