Calcium for Out-of-Hospital Cardiac Arrest

– A Randomized, Double-Blind, Placebo-Controlled Trial

Acronym: COCA

TRIAL PROTOCOL

Version 1.2

December 21, 2020

EudraCT number: 2019-003387-46

ClinicalTrials.gov number: NCT04153435

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Content

Preface

The "Calcium for Out-of-Hospital Cardiac Arrest – A Randomized, Double-Blind, Placebo-Controlled Trial" (COCA) will be conducted according to this protocol. The trial will be conducted in accordance with all applicable national and international laws, regulations, and guidelines including the revised version of the Declaration of Helsinki,[1] European regulations,[2] and the international Good Clinical Practice guidelines.[3] The trial and this protocol are developed in accordance with the International Conference on Harmonization (ICH) guidelines[3-5] and the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) statement.[6,7] Mikael Fink Vallentin and Lars W. Andersen wrote the protocol with input from the steering committee. Any substantial changes or amendments to the protocol will be clearly documented and communicated to all relevant parties.

Lars W. Andersen, M.D., M.P.H., Ph.D., D.M.Sc. Date: 21/12 - 2020

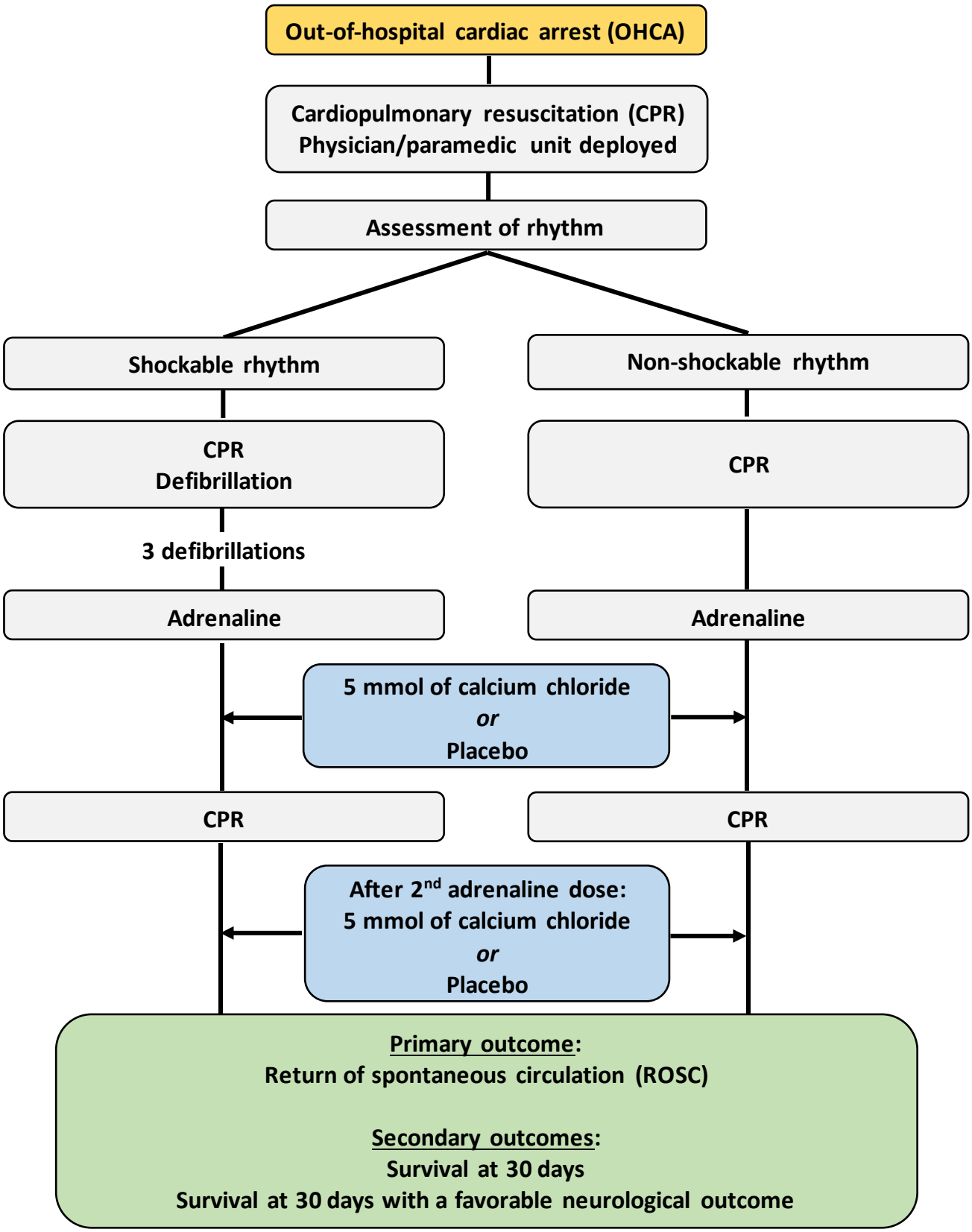
List of abbreviations

AED:	Automated external defibrillator
AHA:	American Heart Association
CaCl:	Calcium Chloride
COCA:	Calcium for Out-of-Hospital Cardiac Arrest
CONSORT:	Consolidated Standards of Reporting Trials
COSCA:	Core Outcome Set for Cardiac Arrest
CPC:	Cerebral performance category
CPR:	Cardiopulmonary resuscitation
ECG:	Electrocardiogram
ECPR:	Extracorporeal cardiopulmonary resuscitation
EMS:	Emergency medical services
EudraCT:	European Union Drug Regulating Authorities Clinical Trials Database
HEMS:	Helicopter emergency medical services
ICH:	International Conference on Harmonization
IDMC:	Independent data-monitoring committee
IHCA:	In-hospital cardiac arrest
ILCOR:	International Liaison Committee on Resuscitation
mRS:	modified Rankin Scale
NaCl:	Sodium Chloride
OHCA:	Out-of-hospital cardiac arrest
PEA:	Pulseless electrical activity
REDCap:	Research Electronic Data Capture
ROSC:	Return of spontaneous circulation
SINE:	"Sikkerhedsnettet"
SOFA:	Sequential Organ Failure Assessment
SOP:	Standard operating procedure
SPIRIT:	Standard Protocol Items: Recommendations for Interventional Trials
SUSAR:	Suspected Unexpected Serious Adverse Reaction
VAM-IHCA:	Vasopressin and Methylprednisolone for In-Hospital Cardiac Arrest

Overview

Registry and trial number	EudraCT number: 2019-003387-46, ClinicalTrials.gov number: NCT04153435
Date of registration	EudraCT: October 28, 2019, ClinicalTrials.gov: November 6, 2019
Funding	The Novo Nordic Foundation, Aarhus University, Central Denmark Region, and the Tryg Foundation
Primary sponsor	Lars W. Andersen, Aarhus University
Contact	Lars W. Andersen, lwandersen@clin.au.dk
Title	Calcium for Out-of-Hospital Cardiac Arrest (COCA) – A Randomized, Double-Blind, Placebo-Controlled Trial
Country of recruitment	Denmark
Condition studied	Out-of-hospital cardiac arrest
Intervention	Calcium chloride (CaCl) (5-10 mmol)
Comparator	Placebo in the form of 0.9% sodium chloride (NaCl) (10-20 mL)
Inclusion criteria	1) Out-of-hospital cardiac arrest 2) Age ≥18 years 3) Received at least one dose of adrenaline during CPR
Exclusion criteria	1) Traumatic cardiac arrest 2) Known or strong suspicion of pregnancy 3) Prior enrollment in the trial 4) Received adrenaline during CPR before arrival of prehospital personnel with the study drug 5) Clinical indication for calcium administration during the cardiac arrest
Study type	Interventional Allocation: Randomized (1:1) Intervention model: Parallel group Masking: Double-blind
Date of first screening	January 20, 2020
Target sample size	674
Recruitment status	Recruiting
Primary outcomes	Return of spontaneous circulation (ROSC)
Key secondary outcomes	Survival at 30 days Survival at 30 days with a favorable neurological outcome (modified Rankin Scale, mRS, of 0-3)

Trial flow chart



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Conflicts of interest

The members of the steering committee have no conflicts of interest related to the current trial. A list of all conflict of interests is provided in Appendix 1.

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Amendments

Version 1.1 to 1.2

- Changed the primary outcome; please see sections 5.1.2 and 5.1.3 for details
- Increased sample size from 430 to 674; please see section 6.1.2 for details
    - The trial's feasibility has been updated based on the new sample size and current enrollment rate (section 11.2)
- Clarified two exclusion criteria without changing their meaning (section 4.3)
- Multiple changes to the statistical analyses plan including (section 6):
    - Change of the primary analysis
    - Addition of a sensitivity analysis for the primary outcome
    - Subgroup analyses on both the relative and absolute scale
    - Only reporting P-values for certain key outcomes
    - Analysis of survival to 90 days as a binary outcome
- Updated information on the steering committee (section "Steering Committee")
- Updated the contact information for the pharmacy (section "Pharmacy")
- Added dates of registration for EUDRA-CT and clinicaltrials.gov
- Added date of first screening
- Updated section "Representatives for the physician-manned ambulances"
- Updated section 1.1.1 in accordance with the newest data
- Clarified the format of the study ID (section 3.3.4)
- Clarified the role of *cardinal signs of death* in the definition of cardiac arrest (section 4.2)
- Clarified that there are other trials in OHCA in Denmark, but in another region (section 4.4)
- Added description of a secondary safety parameter assessing early hypercalcemia (section 5.4.9)
- Clarified the extent of source data (section 7.1)
- Clarified the roles of central and on-site monitoring (section 7.3)
- Clarified that the consent forms are separate for each role (section 9.3.2)
- Added an extra IDMC interim analysis at 400 patients (section 10.2 and appendix 4)
- Clarified result sharing with participating patients (section 12)
- Added additional funding (section 14)
- Added picture of the study drug kit as well as labelling (appendix 2)
- Added three additional variables to the IDMC data set (appendix 4)
- Added "Research ethical committee no." (appendix 4)

Version 1.0 to 1.1

- Clarification that the sponsor will be notified about the occurrence of any serious adverse event within 24 hours (section 5.4.9)
- Clarification to data storage and security (section 7.4)
- Clarification related to the potential role of digitalis glycoside toxicity (section 9.1.2)
- Additional details related to the consent process (section 9.3.2)
- Clarification that the trial findings will be published irrespective of the results (section 12)
- Clarification related to funding (section 14)

1. BACKGROUND

1.1 Out-of-hospital cardiac arrest

1.1.1 Incidence and mortality

Out-of-hospital cardiac arrest (OHCA) occurs in an estimated 4 million people each year globally of which approximately 5000 are in Denmark.[8,9] Unfortunately, survival following OHCA is extremely poor with only approximately 15% being alive after 30 days in Denmark.[8,10] Of those with a non-shockable rhythm, which account for more than 80% of all OHCA, less than 10% are alive after 30 days and, in contrast to those with a shockable rhythm, survival has not improved substantially over the last decade.[8,10] Furthermore, many survivors of OHCA have debilitating long-term sequelae such as neurological deficits, cognitive problems, depression, or anxiety.

