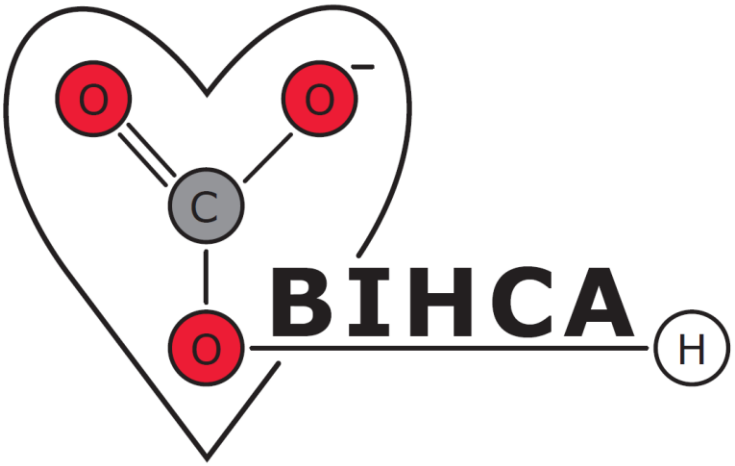
Bicarbonate for In-Hospital Cardiac Arrest

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



TRIAL PROTOCOL

Version 1.5

September 30th, 2024

EU Clinical Trials number: 2022-501304-10-00

ClinicalTrials.gov number: NCT05564130

Principal investigator and sponsor:

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Content

Preface

The “Bicarbonate for In-Hospital Cardiac Arrest – A Randomized, Double-Blind, Placebo-Controlled Trial” (BIHCA) 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 is 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]. The principal investigator 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.

30/9 - 2024

Lars W. Andersen, M.D., M.P.H., Ph.D., D.M.Sc. Date

List of abbreviations

CPC: Cerebral performance category

CPR: Cardiopulmonary resuscitation

CTIS: Clinical Trials Information System

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

OHCA: Out-of-hospital cardiac arrest

ROSC: Return of spontaneous circulation

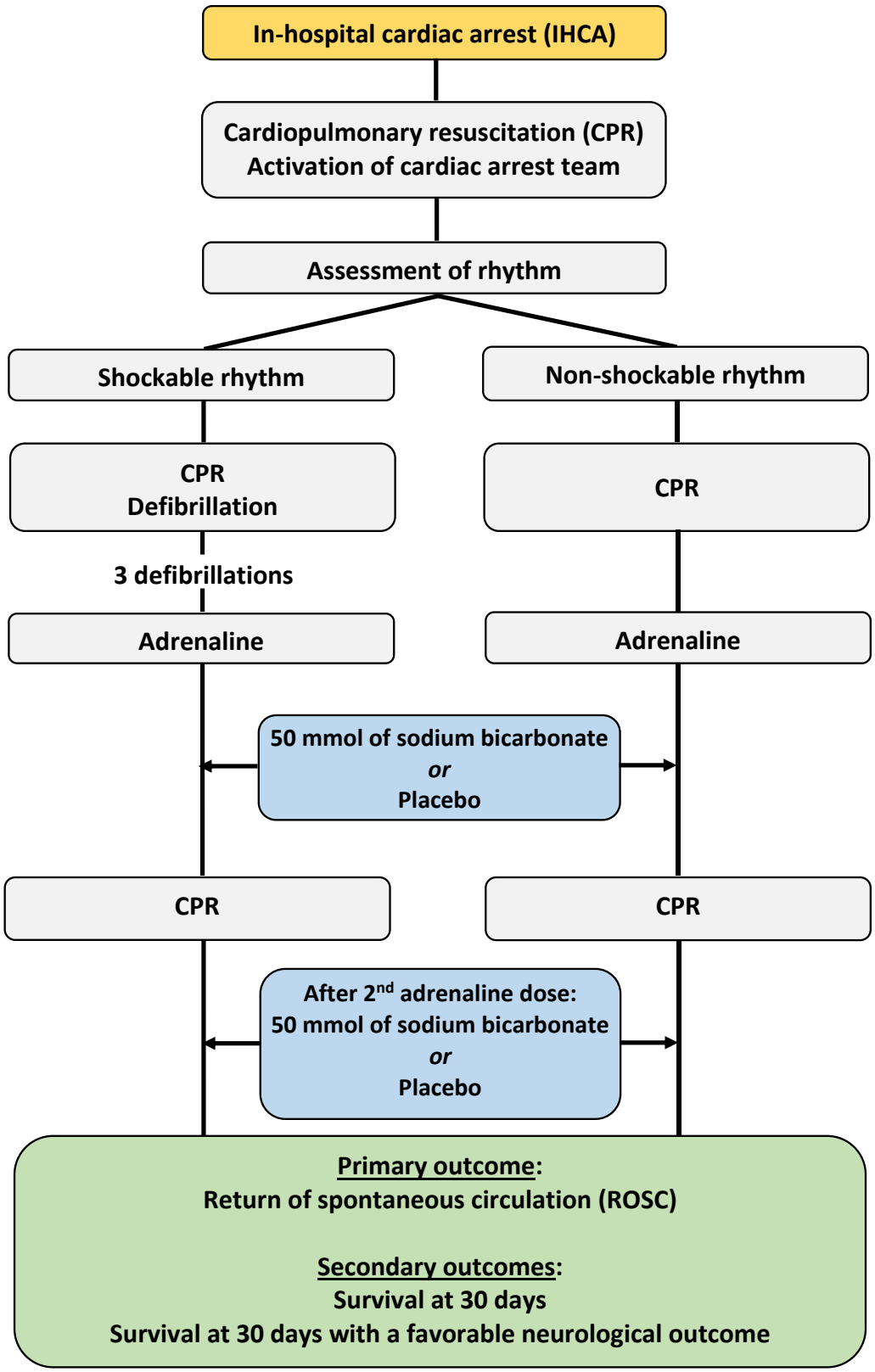
SOFA: Sequential organ failure assessment