1.1.2 Lack of high-quality randomized trials

Multiple medical interventions are used during cardiac arrest.[11] However, there are currently none of these that have shown to definitively improve 30-day survival with a favorable neurological outcome.[11-13] This may be caused by the fact that relatively few randomized trials are conducted in OHCA compared to other high-mortality conditions.[14] Furthermore, cardiac arrest, and critical care in general, has been challenged by multiple neutral trials over the last decade. To advance cardiac arrest science, and thereby improve patient outcomes, it is therefore important that interventions are tested in rigorously performed randomized clinical trials.

1.1.3 Pathophysiology

In broad terms, cardiac arrest can be divided into three phases: pre-cardiac arrest, intra-cardiac arrest, and post-cardiac arrest, where intra-cardiac arrest can be further divided into a no-flow (no circulation) and a low-flow (circulation induced by chest compressions) phase. One of the main drivers of poor outcomes after cardiac arrest is the duration of the cardiac arrest (i.e. no-flow and low-flow time); for each minute increase in the length of the cardiac arrest, mortality substantially increases.[15,16] Because of this, and since return of spontaneous circulation (ROSC) is a prerequisite for more long-term survival, the main goal of intra-cardiac arrest interventions is to establish ROSC and limit the duration of the cardiac arrest.

The pathophysiology of cardiac arrest and the post-cardiac arrest syndrome is complex and has been described in extensive details elsewhere.[17-19] Ischemia during the cardiac arrest and subsequent ischemia-reperfusion injury activates multiple harmful pathways including systemic inflammation, endothelial activation, activation of immunological and coagulation pathways, adrenal insufficiency, mitochondrial

damage, and microvascular dysfunction.[17] Consequently this leads to a clinical state (the post-cardiac arrest syndrome) with potential global brain injury, impaired myocardial function, macrocirculatory failure, and increased susceptibility to infections.[17] Patients are often hemodynamically unstable following a cardiac arrest, and early post-cardiac arrest hypotension is strongly associated with poor outcomes.[20]

1.2 Calcium

1.2.1 Pharmacology

Calcium is the most abundant mineral in the body with more than 99% residing in the teeth and bones as hydroxyapatite, an essential molecule for these organs' strength. This enormous quantity also makes up an ample reservoir for a smaller amount of serum calcium, which is tightly regulated mainly through parathyroid hormone, vitamin D3, and calcitonin from the thyroid. Serum calcium exists in three forms: protein-bound (40%), chelated (9%), and ionized (51%, "free calcium"), the latter being the physiologic active.

Ionized calcium serves many important biochemical functions for example for enzymes and intracellular signaling, but its greatest role is in muscle contraction. In short, in the cardiac muscle cell, depolarization leads to a small influx of extracellular calcium that causes a much larger influx from the sarcoplasmic reticulum (calcium-induced calcium release). On the intracellular actin-myosin complexes, calcium binds to tropomyosin exposing actin's active site, which then triggers the molecular cross bridge action. On the larger scale, this leads to muscle contraction. This role in muscle contraction explains exogenous calcium administration's well-recognized effect as an inotropic agent.[21,22]

When calcium chloride (CaCl) is given as a rapid intravenous injection, plasma ionized calcium peaks after 30 seconds and then falls quickly the next 30 seconds to settle at a more stable concentration falling slowly over the course of hours.[23,24] In a 70 kg patient, a rapid dose of 5 mmol CaCl is expected to lead to a 30-second peak in ionized calcium of Δ1.2-1.5 mmol/L falling to Δ0.4 mmol/L and Δ0.3 mmol/L after three and five minutes, respectively.[24]

1.2.2 Use outside cardiac arrest

Since hypocalcemia is frequent in the critical ill,[25,26] calcium is closely monitored in the intensive care unit, and it is common to give day-to-day intravenous calcium doses, if ionized calcium drops below a determined threshold (e.g., <1.1 mmol/L). Calcium administration is always recommended in symptomatic hypocalcemia, which can manifest as focal muscle cramps, distal extremity paresthesia, circumoral numbness, or – in severe cases – generalized cramps.[27]

Lastly, calcium is closely monitored in situations where iatrogenic hypocalcemia is expected: transfusion with citrate-containing products (erythrocytes and fresh frozen plasma), iatrogenic hypoparathyroidism (thyroidectomy), or plasma dilution (fluid administration). For example, in a hemodynamically unstable patient with hemorrhage, it is recommended to routinely give intravenous calcium along with blood products.

1.2.3 Use in cardiac arrest

Calcium is currently recommended as a therapy during cardiac arrest, when pulseless electrical activity (PEA) is present along with one of the following conditions: 1) hyperkalemia, 2) hypocalcemia, or 3) calcium channel blocker overdose.[11] The rationale is based on expert opinion that has its foundation in calcium's physiology rather than clinical evidence.

Previously, calcium was recommended broadly for cardiac arrest, but the evidence was contradictory, and it has since been limited to the above-mentioned conditions. A few small observational studies of limited quality found no association between calcium administration and outcomes in cardiac arrest,[28-30] while two studies found an association with worse outcomes.[31,32] However, since calcium are most likely administered in cardiac arrests that are prolonged, these studies might be severely biased towards a harmful effect of calcium.[33] In fact, one study found that early as compared to late calcium administration was associated with improved outcomes.[32]

Despite the lack of new evidence in the field, the rate of calcium administration in in-hospital cardiac arrest (IHCA) has increased over time: in an American cohort of patients with a non-shockable rhythm, 20% received calcium in 2001 increasing to around 30% in 2016.[34]

1.2.4 Hyperkalemia and hypocalcemia in cardiac arrest

In the face of hyperkalemia, calcium is thought to increase cardiac myocytes' resting membrane potential back towards normal.[35] Potassium is released from cells in the presence of ischemia. Both animal models[36-38] and human studies[39-41] have shown that potassium levels increase during cardiac arrest and often reach high levels (i.e., hyperkalemia). Secondly, several studies have found hypocalcemia in cardiac arrest patients upon admission, and there is an inverse correlation between serum ionized calcium and time until hospital admission as well as no flow time.[21,28,29,42] These findings indicate a relative hyperkalemic and hypocalcemic state during and immediately after cardiac arrest.

1.3 Randomized controlled trials concerning calcium for OHCA

In two trials, published in 1985, Stueven et al. examined the effect of adding calcium to the standard OHCA-treatment at that time.[43,44] In these American, randomized, double-blind trials, the authors compared placebo (0.9% saline) with a single dose of 500 mg (≈4.5 mmol) CaCl to treat refractory PEA and asystole, respectively. Refractory PEA was defined as continued PEA despite cardiopulmonary resuscitation (CPR), oxygenation, adrenaline, and bicarbonate. Refractory asystole was defined correspondingly, but with an asystolic cardiac rhythm and the addition of 1 mg of atropine. The primary outcome was in-field ROSC defined as palpable pulse and a heart rhythm at hospital arrival.

The results showed a combined rate of ROSC of 11/87 (13%) in the intervention group and 3/76 (4%) in the control arm (fixed-effect meta-analysis, Figure 1, p = 0.06). Only one patient survived until hospital discharge (PEA, placebo). In patients with PEA and an electrocardiogram displaying either wide QRS-complexes (>0.12 mm) *or* ischemia (peaked T-wave *or* ST-elevations) there was a significantly higher rate of ROSC in the calcium group than in the placebo group (8/39 [21%] vs. 1/31 [3%], p = 0.03).

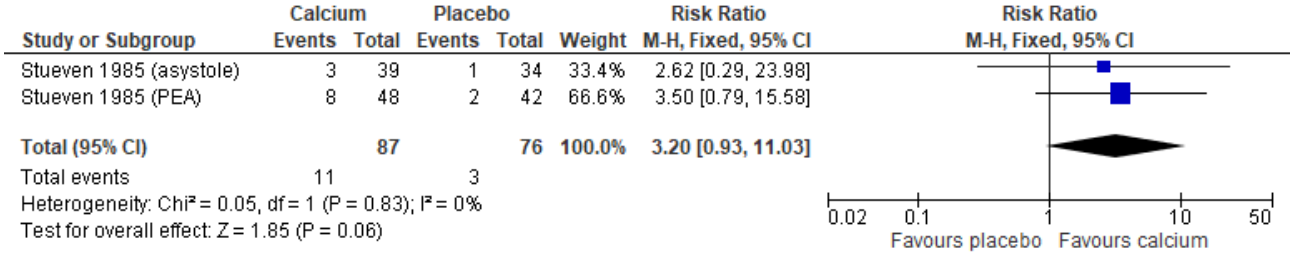


Figure 1

1.4 Guidelines regarding calcium

Calcium was initially recommended broadly in the 1974 guidelines from the American Heart Association (AHA),[45] but after a series of neutral and negative cohort studies (see section 1.2.3), its use was limited to patients with PEA due to either hyperkalemia, hypermagnesemia, hypocalcemia, or calcium channel blocker toxicity.[11,46] The International Liaison Committee on Resuscitation (ILCOR) elaborates: "More data are needed on the administration of calcium for specific circumstances, such as hyperkalemia, documented hypocalcemia, hypermagnesemia, calcium channel blocker overdose, or wide QRS complexes".[47]

1.5 Standard of care

The standard of care during cardiac arrest is described by guidelines from the European Resuscitation Council (ERC) and the AHA.[48,49] Pharmacological treatment is generally limited to amiodarone/lidocaine and adrenaline for patients with a refractory shockable rhythm and adrenaline for patients with a non-shockable rhythm.[11,50] Although the evidence for amiodarone/lidocaine and adrenaline is limited and controversial,[12,13]

these drugs are currently recommended and are given, when applicable, to most patients with cardiac arrest. The intervention of the current trial (CaCl) will therefore be compared to a placebo and both groups will receive the established standard of care.

2. TRIAL OBJECTIVES AND HYPOTHESES

Primary objective: To determine whether calcium administration during adult OHCA will improve ROSC.

Hypothesis, primary: Calcium administration administered during OHCA will increase ROSC.

Secondary objective: To determine whether calcium administration during adult OHCA will increase survival at 30 days and survival at 30 days with a favorable neurological outcome (modified Rankin Scale, mRS)

Hypotheses, secondary: Calcium administration during adult OHCA will increase survival at 30 days and survival at 30 days with a favorable neurological outcome (mRS)

3. TRIAL DESIGN

3.1 Overview

The COCA trial will be an investigator-initiated, randomized, placebo-controlled, parallel group, double-blind, superiority trial of calcium administration during adult OHCA. The trial will be conducted in the Central Denmark Region. The primary outcome will be ROSC, and 674 patients will be included. Key secondary outcomes include survival at 30 days and survival at 30 days with a favorable neurological outcome.

3.2 Allocation

Patients will be randomized in a 1:1 ratio to either calcium or placebo in blocks with random sizes of 2, 4 or 6. The randomization will be stratified according to each ambulance station (hereon forth "stations").[51] An independent statistician will create the randomized allocation list using a random number generator. The list will only be shared with the pharmacy, which will not be involved in clinical care. The pharmacy and the independent statistician will both store the randomization list. As described in section 3.3 and section 3.4, stations will be provided with numbered blinded ampoule bundles containing either CaCl or placebo ensuring allocation concealment.

3.3 Interventions

3.3.1 Calcium

The intervention will consist of 5 mmol (10 mL ampoule) of CaCl administered immediately after the first dose of adrenaline and again after the second dose of adrenaline. No further doses will be administered, and the study has no other interventions. The drugs will be produced, managed, and stored according to all relevant guidelines and regulations.

3.3.2 Placebo

The placebo will consist of 10 mL of 9 mg/mL sodium chloride (NaCl, "normal saline") from a 10 mL ampoule identical to the CaCl ampoules.

3.3.3 Procedures

The study drugs will be contained in two bundled ampoules of 10 mL (Appendix 2). The ampoules will be prepared at Skanderborg Pharmacy – a company that specializes in the production of medicine and is approved by the Danish Health authorities –, shipped to the participating stations regularly, and brought to the OHCA by a member of the prehospital team. Once it is anticipated that the patient will receive at least one

dose of adrenaline, the ampoules will be split and opened consecutively. Once the first ampoule is opened, the patient will be considered randomized. A designated member of the prehospital team will then prepare the study drugs. We expect that study drug preparation and administration will take approximately 30 seconds, and that this will not interfere with clinical management. Once prepared, the drug will be administered as soon as possible after the first dose of adrenaline either through an intravenous or intraosseous line. An additional dose will be administered with the second dose of adrenaline given after 3-5 minutes irrespective of the underlying rhythm.[11] A maximum of two doses will be administered.

3.3.4 Overview of study medication

Ampoules will be produced and labelled centrally (Skanderborg Pharmacy). Ampoule bundles will be labelled with a unique ID consecutively according to the stations (e.g., 10XXX for station 1, 11XXX for station 2, etc.). Ampoule bundles will be clearly labelled according to standard practices for clinical trials (Appendix 2). Ampoule bundles will be prepared and shipped to the participating stations on a regular basis. Once an ampoule is opened, the station investigator and the coordinating investigator will be informed. The coordinating investigator will keep tally of all ampoule bundles and make sure, along with the station investigator, that stations are always equipped with enough ampoule bundles. The coordinating investigator will contact the central pharmacy when extra ampoule bundles are needed. Data on actual drug administration (see section 3.3.3) will be entered on an electronic case form (see section 7). This will ensure optimal tracking of study drug delivery.

3.4 Blinding

The trial will be double-blind; patients, investigators, and the clinical team will be blinded to the allocation. Only the pharmacy providing the blinded, numbered ampoules will be aware of the allocation. The pharmacy will not be involved with clinical care or outcome evaluation.

Placebo will consist of normal saline which is indistinguishable from CaCl in that it is colorless and without any identifying features. The normal saline will be stored in 10 mL ampoules that are identical to the CaCl ampoules. Furthermore, except for potential slight and temporary hypercalcemia, CaCl has no distinctive rapid effects resulting in possible identification. The risk of unblinding is therefore at an absolute minimum.

The emergency medical services (EMS) dispatch center will keep sealed opaque envelopes containing the allocation assignment for each ampoule bundle's unique ID – this will allow for emergency unblinding. The dispatch center is available at all times to both the prehospital as well as the in-hospital team through either a direct phone call or radio communication on a specialized network ("Sikkerhedsnettet", SINE). The decision

to unblind will be at the complete discretion of the treating physician. However, we do not expect scenarios where emergency unblinding will be necessary. In case unblinding occurs, the reason(s) will be clearly documented in the case report form. The patient will remain in the trial.

3.5 Trial procedures

3.5.1 Patients

The trial procedures will be limited to the interventions given during the cardiac arrest (see section 3.3) and the telephone interviews for long-term follow-up (see section 5.3 and 5.5). There will be no planned blood draws, other interventions, or additional procedures. Data will be obtained from the study-specific case report form as well as prehospital- and in-hospital electronic medical records.

3.5.2 Clinical personnel

Prior to the beginning of patient enrollment and continuously throughout the enrollment period, the clinical teams involved in OHCA resuscitation at the participating stations will be informed about the trial. This includes the trial's background, objectives, the inclusion/exclusion criteria, the interventions, and the trial procedures they are involved in (see section 3.3.3 and 9.3.2). A demonstration of correct procedures using the ampoule bundles will be included.

4. SETTING AND PATIENT POPULATION

4.1 Setting

The trial will be conducted in the Central Denmark Region's prehospital setting, where three distinct units can give adrenaline to a patient with OHCA: physician-manned ambulances, paramedic-manned ambulances, and helicopter-based emergency medical services (HEMS). Patients, where HEMS are the first to give adrenaline, will not be enrolled in our study, since the unit is often manned by personnel from outside the region. Moreover, HEMS very rarely attend OHCA as the primary unit.

Participating stations will be any regional ambulance station which holds one or more physician- and/or paramedic-manned ambulances.

4.2 Inclusion criteria

Inclusion criteria:

1) OHCA

2) Age ≥ 18 years

3) Received at least one dose of adrenaline during CPR

Cardiac arrest is defined as unconsciousness, abnormal breathing, and a loss of pulses requiring chest compressions and/or defibrillation. If a member of the prehospital personnel determines either rigor mortis, livor mortis, maceration, or putrefaction, the patient will be considered to have been found dead and not in cardiac arrest even though CPR has been initiated by lay responders. This is in accordance with the Danish Cardiac Arrest Registry.[8]

OHCA is defined as any individual with a cardiac arrest outside hospital grounds where the prehospital system is activated. These broad inclusion criteria were chosen to reflect the pragmatic scope of the trial and to allow for optimal external validity.

4.3 Exclusion criteria

Exclusion criteria:

1) Traumatic cardiac arrest – including drowning and external asphyxia (e.g., hanging, strangulation, or foreign object airway obstruction)
2) Known or strongly suspected pregnancy
3) Prior enrollment in the trial
4) Received adrenaline during CPR before arrival of prehospital personnel with the study drug
5) Clinical indication for calcium administration during the cardiac arrest

Traumatic OHCA will be excluded, because the patient population and the pathophysiology are vastly different from those of medical OHCA.

OHCA during pregnancy is exceedingly rare,[52] and we expect that this exclusion criterion will lead to only few, if any, exclusions. If pregnant patients are included (i.e., if the pregnancy is not known and not obvious), we do not expect our intervention or trial in general to put the patient or fetus at harm. Guidelines recommend that cardiac arrest in pregnancy is treated according to usual guidelines including intra-cardiac arrest medications.[53]

Patients previously included in the trial will be excluded to avoid statistical complexity related to correlated data. Since this is documented (but might not be known by the cardiac arrest team) prior to the cardiac arrest and the intervention, any post-randomization exclusions will not lead to bias.[54]

OHCA-patients in our setting could on rare occasions receive adrenaline by a non-participating prehospital unit (see section 4.1). These patients will be excluded to avoid excessive time to study drug administration.

Calcium is recommended in certain scenarios of cardiac arrest (see section 1.2.3). These patients are excluded to avoid that they do not receive guideline-based therapy. A clinical indication for calcium is determined by the treating clinician.

4.4 Co-enrollment

There will be no general restrictions on entry into other (post-cardiac arrest) clinical trials although this will be evaluated on a case-by-case basis.[55] We are not aware of any ongoing or planned intra-cardiac arrest trials in this patient population in the Central Denmark Region.

5. OUTCOMES

5.1 Primary outcome

5.1.1 Original definition

The original primary outcome was ROSC at hospital arrival defined as palpable pulses or other signs of circulation at time of hospital arrival consistent with the Danish Cardiac Arrest Registry[10] and other large trials.[56,57]

5.1.2 Updated definition

As per December 21st, 2020 (time stamp of protocol version 1.2), the definition of the primary outcome has been changed to sustained ROSC. Sustained ROSC is defined as palpable pulses or other signs of circulation without a need for chest compressions lasting at least 20 minutes.

5.1.3 Rationale

The rationale for any intra-cardiac arrest intervention is primarily to increase the rate of ROSC to subsequently improve the rate of meaningful survival. Since ROSC is a prerequisite for more long-term survival and since the focus of this investigation is an intra-cardiac arrest intervention, ROSC is a logical and meaningful primary outcome. ROSC is a core outcome measure in both the IHCA[58] and OHCA[11] Utstein guidelines and is suggested as a potential primary outcome measure by the AHA.[59]

The original definition of the primary outcome, ROSC at hospital arrival, was chosen to ensure full data completeness, which was uncertain for sustained ROSC. Yet, at 294 patients included, there is no missing data on sustained ROSC. ROSC at hospital arrival has the disadvantage of being cross-sectional, while sustained ROSC better represents what clinicians are trying to achieve. The change of the primary outcome to sustained ROSC was made based on blinded data.

5.2 Secondary outcomes

5.2.1 Definitions

Key secondary outcomes will include survival as well as neurological outcome at 30 days. Neurological outcome will be assessed with the modified Rankin Scale (mRS, Table 1); scores 0-6 will be presented as counts and percentages, while the outcome will be dichotomized as favorable (mRS 0-3) vs. unfavorable (mRS 4-6).

Table 1. modified Rankin Scale (mRS)[60]

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

5.2.2 Rationale

Survival at 30 days and survival at 30 days with a favorable neurological outcome are considered key outcome measures in cardiac arrest research.[11,58,59] All follow-up survival data will be obtained from electronical medical records or the Danish Central Personal Register which allows for accurate and virtually complete follow-up.[61] The use of 30-day outcomes as compared to outcomes at hospital discharge avoids limitations related to potential differences in discharge practices.[62-64]

A centrally-located, trained researcher will assess mRS using a standardized telephone interview, which ensures good reliability.[65-67] The dichotomy with favorable at 0-3 and unfavorable at 4-6 is widely used in cardiac arrest research and is consistent with a recent large OHCA-trial.[68] In case the patient is still

hospitalized, the interview will be face-to-face. Assessment of neurological outcome by telephone is valid and reliable.[69]

In accordance with the recent Core Outcome Set for Cardiac Arrest (COSCA)-initiative, we will also assess the Cerebral Performance Category (CPC).[70] CPC will not be considered a key outcome of neurological status.

5.3 Tertiary outcomes

We will include 90-day survival as a measure of long-term survival. 90 days were chosen since it is unlikely that later mortality will be directly linked to the cardiac arrest or the trial intervention. 90 days is also consistent with recommendations from the AHA.[59]

Health-related quality of life at 30 and 90 days will be assessed by the questionnaire EQ-5D-5L,[71] which is supported by the AHA[59] as well as the COSCA-initiative.[70] EQ-5D-5L is a generic approach with five items covering symptomatic, physical, psychological, and social consequences of a disease. It is preferred to HUI3 and SF-36, because it is free to use and requires a shorter interview. Assessment of health-related quality of life by telephone is valid and reliable.[72] EQ-5D-5L allows for potential future cost-effectiveness analyses and comparison to the background population.

During the same 90-day interview, we will reassess neurological outcome (mRS and CPC).

In addition to the above, we will collect outcome data related to hemodynamics, laboratory values, mechanical ventilation, organ failure, and hospital disposition.

To assess the potential beneficial effects of the intervention on hemodynamics, we will measure vasopressor-free days. A vasopressor will be defined as any continuous infusion of noradrenaline, dopamine, dobutamine, terlipressin, vasopressin, phenylephrine, and/or adrenaline. Vasopressor-free days will be defined as the number of days within the first 7 days after the cardiac arrest where the patient is not receiving vasopressors and is alive. Receiving vasopressors for at least 6 hours on a given day is defined as receiving vasopressors for that day. Contrary to other vasopressor outcomes, such as time to weaning from vasopressors, this outcome accounts for both vasopressor use and mortality.[73] Invasive ventilation-free days will be defined in a similar manner. Invasive ventilation is defined as mechanical ventilation through an endotracheal or tracheostomy tube.

To assess hemodynamics and organ failure, we will calculate the Sequential Organ Failure Assessment (SOFA)-score[74] at 2, 24, 48 and 72 hours after the cardiac arrest in those alive. The SOFA score is a validated and widely used measure of organ failure assessing the respiratory, nervous, cardiovascular, hepatic, coagulation, and renal systems.[74] We will assess both the cardiovascular sub score as well as the overall SOFA score. The calculation of the SOFA score will be based on available clinical and laboratory data.

Laboratory and clinical data closest to the given time point will be used. If a given component (e.g., bilirubin) is not available it will be assumed to be within normal ranges. If PaO_2 values are not available, they will be imputed using imputations based on SpO_2 values.[75,76]

Laboratory values, specifically pH, potassium, calcium, and lactate from the first arterial (or venous) gas will be compared between groups.

Hospital disposition (e.g., home, rehabilitation, nursing home, hospice) will be defined at the time of discharge from the initial acute care hospital.

5.4 Harm

5.4.1 General consideration

Patients with OHCA have a 85% mortality rate in the first 30 days,[8] and survivors will in the adjacent time risk complications such as global brain injury, impaired myocardial function, macrocirculatory failure, and increased susceptibility to infections.[17] Furthermore, OHCA-patients have a high prevalence of pre-resuscitation morbidity with cardiovascular- and cerebrovascular disease as well as chronic obstructive lung disease, diabetes, and psychiatric disease.[77] The immediately preceding cause may be circulatory failure (coronary heart disease, primary arrhythmia, pulmonary embolism, hypovolemia), respiratory failure (medical, drowning, asphyxia), or more rarely neurologic disorders.[68] Given this, it is difficult, if not impossible, to comprehensively report all adverse events and assess their possible relationship with the intervention.

Generally, CaCl is considered safe and is commonly used in clinical practice (see section 1.2.2). The overall benefit and potential harm will be captured in our primary and secondary outcomes, and the clinical team will document any specific adverse events suspected to be related to the intervention.

In an awake patient, CaCl is normally given slowly due to risk of brief paresthesia, calcium taste, and/or flushing. This is not a concern for our population group, who will be unconscious at the time of administration.

5.4.2 Subcutaneous injection

Accidental subcutaneous injection of CaCl can result in necrosis. However, the study drug – if given intravenously – is given immediately after adrenaline, which carries a similar risk and hence the same precautions; a misplaced peripheral catheter should be recognized here. The risk of necrosis due to the intervention is therefore minimal.

5.4.3 Hypercalcemia and arrhythmias

There is concern that hypercalcemia can cause tachyarrhythmias, but this is only based on physiological theory[78] and a few case reports concerning prolonged and often severe hypercalcemia seen in primary hyperparathyroidism and malignancy.[79-84] There are, to our knowledge, no case reports of arrhythmias following short-lived hypercalcemia. Secondly, a recent cohort study of 31 patients admitted to the emergency department with severe hypercalcemia (albumin-corrected total calcium >4 mmol/L, median 4.3 mmol/L) found no life-threatening cardiac arrhythmias or neurological complications during the patients' admissions.[85]

Potentially hypercalcemic patients will therefore not be excluded. This keeps the pragmatic scope of the trial, as hypercalcemia will hardly ever be recognized in the prehospital setting. Also, hypercalcemia has a general prevalence of 1/1000 and should be a rare encounter.[86] If a hypercalcemic patient should receive 5-10 mmol of CaCl, the serum ionized calcium peak is very short-lived (≈30 seconds), while the expected effect over the course of hours is Δ<0.3 mmol/L (see section 1.2.1). Consequently, we consider the risk of significant hypercalcemia low and the risk of tachyarrhythmias very low.

5.4.4 Digitalis glycoside toxicity

Similar caution exists regarding calcium administrations in patients treated with digitalis glycosides (e.g. Digoxin®) due to the "stone heart" theory: in digitalis glycoside toxicity, calcium excess may lead to impaired diastolic relaxation and hence a non-contractile state. This is based on physiological theory, a few case reports, and an animal model that found a pro-arrhythmic effect of serum calcium >15 mmol/L in the face of digitalis glycoside toxicity.[87,88] A 2011 retrospective cohort study identified 161 patients with chronic digitalis glycoside toxicity (>2.0 ng/dL) and found that those who received intravenous calcium (*n*=23) did not have increased odds of mortality (adjusted OR 0.76, 95% confidence interval 0.24-2.5).[89] Also, no arrhythmias occurred within 1 hour of intravenous calcium administration. A 1983 chart review of 480 OHCA patients receiving intravenous calcium, found no arrhythmias in seven patients taking digitalis.[90]

Patients treated with digitalis glycosides will therefore not be excluded. This keeps the pragmatic scope of the trial, as a reliable drug list will rarely be available in the prehospital setting. Lastly, digitalis glycoside toxicity should be a rare encounter.

5.4.5 Acute kidney injury

There is a well-established association between prolonged ("chronic") hypercalcemia and acute kidney injury with numerous case reports in primary hyperparathyroidism,[91-93] malignancy,[94,95] sarcoidosis,[96-98] infection,[99] and milk-alkali syndrome.[100-102] Likewise, the association has been established in iatrogenic hypercalcemia

after long-term overdose of vitamin D, calcium supplement, or denosumab.[103-106] A recent study of 12,784 patients found an association between total calcium at admission and the risk of developing acute kidney injury during admission.[107] There are, to our knowledge, no case reports of short-lived hypercalcemia associated with acute kidney injury.

The pathogenesis has been hypothesized in animal models of chronic severe hypercalcemia[108-110] as well as through human renal biopsies taken from patients with severe disease of the calcium metabolism.[111] Only a few animal models of renal arterial flow have studied the effect of short-lived hypercalcemia, yet only in ranges with ionized calcium >1.88 mmol/L: at this level, the relative effects on renal arterial flow and glomerular filtration rate were small.[112-115]

Hypercalcemia is unwanted in chronic kidney failure due in part to the above-mentioned associations, but mostly because renal calcium excretion can be affected, and chronic hypercalcemia can – besides the already mentioned risks – lead to nausea, vomiting, obstipation, fatigue, and confusion.[116] However, calcium administration is of particular interest in OHCA patients with kidney failure as it may help to treat a possible hyperkalemia. Therefore, patients with known or suspected kidney failure will not be excluded from the study.

5.4.6 Peptic ulcer disease

In patients with diagnosed peptic ulcer disease, hypercalcemia is associated with a hypergastrinemia-induced increase in gastric secretion volume as well as acid secretion – yet, this is not the case for patients without diagnosed peptic ulcer disease.[117-122] Also, the hypersecretion returns to normal within a few hours, when hypercalcemia is corrected.[120] Chronic hypercalcemia due to primary hyperparathyroidism has been linked to *de novo* peptic ulcer disease, and parathyroidectomy seems to relieve the symptoms.[123,124] To our knowledge, short-lived hypercalcemia has not been associated with *de novo* peptic ulcer disease, nor has it been linked to aggravating symptoms or prognosis in patients who already have the diagnosis.

5.4.7 Acute pancreatitis

Calcium is essential for intracellular messaging in the exocrine pancreas. However, in vitro studies show that hypercalcemia can lead to pancreatitis through raised trypsinogen activity, acinar cell apoptosis, and ductal outflow obstruction.[125] Primary hyperparathyroidism has been associated with acute pancreatitis responsive to parathyroidectomy,[126] while there are case reports with similar associations for other conditions with prolonged hypercalcemia.[127-130] To our knowledge, short-lived hypercalcemia has not been associated with *de novo* pancreatitis, nor has it been linked to aggravating symptoms or prognosis in patients who already have the diagnosis.

5.4.8 Definitions

The following definitions will be used:[2]

Adverse event: any untoward medical occurrence in a subject to whom a medicinal product is administered and which does not necessarily have a causal relationship with this treatment.

Serious adverse event: any untoward medical occurrence that at any dose requires inpatient hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, results in a congenital anomaly or birth defect, is life-threatening, or results in death.

Unexpected serious adverse reaction: a serious adverse reaction, the nature, severity or outcome of which is not consistent with the reference safety information.

5.4.9 Specific adverse events

To assess specific adverse and potentially serious adverse events, we will collect data on hypercalcemia, arrhythmias, acute kidney failure requiring dialysis, ulcers, and acute pancreatitis. Assessment of adverse events will be based on available laboratory values and clinical data. No specific procedures or blood draws will be performed. Other potential adverse events or serious adverse events will not be collected (see section 5.4.1). The sponsor will be notified about the occurrence of any serious adverse event within 24 hours.

The normal range of serum ionized calcium is 1.18-1.32 mmol/L.[131] Hypercalcemia is rarely symptomatic and does not affect kidney function until albumin-corrected total plasma calcium rises to >3.2 mmol/L (ionized calcium >1.46 mmol/L).[132] A hypercalcemic crisis is defined as a) >3.7 mmol/L (ionized calcium >1.8 mmol/L) with acute kidney failure and/or poor general condition or b) >4.0 mmol/L (ionized calcium >2.0 mmol/L.). Hypercalcemia will be defined by the peak serum pH-corrected ionized calcium concentration within the first 24 hours of hospital admission and – in line with the above-mentioned definitions – stratified in to mild (1.33-1.46 mmol/L), moderate (1.47-2.0 mmol/L), and severe (>2.0 mmol/L). As a secondary safety parameter, we will assess the uncorrected ionized calcium concentration in the first blood sample taken upon hospital arrival.

Arrhythmia will be defined as any supraventricular or ventricular tachyarrhythmia requiring an intervention from the time of ROSC until 24 hours after hospital admission. Supraventricular tachyarrhythmias will not include sinus tachycardia.

Acute kidney injury will be defined as the need for acute dialysis (continuous veno-venous hemofiltration or acute hemodialysis) within the first week of hospital admission. Acute dialysis for conditions not related to failing kidney function (e.g. removal of toxins) will not be included in this parameter.

Peptic ulcer disease will be defined as gastroscopy-confirmed ulcerative disease of the stomach or duodenum within the first week of hospital admission.

Acute pancreatitis will be defined as plasma amylase levels >360 units/L within the first week of hospital admission.

5.4.10 Timeline

Data on hypercalcemia and tachyarrhythmias will be collected from the time of sustained ROSC and through the first 24 hours of hospital admission, as a patient without calcium metabolism disease should be able to correct a slight iatrogenic hypercalcemia within this time frame. We will collect data on delayed potential adverse events (acute dialysis, peptic ulcer disease, and acute pancreatitis) in the first week of hospital admission since any event after this time frame will have poor association with our intervention. We do not expect any survivors to be discharged within one week, as OHCA survivors usually have longer hospital admissions.[133]

5.4.11 Suspected Unexpected Serious Adverse Reaction (SUSAR)

Suspected Unexpected Serious Adverse Reactions (SUSAR) will be reported to the independent data-monitoring committee (IDMC) (see section 10.2) and the regulatory authorities as applicable. Given the consideration outlined in section 5.4.1, most events or conditions, including but not limited to organ failure, infection, tissue ischemia, brain damage, cardiac arrest, and death, will not be considered SUSARs. This approach is compatible with an ongoing international, multicenter trial in post-cardiac arrest (ClinicalTrials.gov Identifier: NCT02908308) and the ongoing Danish trial Vasopressin and Methylprednisolone for In-Hospital Cardiac Arrest (VAM-IHCA) (ClinicalTrials.gov Identifier: NCT03640949). No events, including those outlined in section 5.4.3, will automatically lead to unblinding.

5.4.12 Reporting

Once a year the sponsor will submit a list of all registered adverse events that have occurred during the trial period as well as a report on safety of the trial subjects to the Danish Medicines Agency and the National Committee on Health Research Ethics. The sponsor will notify both agencies when the trial has been completed (no later than 90 days thereafter) or if earlier than planned, the reasons for stopping the trial will be given. The results from the trial including important adverse events will be recorded on EudraCT.

5.5 Additional follow-up

The primary trial and publication will be related to the study outcomes (section 5.1, 5.2, and 5.3). However, extended follow-up at 180 days and 1 year, including overall survival, neurological outcomes, and health-related quality of life, will be collected and reported. Data will be collected and analyzed like the 90-day outcomes and will be reported in a separate publication. Although the overall trial will be unblinded after the collection of the 90-day outcomes, the person assessing 180 days and 1-year outcomes will be blinded to treatment assignment.

6. SAMPLE SIZE CALCULATION AND STATISTICAL ANALYSIS PLAN

6.1 Sample size calculation

6.1.1 Original sample size calculation

The original sample size was based on the primary outcome of ROSC at hospital arrival. Based on the best available data,[10,134] we assumed that the ROSC rate would be 25.0% in the placebo group. We anticipated a ROSC rate of 37.5% in the calcium group corresponding to an absolute treatment effect of 12.5% and a relative treatment effect of 50%. Based on a chi-squared test and an alpha of 0.05, a sample size of 430 was needed to obtain 80% power.

6.1.2 Updated sample size calculation

From Jan. 20th to November 18th, 61 out of 270 patients (23% [95%CI 14, 26]) met the updated primary outcome of sustained ROSC. This is lower than anticipated.

We have re-estimated the sample size based on this lower combined ROSC proportion. We anticipate a ROSC proportion of 18% in the placebo group and 27% in the calcium group, corresponding to an absolute treatment effect of 9% and a relative treatment effect of 50%. With a chi-squared test, an alpha of 0.05, and 80% power, a sample size of 674 patients is needed.

We anticipate no loss to follow-up for the primary outcome.

Of note, a recent trial of adrenaline administration during OHCA found that this increased ROSC approximately 3-fold[68] illustrating that intra-cardiac arrest interventions have the potential to substantially increase the rate of ROSC. Similarly, the 1985-trials found a 3-fold increase in ROSC with calcium administration (section 1.3).[43,44]

6.2 Statistical analysis plan

6.2.1 General considerations

The statistical analyses and reporting will adhere to the Consolidated Standards of Reporting Trials (CONSORT)-guidelines.[135,136] All tests will be two-sided, a p-value <0.05 will be considered significant, and all confidence intervals will have 95% coverage. P-values will only be reported for the primary outcome and the two key secondary outcomes.

Patient inclusion and exclusion will be illustrated in a CONSORT flow diagram (see Appendix 3 for a draft).

All analyses will be conducted on a modified intention-to-treat basis only including patients receiving at least one dose of the study drug and meeting all inclusion criteria and no known exclusion criteria at the time of drug administration. In a double-blind trial, this approach is unbiased while increasing precision.[54]

The two groups will be compared in relation to baseline patient and cardiac arrest characteristics using descriptive statistics.

The persons conducting the statistical analysis will be blinded to the randomized allocation and the statistical analysis will be performed separately by two investigators. Groups will be designated as "A" and "B" until all pre-specified analyses are performed and shared with all authors and the IDMC (see section 10.2).

6.2.2 Primary and secondary outcomes

The primary and secondary outcomes (binary variables) will be presented as counts and proportions in each group. Results will be reported as both risk ratios and risk differences. 95% confidence intervals will be obtained using methods described by Miettinen and Nurmimen.[137] In the case where results are significantly different between groups, the number needed to treat (with 95% confidence intervals) will also be provided. P-values will be obtained from Fisher's Exact test.

As a sensitivity analysis, we will estimate the risk ratio with 95% confidence intervals for the primary outcome while adjusting for station (stratification variable) and strong prognostic factors as covariates: this includes age, whether the cardiac arrest was witnessed, whether bystander CPR was initiated or not, and the initial rhythm.[138-141] Small stations (i.e. those with less than 30 patients included) will be combined. The risk ratio will be estimated from a log-binomial regression model.[142] If this model fails to converge, a modified Poisson regression model will be used instead.[142,143] Age will be included as a linear continuous variable, and witness-status, bystander CPR as well as the initial rhythm will be included as binary variables (i.e. witnessed vs. unwitnessed, bystander CPR vs. no bystander CPR, and shockable vs. non-shockable, respectively).

6.2.3 Subgroup analyses

Subgroup analyses will be performed on both the absolute and relative scale. The analyses will be performed according to the initial rhythm (shockable vs. non-shockable), the timing of the drug administration (dichotomized by the median), intravenous vs. intraosseous administration, whether or not the OHCA was witnessed by a bystander, whether the OHCA was witnessed by the ambulance staff, and whether bystander CPR was performed. The trial is not powered to detect subgroup differences, and these will be considered exploratory and hypothesis generating.

Additional exploratory subgroup analyses will be performed in patients with PEA as the presenting rhythm. These will include subgroup analyses related to electrocardiogram (ECG) characteristic (e.g., QT length) and will be presented in a separate manuscript.

6.2.4 Additional analyses and outcomes

Continuous outcomes (e.g. health-related quality-of-life) will be compared using linear regression with station included as a random effect.[145] Health-related quality of life and SOFA-scores will only be assessed in those alive at the time of measurement.

Survival until 90 days will be presented with Kaplan-Meier curves,[146] but will otherwise be analyzed as a binary outcome as described section 6.2.2.

Adverse events and other binary outcomes will be presented and analyzed like the primary and secondary outcomes.

6.2.5 Missing data

Missing data will be reported in the relevant publications. We do not expect any missing data for the primary outcome or the key secondary outcomes. For mortality up to 90 days, there may be some very limited loss to follow-up.

There might be some limited missing data for neurological outcomes and health-related quality of life at 90 days due to loss to follow-up. Multiple imputation using known risk factors for outcomes after OHCA will be used to impute values for patients with missing data if missing data is substantial (>10%).

6.2.6 Multiple comparisons

No adjustments will be made for multiple comparisons. The rationale for this approach is three-fold. First, the trial has a clearly defined primary outcome which will ensure that the risk of a Type I error (i.e. false positives) is equal to the set alpha (i.e. 0.05) for this outcome. Second, the simplest procedure to control the family-wise error rate is the Bonferroni correction where the alpha is divided by the number of tests

performed within the "family" of tests. However, defining the "family" is difficult and at best arbitrary.[149,150] Third, any adjustment for multiple comparisons to control the family-wise error rate increases the chance of Type II errors (i.e. false negatives).[150]

Given that the risk of Type I errors is not well defined when conducting multiple secondary analyses, these specific analyses should be considered exploratory and hypothesis generating.

6.2.7 Statistical stopping criteria

Since the primary outcome is not mortality, there will be no formal stopping criteria for efficacy. There will be no predefined stopping criteria for futility since enrollment of the full cohort might allow for detection of efficacy in subgroups or in other outcomes even if the primary outcome is negative. Furthermore, since two previous randomized clinical trials have shown a potential pooled efficacy,[43,44] a negative trial with an adequate sample size will be important. For potential stopping due to safety concerns, see section 10.2.

6.2.8 Secondary Bayesian analyses

We will perform secondary Bayesian analyses for the primary and key secondary outcomes in order to aid interpretation of the results.[151] Given the limited evidence on calcium use in cardiac arrest, we will primarily use noninformative prior probability distributions and the results obtained from the trial to obtain posterior probability distributions for both risk differences and risk ratios. More skeptical neutral prior probability distributions will also be used. These will be based on an assumed trial of a quarter of the sample size with no treatment effect.[151] For the outcome ROSC, an analysis will also be made using a prior probability distribution based on the previous two calcium trials (section 1.3). The posterior probability distributions will be illustrated graphically, and the probability that the true treatment effect is larger than various thresholds for risk ratios and differences will be provided. Lastly, we will provide the median risk ratio and risk difference with 95% credibility intervals.

7. DATA COLLECTION AND MANAGEMENT

7.1 Data collection process

A trained member of the research team, along with the station investigators, will be responsible for data collection and entry. Very limited data will be obtained by the prehospital team on an electronic case report form. This will include the patient identifier (i.e., Danish Central Personal Register number), study ID, timing of the first adrenaline and calcium dose, route of administration, number of doses, and name of the prehospital personnel responsible for inclusion. This, along with the telephone interviews for long-term

follow-up, will be the only source data; all additional data will be obtained from pre- and in-hospital electronical medical records, as well as linkage with relevant registries, and will be based on measurements and assessments made by the clinical team. All ECG-data from monitors and defibrillators will be uploaded to a safe electronic database.

7.2 Variables

7.2.1 Overview

Based on the definitions in section 4.2, all OHCAs will be entered into a screening log. OHCAs will be identified by review of prehospital records and logs. For those not randomized, a specific reason for non-inclusion/exclusion will be documented. All randomized patients (i.e., those where the ampoule is opened) will be entered into the main database. For those randomized that did not receive the study intervention, only a very limited amount of data will be collected.

A detailed data dictionary that clearly defines all included variables will be created prior to patient enrollment. The data dictionary will provide the name of the variable (including the code used in the database), a detailed definition of the variable, categories for categorical variables, and units and ranges for continuous variables.

The number of collected variables will be kept relatively small to limit resource use and data entry mistakes. The included variables largely follow the OHCA Utstein guidelines from 2015.[11] Below is provided a brief overview of the included variables, but details are reserved for the data dictionary.

7.2.2 Pre-cardiac arrest characteristics

Patient demographics and characteristics

- Name
- Unique patient identifier (Danish Central Personal Register number)
- Age
- Sex
- Race
- Height
- Weight

Conditions/medications prior to the cardiac arrest

- Co-morbidities

    - Cardiac
    - Non-cardiac
- mRS (and CPC) prior to cardiac arrest
- Clinical fragility index

7.2.3 Cardiac arrest characteristics

Pre-intervention variables

- Date and time of the cardiac arrest
- Location of the cardiac arrest
- Witnessed (bystander, EMS, none)
- Bystander CPR
- Bystander shock with automated external defibrillator (AED)
- Date and time of the first dose of adrenaline
- Initial rhythm
- Rhythm when intervention administered
- Date and time of first defibrillation
- Response time by EMS
    - Primary ambulance
    - Physician-manned- *or* paramedic ambulance

Post-intervention variables

- Date and time of the end of resuscitation (ROSC or termination without ROSC)
- Extracorporeal cardiopulmonary resuscitation (ECPR)

Other variables

- Other drugs during resuscitation
- Pathogenesis
    - Medical
    - Drug overdose
    - Drowning
    - Electrocution
    - Asphyxia

Trial related variables

- Study ID
- Station
- Receipt of study medication
    - If no, reason for no study medication provided
- Paramedic or physician
- Intravenous vs. intraosseous administration
- Timing of study drug administration
- Doses of study medication provided
- Requirement for emergency unblinding
- Inclusion criteria
- Exclusion criteria
- Date and time consent for data collection is obtained

7.2.3 Post-cardiac arrest characteristics

- Targeted temperature management
    - <u>If yes:</u> Temperature target, duration
- Coronary reperfusion attempted
    - <u>If yes:</u> Type and timing
- Adverse events (see section 5.4.3)

7.2.4 Outcomes

- ROSC
- Laboratory values
- Vasopressor-free days
- Ventilator-free days
- SOFA scores at 2, 24, 48 and 72 hours
- Survival at 30 days, 90 days, 180 days and 1 year
- mRS and CPC at 30 days, 90 days, 180 days and 1 year
- EQ-5D-5L at 30 days, 90 days, 180 days and 1 year

7.3 Data quality and validity

7.3.1 Central monitoring

Data quality and validity will be optimized by having trained researchers enter all data according to a detailed data dictionary. Research Electronic Data Capture (REDCap) (see section 7.4) is designed such that data forms contain field-specific validation checks ensuring that mandatory fields are filled out and that continuous variables are within predefined ranges. Furthermore, REDCap allows for data quality rules warning of potential incorrect data (e.g., administration of study drug before arrival of prehospital personnel); this data is assessed and – if relevant – corrected.

Given its limited utility, double-data entry will not be performed.[152,153]

7.3.2 On-site monitoring

On-site monitoring will be performed by the Good Clinical Practice unit according to the developed monitoring plan. Please see section 10.1.

7.4 Data storage and security

The database application we will use is REDCap.[154] REDCap is a professional database that provides a user-friendly interface. The REDCap data management system is secure, fully compliant with all regulatory guidelines and includes a complete audit-trail for data entry validation. Through these mechanisms, as well as relevant training for all involved parties, patient confidentiality will be safeguarded. REDCap is available for free at Aarhus University. The case report form will be digital.

Data will be handled according to all relevant Danish laws including the General Data Protection Regulation ("Databeskyttelsesforordningen") and the Data Protection Act ("Databeskyttelsesloven"). The project will be registered with the Central Denmark Region's internal list of research projects.

7.5 Data access

During the trial, relevant members of the steering committee along with the station investigators will have access to the entire database. Once the database is locked, a deidentified version of the database will be made available to the members of the steering committee. The IDMC, the Good Clinical Practice unit, regulatory agencies, and other relevant monitoring entities will have direct access to patients' records and to all relevant trial data including all source data as applicable.

8. CLINICAL TREATMENT

The clinical management of included patients will be at the complete discretion of the treating prehospital and in-hospital teams in order to test the interventions in a real-life clinical scenario. In general, management will adhere to the intra- and post-cardiac arrest guidelines provided by the ERC[49] and the Danish Resuscitation Council,[155] but no specific treatments will be prohibited or mandated. The stations will be informed about the most recent guidelines for intra-cardiac arrest care and will be encouraged to limit premature termination of resuscitation efforts.[156] Hospitals will also be encouraged to follow ERC post-cardiac arrest guidelines including appropriate neurological prognostication.[157]

9. ETHICAL CONSIDERATIONS

9.1 Clinical equipoise

9.1.1 Potential benefits

Details about the potential benefits of the intervention are provided in the background section (section 1.2 and 1.3). In brief, two randomized, double-blind trials found that calcium might lead to a clinically meaningful increase in ROSC in patients with OHCA and a refractory non-shockable rhythm.[43,44]

9.1.2 Potential harms

The two trials with intravenous calcium administration in OHCA found no signs of significant harm.[43,44] Based on case reports, there is concern that hypercalcemia could lead to tachyarrhythmia or – in the setting of digitalis glycoside toxicity – impaired diastolic relaxation, but the clinical evidence indicates that it is safe (section 5.4.3 and 5.4.4). There is an association with gastric hypersecretion, but only in patients who already have peptic ulcer disease, and even in these patients there are no data showing calcium should worsen symptoms or outcomes (section 5.4.6). Lastly, prolonged hypercalcemia has been linked with acute kidney injury and acute pancreatitis, but no evidence shows an association with short-lived hypercalcemia (section 5.4.5 and 5.4.7).

9.1.3 Risk/benefit ratio

From the data provided above in section 9.1.1. and 9.1.2 and in the background section (section 1.2 and 1.3), the current risk/benefit ratio is encouraging for calcium administered during OHCA. However, due to the previous trials' non-significant result (p=0.06), their small sample size (n=163), and some contrary evidence from observational studies,[30,31] international guidelines are calling for additional clinical trials.[47] Taken together, there is clear clinical equipoise for calcium administration during OHCA.

9.2 Research in cardiac arrest

9.2.1 General considerations

Research in cardiac arrest is ethically challenging for two reasons: 1) Patients are unconscious and can therefore not provide informed consent and 2) treatment must be administered within minutes limiting the possibility of obtaining informed consent from a legally authorized representative.[158,159] Despite these challenges, there is an ongoing need to conduct research in this, and similar, patient populations to improve outcomes. International guidelines, such as the revised Declaration of Helsinki,[1] European regulations,[2] and the Good Clinical Practice guidelines,[3] clearly supports research in such populations. For example, the revised Declaration of Helsinki states:

"Research involving subjects who are physically or mentally incapable of giving consent, for example, unconscious patients, may be done only if the physical or mental condition that prevents g iving informed consent is a necessary characteristic of the research group. In such circumstances the physician must seek informed consent from the legally authorised representative. If no such representative is available and if the research cannot be delayed, the study may proceed without informed consent provided that the specific reasons for involving subjects with a condition that renders them unable to give informed consent have been stated in the research protocol and the study has been approved by a research ethics committee. Consent to remain in the research must be obtained as soon as possible from the subject or a legally authorised representative."[1]

The current trial will adhere to the revised Declaration of Helsinki as well as all applicable laws and regulatory guidelines.

9.2.2 Danish regulations

Danish law allows research without informed consent in situation where the following criteria are met:[160,161]

1) The research can only be conducted in the given acute situation
2) The patient is incapable of providing informed consent
3) Consent cannot be obtained from a surrogate given the urgency of the intervention
4) The research specifically involves the patient's current condition
5) There is a possibility of benefit to the patient

The current trial fulfils all the above criteria as described in section 9.2.3 for #1-4 and for #5 in section 9.1. Under these circumstances, research with pharmacological interventions is allowed if the following is obtained:[160-162]

1) Consent is obtained from a designated "legal guardian" ("forsøgsværge" in Danish)
2) Informed consent is obtained from the patient or a surrogate as soon as feasible

A "legal guardian" is a physician not involved in the research related to the specific patient and who is not in an inferior/superior position to the investigator/sponsor. The "legal guardian" should act according to the interest of the research participant.

9.2.3 Regulations in relation to the current trial

#1. The research can only be conducted in the given acute situation

Given the high morbidity and mortality of OHCA (see section 1.1.1), clinical trials are highly needed to improve patient outcomes. Animal studies do not adequately reflect the clinical condition of cardiac arrest,[163] and human trials are needed to advance the treatment of cardiac arrest patients. There is no other clinical condition that reflects cardiac arrest, and any study aimed to improve outcomes for cardiac arrest patients can therefore only be conducted in this population.

#2. The patient is incapable of providing informed consent

OHCA is an unpredictable and sudden event. It is therefore impossible to obtain consent prior to the event. During the cardiac arrest, patients are unconscious and therefore not able to provide consent.

#3. Consent cannot be obtained from a surrogate given the urgency of the intervention

Cardiac arrest is an acute event that often lasts for less than 30 minutes. The intervention will be administered as soon as possible after the first adrenaline dose, which is given as soon as possible in patients with a non-shockable rhythm (most often <20 minutes from cardiac arrest onset), and after the third defibrillation in patients with a shockable rhythm (approximately 6-7 minutes after the beginning of advanced resuscitation efforts[11]). Given these time frames, it would be impossible to obtain consent from a surrogate.

#4. The research specifically involves the patient's current condition

The interventions in this trial is specifically targeted for OHCA patients and if proven effective, will benefit this patient population.

9.3 Procedures

9.3.1 Ethical review committee

The trial will be sent for approval by the regional ethics committee.

9.3.2 Trial-specific procedures

The "legal guardian" will be a prehospital physician not involved in trial procedures related to the specific patient. Consent for enrolment from the "legal guardian" will be obtained either through direct conversation or a phone call, while written consent will be obtained as soon as possible thereafter. As the "legal guardian" could be from a station involved in trial enrollment, he/she could be involved in trial procedures for other unrelated patients. All potential "legal guardians" will be made aware of the trial including background, significance, inclusion- and exclusion criteria, as well as potential risks and benefits. This allows for an informed and prompt decision about patient enrollment.

As soon as possible, a physician will obtain consent for further data collection from the patient or – if the patient is not able to provide consent – by a secondary "legal guardian" and a surrogate. The physician obtaining consent will be a member of the steering committee or a physician with sufficient knowledge about the patient, the condition, and the trial (i.e., a member of the clinical team who has been formally educated about the trial and relevant procedures). Trial information and the consent request will take place in an undisturbed room, and the patient or the surrogate will have the opportunity to request an assessor. Between the trial information and the consent request, the patient or surrogate will be provided with an appropriate amount of time for consideration, and further time can be requested as needed.

The patient, surrogate, the person obtaining the consent, and the secondary "legal guardian" will sign individual digital consent forms as appropriate. If a patient dies before it is possible to obtain consent (we anticipate that approximately 75-80% will not achieve ROSC, see section 6.1), patient data will be included in the trial.[164] If a patient denies future participation in the trial, no additional data will be collected but all data collected up until the point of withdrawal will be included consistent with Danish law.[165]

When approached, the patient or a surrogate will be informed, verbally and in writing, about the background and significance of the study, inclusion criteria, potential risks and benefits, as well as a brief description of the study protocol. They will be informed that no additional interventions or procedures, except the telephone interviews for long-term follow-up, will be performed and that future participation will only include data collection. The patient or the surrogate will then provide written informed consent

through the informed consent form approved by the ethical review committee. When consent is obtained from participants or a surrogate, information about potential deidentified data sharing will also be included.

The consent forms will be digital, and all signatures will be written on a smart phone or tablet using REDCap which has dedicated functionalities for written consent.

9.3.3 Insurance

The patients in the study are covered by the Danish patient insurance.[166]

10. MONITORING

10.1 Good Clinical Practice monitoring

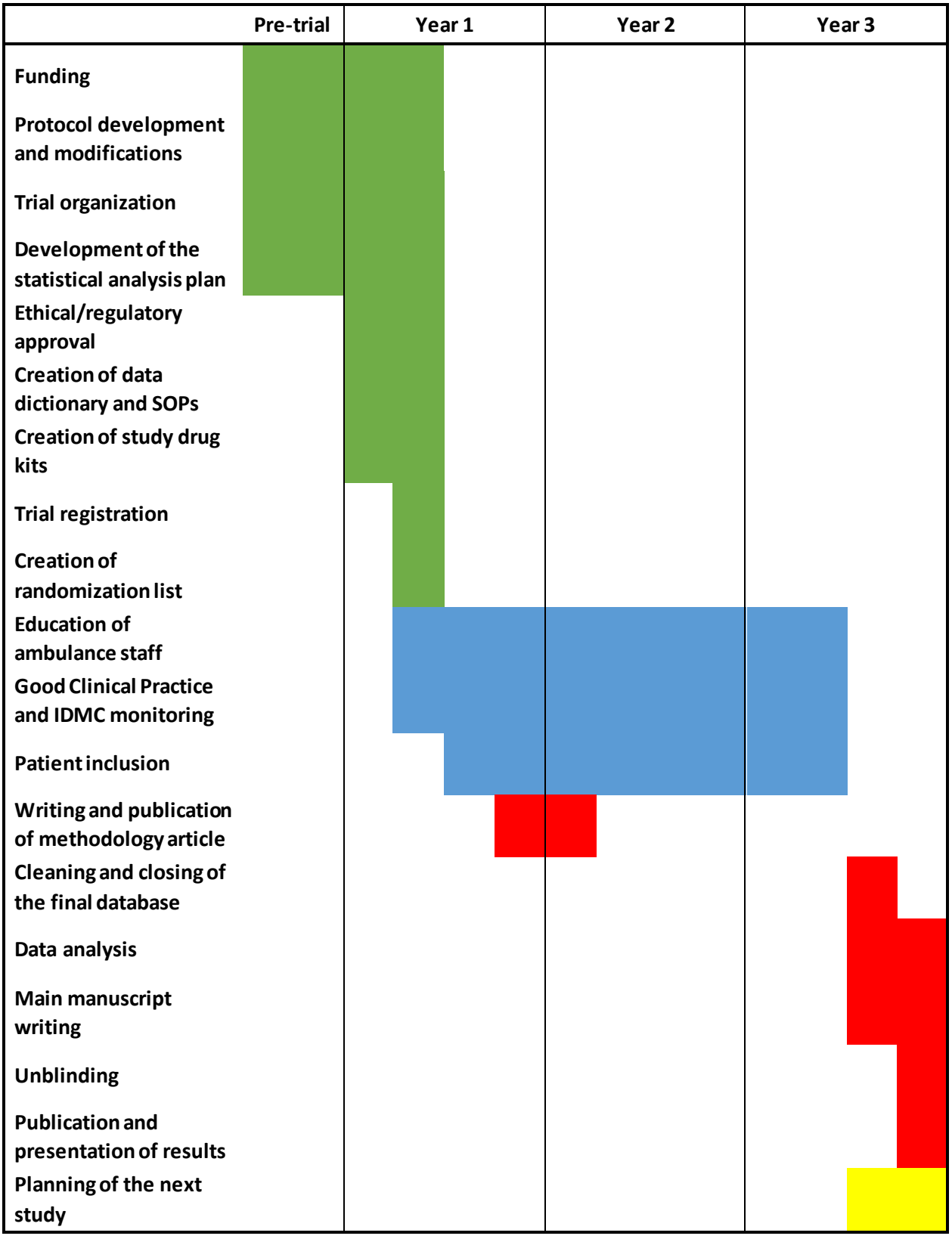
The trial will be monitored by the regional Good Clinical Practice monitoring unit. A detailed monitoring plan will be developed prior to trial commencement. The monitoring unit will have full access to all data in the trial.

10.2 Independent data-monitoring committee (IDMC)

The IDMC will be responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the clinical trial. The IDMC will consist of three clinicians/trialist with expertise in cardiac arrest research. The IDMC members are chosen such to avoid any financial or intellectual conflicts of interest. The IDMC will be independent from the sponsor and the trial investigators. The IDMC will review deidentified data for safety at three predetermined milestones (50, 200, and 400 enrolled patients, respectively), but can – at any time – require extra reviews. Unless there are group differences necessitating unblinding (as determined by the IDMC), the IDMC will be blinded to treatment groups. The trial will continue while the IDMC review data. After the reviews, the IDMC will create a short report to the steering committee with recommendations for continuation, modifications, or termination of the trial. As noted in section 6.2.7, there will be no formal stopping criteria for efficacy or futility. Criteria for recommending termination will be at the discretion of the IDMC, and there will be no formal statistical criteria for termination due to safety. The final decision regarding potential modifications or termination will rest with the steering committee and the principal investigator. A detailed charter for the IDMC is provided in Appendix 4.

11. TIMELINE AND ENROLLMENT

11.1 Timeline



11.2 Feasibility

From Jan. 20th, 2020 to December 10th, 2020, we have included 294 patients corresponding to nearly 1 patient per day. We therefore anticipate that we will be able to enroll 330 patients per year. Based on the current enrollment rate, we will reach the updated sample size of 674 patients by spring of 2022.

11.3 Enrollment

Enrollment at each station will be continuously monitored by the station investigator, the coordinating investigator, and the principal investigator. Formal reports outlining the number of OHCA and the proportion of those enrolled at each station will be shared with the steering committee monthly. In case multiple eligible OHCA are not enrolled, a root cause analysis will be performed, and efforts will be made to avoid such issues in the future. Given the urgency of OHCA, we do not expect 100% enrollment rate. However, we will aim for enrollment of >50% of eligible OHCA. In case that a station continuously underperforms despite troubleshooting and feedback, the steering committee will evaluate whether enrollment will continue at that station.

11.4 Additional sites

In case target enrollments are not met after 6 months to 1 year of enrollment, additional regions of Denmark will be approached regarding participation in the trial.

12. PUBLICATION PLAN

Four manuscripts are planned from the current trial. Prior to unblinding of the results, a methodology article will be published including a detailed description of the trial and the statistical analysis plan. The second and primary manuscript will include the main results including pre-defined primary, secondary, and tertiary outcomes. The manuscript will adhere to the CONSORT guidelines.[135,136] The coordinating investigator will be the first author, and the principal investigator will be the last and corresponding author. Additional authorship will follow authorship guidelines from the International Committee of Medical Journal Editors[167] and will include members of the steering committee and representatives from the stations as appropriate. The trial results will be shared with participating stations and via press releases, as well as with participating patients if they requested so on their consent form. The third manuscript will include long-term follow-up at 180 days and 1 year (see section 5.5). The fourth manuscript will focus on the subgroup of patients with PEA. Study findings will be published irrespective of the results. Trial findings will be published irrespective of the results.

13. DATA SHARING

Six months after the publication of the last results, all deidentified individual patient data will be made available for data sharing.[168] Procedures, including re-coding of key variables, will be put in place to allow for complete deidentification of the data. Data will be completely anonymized according to Danish law.

All relevant trial-related documents, including the protocol, data dictionary, and the main statistical code, will be shared along with the data. There will be no predetermined end date for the data sharing. Data will be available for any research purpose to all interested parties who have approval from an independent review committee and who have a methodological sound proposal as determined by the steering committee of the current trial. Only the methodological qualities and not the purpose or objective of the proposal will be considered. Interested parties will be able to request the data by contacting the principal investigator. Authorship of publications emerging from the shared data will follow standard authorship guidelines from the International Committee of Medical Journal Editors[167] and might or might not include authors from the steering committee depending on the nature of their involvement.

14. FUNDING

Funding for the trial is provided by the Novo Nordic Foundation (DKK 2,942,996), Aarhus University (DKK 180,000), the Health Research Foundation of Central Denmark Region (DKK 782,449), and the Tryg Foundation (DKK 271,349). Funding is administered at the Prehospital Emergency Medical Services, Central Denmark Region and is used for salary support, pharmacy and medications costs, monitoring, and additional operational expenses. Additional funding will be applied for at various private and public foundations. The funding agencies will have no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or the decision to submit the manuscript for publication.

15. TASKS AND RESPONSIBILITIES

Principal investigator, sponsor, and coordinating investigator: Overall responsibility for protocol development, funding, budget overview, data dictionary development, ethical approval, trial registration, daily management, trial oversight, contact to the pharmacy, contact to Good Clinical Practice monitoring unit and the data and safety monitoring board, assessment of overall recruitments, potential recruitment of additional sites, data analysis, and dissemination and presentation of results. Also, the responsibility to

educate station personnel, evaluation of eligible patients not included, data entry and management, and patient follow-up.

Steering committee: Protocol development, funding, budget overview, data dictionary development, trial oversight, dissemination of results, responsibilities as principal investigator for short time periods .

Station investigators: Responsible for station-specific enrollment, evaluation of eligible patients not included, education of personnel at participating stations, reporting of station-specific issues or challenges to the principal investigator, participant consent for data collection.

Clinical team: Administration of the study drug, participant consent for data collection

Good Clinical Practice-unit: See section 10.1.

IDMC: See section 10.2.

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Appendices

Appendix 1: Conflict of interest disclosures for the steering committee members

Lars W. Andersen

Industry:

- None

Other:

- None

Hans Kirkegaard

Industry:

- None

Other:

- None

Asger Granfeldt

Industry:

- None

Other:

- None

Mikael Fink Vallentin

Industry:

- None

Other:

- None

Thomas Dissing

Industry:

- None

Other:

- None

Christian Fynbo Christiansen

Industry:

- None

Other:

- None

Christian Juhl Terkelsen

Industry:

- None

Other:

- None

Steffen Christensen

Industry:

- None

Other:

- None

Carsten Meilandt

Industry:

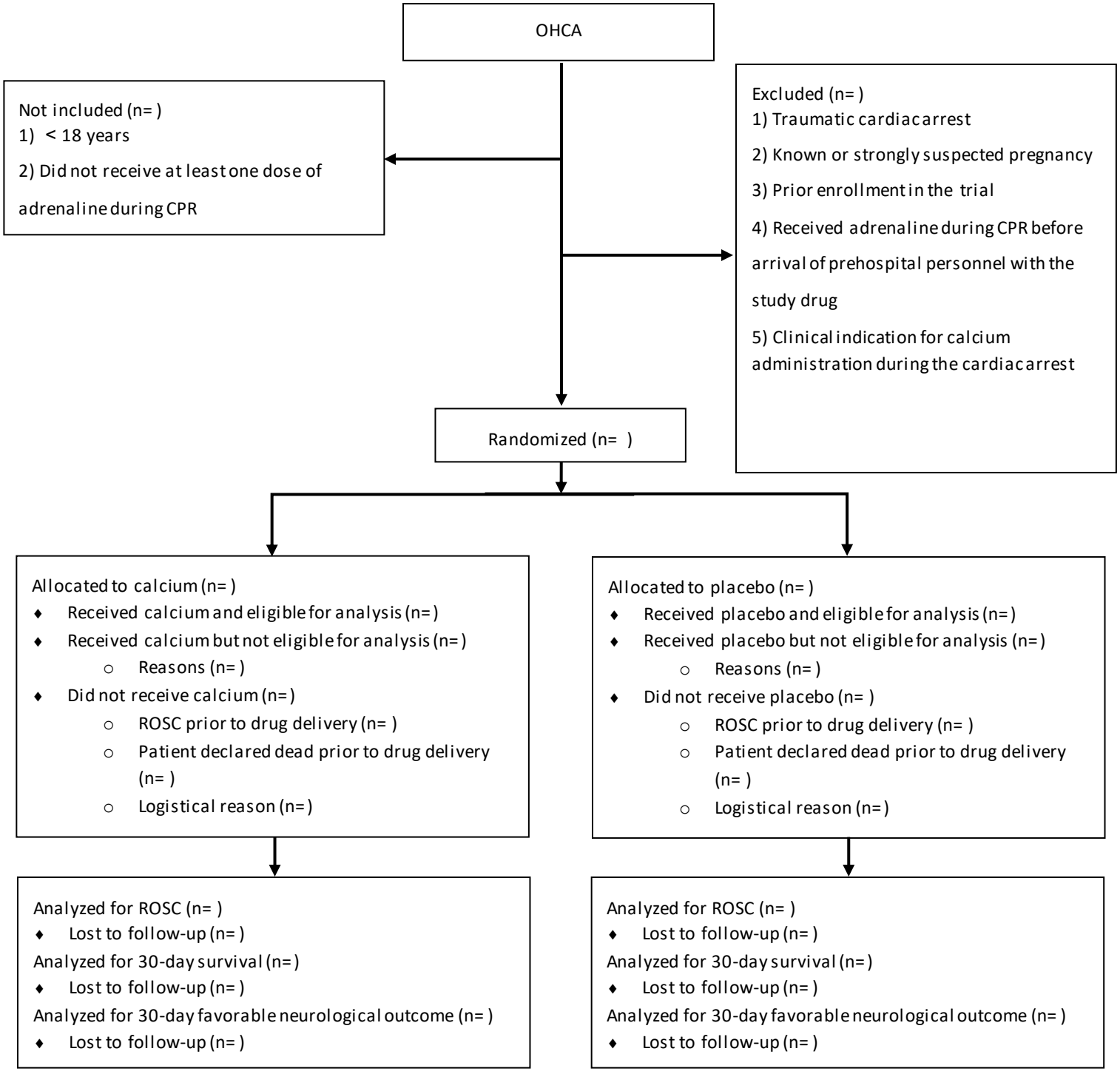
- None

Other:

- None

Appendix 2: Study kit and drug labeling (Danish)

Appendix 3: Draft of CONSORT flow diagram



Charter for the independent data-monitoring committee (IDMC) for the COCA trial

Version 1.1

March 3, 2021

Trial name: Calcium for Out-of-Hospital Cardiac Arrest – A Randomized, Double-Blind, Placebo-Controlled Trial

Principal investigator and sponsor: Associate professor Lars W. Andersen, M.D., M.P.H., Ph.D., D.M.Sc.

EudraCT Number: 2019-003387-46

Research ethical committee no.: 1-10-72-215-19

Amendments

Version 1.0 to 1.1

- Added three additional variables to the IDMC data
- Added an additional interim analysis at 400 patients due to an increase in sample size

Introduction

This charter will define the primary responsibilities of the IDMC, its relationship with other trial components, its membership, and the purpose and timing of its meetings. The charter will also provide the procedures for ensuring confidentiality and proper communication, the statistical monitoring guidelines to be implemented by the IDMC, and an outline of the content of the data that will be provided to the IDMC.

Responsibilities of the IDMC

The IDMC will be responsible for safeguarding the interests of trial participants, assessing the safety and efficacy of the interventions during the trial, and for monitoring the overall conduct of the clinical trial. The IDMC will provide recommendations about stopping or continuing the trial to the steering committee of the COCA trial. To contribute to enhancing the integrity of the trial, the IDMC may decide to also formulate recommendations relating to the selection/recruitment/retention of participants, their management, improving adherence to protocol-specified regimens and retention of participants, and the procedures for data management and quality control. Any such recommendations will be at the discretion of the IDMC.

The IDMC will be advisory to the steering committee. The steering committee will be responsible for promptly reviewing the IDMC recommendations, to decide whether to continue or terminate the trial, and to determine whether amendments to the protocol or changes in trial conduct are required.

The IDMC will be notified of all changes to the trial protocol or conduct. The IDMC concurrence will be sought on all substantive recommendations or changes to the protocol or trial conduct prior to their implementation.

The members of the IDMC will be unpaid.

Members of the IDMC

The IDMC is an independent multidisciplinary group consisting of physicians with epidemiological expertise that, collectively, has experience in the management of cardiac arrest patients and in the conduct, monitoring and analysis of randomized clinical trials.

The members of the IDMC are:

Jesper Kjærgaard, M.D., Ph.D., D.M.Sc. (chairman)
Consultant
Department of Cardiology
Rigshospitalet, Copenhagen, Denmark

Jerry P. Nolan, FRCA, FRCP, FFICM, FCEM (Hon.)
Professor, Consultant
Anesthesia and Intensive Care
Royal United Hospitals, Bath, United Kingdom

Theresa M. Olasveengen, M.D., Ph.D.
Consultant
Division of Emergencies and Critical Care
Oslo University Hospital, Oslo, Norway

Conflicts of interest

IDMC membership has been restricted to individuals free of conflicts of interest. The source of these conflicts may be financial, scientific, or regulatory in nature. The IDMC members will disclose to fellow members any consulting agreements or financial interests they have with the sponsor of the trial or with other sponsors having products that are being evaluated or having products that are competitive with those being evaluated in the trial. The IDMC will be responsible for deciding whether these consulting agreements or financial interests materially impact their objectivity. The IDMC members will be responsible for advising fellow members of any changes in these consulting agreements and financial interests that occur during the trial. Any IDMC members who develop significant conflicts of interest during the trial should resign from the IDMC.

IDMC membership is to be for the duration of the clinical trial. If any members leave the IDMC during the trial, the steering committee will appoint the replacement(s).

Evaluations of trial data

The IDMC will review deidentified data for safety at three predetermined milestones (50, 200, and 400 enrolled patients, respectively), but can – at any time – require extra reviews; unless there are group differences necessitating unblinding (as determined by the IDMC), the IDMC will be blinded to treatment

groups. The trial will continue while the IDMC review data. After the review, the IDMC will create a short report to the steering committee with recommendations for continuation, modifications, or termination of the trial. There will be no formal stopping criteria for efficacy or futility. Criteria for recommending termination will be at the discretion of the IDMC, and there will be no formal statistical criteria for termination due to safety.

Raw data will be provided to the IDMC in Excel in the following format:

Row 1 contains the names of the variables (to be defined below)

Row 2 to N (where N-1 is the number of patients who have entered the trial) each contains the data of one patient

Column 1 to p (where p is the number of variables to be defined below) each contains in row 1 the name of a variable and in the next N-1 rows the values of this variable.

The values of the following variables will be included:
1: id: a number that uniquely identifies the patient.
2: group: The randomization code (group A or B)
3: rosc_sustained: The primary outcome return of spontaneous circulation (ROSC) (1 for ROSC, 0 for no ROSC)
4: surv_30: Survival at 30 days (1 for survival at 30 days, 0 for death prior to 30 days)
5: mrs_30: modified Rankin Scale (mRS) at 30 days (0-6)

Specific adverse events (see section 5.4.3 in the protocol):
6: hyp_cal: Hypercalcemia (3 for severe, 2 for moderate, 1 for mild, 0 for no)
7: tac_arr: Tachyarrhythmia (1 for yes, 0 for no)
8: aki: Acute kidney injury (1 for yes, 0 for no)
9: pud: Peptic ulcer disease (1 for yes, 0 for no)
10: panc: Acute pancreatitis (1 for yes, 0 for no)
11: ca_peak_corrected_24h: Peak pH-corrected calcium ion plasma concentration within the first 24 hours after sustained ROSC (the numeric value on which hyp_cal is based)

12: hyp_cal_blood_0: Hypercalcemia based on the uncorrected calcium ion plasma concentration in the first in-hospital arterial blood sample
13: ca_uncorrected_blood_0: Uncorrected calcium ion concentration in the first in-hospital arterial blood sample (the numeric value in which hyp_cal_blood_0 is based)

Variables #1 and #3-13 will be provided by the steering committee and item #2 will be provided by the pharmacy.

An independent biostatistician or a member of the IDMC will provide aggregate data for each of the variables #3-13 stratified by treatment group (variable #2) in two-by-two tables. No statistical tests will be performed unless explicitly requested by the IDMC.

In addition to the above, the steering committee will provide the IDMC with data on the number of patients screened (i.e. all OHCA at participating stations), number of patients included, and the number of patients who have provided consent for additional data collection and long-term follow-up. Data will be provided on the specific reasons for non-inclusion and exclusion.

All data will be provided to the IDMC at least 5 days prior to their meeting.

Meeting, communication and reports

The steering committee, along with the IDMC chairman, will be responsible for scheduling and arranging the IDMC meeting. The meeting will start with a study overview provided by the principal investigator. This will include an overview of recruitment and potential problems and issues. The remainder of the meeting, which will only be attended by the IDMC members, will be related to evaluations of trial data as described above.

The IDMC is not planned to meet physically to evaluate data. In addition to the scheduled meeting, the IDMC may, whenever they decide, contact each other by telephone, videoconference, or e-mail to discuss the safety for trial participants. The recommendations of the IDMC regarding stopping, continuing or changing the design of the trial should be communicated in writing without delay to the steering committee. The steering committee has the responsibility to inform, as fast as possible, and no later than 72 hours, all investigators of the trial and the stations including patients in the trial about the recommendation of the IDMC and the steering committee decision hereof.

The IDMC will prepare minutes of their meetings. The closed minutes will describe the proceedings from all sessions of the IDMC meeting, including the listing of recommendations by

the committee. Because it is possible that these minutes may contain unblinded information, it is important that they are not made available to anyone outside the IDMC. The IDMC and the independent biostatistician are obligated to keep all patient-level data confidential.

Read and agreed by the IDMC members

Name: Jesper Kjærgaard

Date: 5/3-21

Signature:

Jesper Kjærgaard
Overlæge, dr. med.
Hjertemedicinsk Klinik B 2142
Hjertecentret, Rigshospitalet
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Name: Jerry P. Nolan

Date:

Signature:

Name: Theresa M. Olasveengen

Date:

Signature:

Read and agreed by the IDMC members

Name: Jesper Kjærgaard

Date:

Signature:

Name: Jerry P. Nolan

Date: 07 March 2021

Signature:

Name: Theresa M. Olasveengen

Date:

Signature:

Read and agreed by the IDMC members

Name: Jesper Kjærgaard

Date:

Signature:

Name: Jerry P. Nolan

Date:

Signature:

Name: Theresa M. Olasveengen

Date: 18.03.2021

Signature:

Theresa Olasveengen