SPIRIT: Standard Protocol Items: Recommendations for Interventional Trials

Overview/Synopsis

Registry and trial number	EU Clinical Trials: 2022-501304-10-00, ClinicalTrials.gov: NCT05564130	
Date of registration	EU Clinical Trials: Sept. 26, 2022, ClinicalTrials.gov: Oct. 3, 2022	
Funding	Novo Nordisk Foundation	
Primary sponsor	Lars W. Andersen, Aarhus University	
Contact	Lars W. Andersen, lwandersen@clin.au.dk	
Title	Bicarbonate for In-Hospital Cardiac Arrest (BIHCA) – A Randomized, Double-Blind, Placebo-Controlled Trial	
Country of recruitment	Denmark	
Condition studied	In-hospital cardiac arrest	
Interventions	Sodium bicarbonate 50 ml (1 mmol/ml) for up to two doses	
Comparator	Placebo 50 ml (0.9% NaCl) for up to two doses	
Inclusion criteria	1) In-hospital cardiac arrest 2) Age ≥ 18 years 3) Received at least one dose of adrenaline during cardiac arrest	
Exclusion criteria	1) Clearly documented "do-not-resuscitate" order prior to the cardiac arrest 2) Prior enrollment in the trial 3) Invasive mechanical circulatory support at the time of the cardiac arrest 4) Known or suspected pregnancy at the time of the cardiac arrest 5) Known objection by the patient to participate in the trial 6) Clinical indication for bicarbonate administration	
Study type	Interventional	Allocation: Randomized (1:1)
	Intervention model: Parallel group	Masking: Double-blind
Date of first screening	February 6th, 2023	
Target sample size	778	
Recruitment status	Recruiting	
Primary outcomes	Return of spontaneous circulation	
Key secondary outcomes	Survival at 30 days Survival at 30 days with a favorable neurological outcome (modified Rankin Scale 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.

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Amendments

Version 1.4 (Mar. 23, 2023) to version 1.5 (Sept. 30, 2024)

- Change of or addition of investigators at Copenhagen University Hospital, Hvidovre Hospital, Odense University Hospital, Zealand University Hospital – Køge, Holbæk Hospital, Slagelse Hospital, Hospital of Southern Jutland – Aabenraa, Copenhagen University Hospital – Roskilde, and Nykøbing Falster Hospital.
- Randers Regional Hospital was removed as a participating site
- Clarification regarding telephone interview follow-up (section 5.2.2)
- Included section on patients who do not speak Danish (section 9.3.5)
- Correction of minor typos (multiple sections)

Version 1.3 (Oct. 19th, 2022) to version 1.4. (Mar. 23, 2023)

- Changed first date of screening and recruitment status
- Change of investigators at Hospital of Southern Jutland – Aabenraa
- Change of investigators at Copenhagen University Hospital - Bispebjerg
- Change of investigators at Slagelse Hospital
- Change of site investigator at Hvidovre Hospital
- Correction noting that data will be saved for 25 years (section 7.3)

Version 1.2 (Sept. 27th, 2022) to version 1.3. (Oct. 19th, 2022)

- Addition of ClinicalTrials.gov number and changed the registration date
- Addition of anticipated date of first screening
- Clarified the definition of in-hospital (section 4.2)
- Changed “bicarbonate” to “standard bicarbonate” (section 5.3)
- Modifications to section 9.3.3 and minor modifications to 9.3.4
- Addition of pictures of the trial kit and minor updates to the design of the labels (Appendix 1)

Version 1.1 (Sept. 5th, 2022) to version 1.2 (Sept. 27th, 2022)

- Addition of trial registration dates to the trial overview/synopsis
- Addition of secondary Bayesian analyses (section 6.2.10)
- Modifications to section 9.3.3

- Appendix 4 removed

Version 1.0 (July 8th, 2022) to 1.1 (Sept. 5th, 2022)

- Correction of minor typos and investigator names
- Change of investigator Daniel Hägi-Pedersen to Morten Plambech
- Added justification for providing the trial drug as a bolus (section 3.3)
- Clarification of the power in the sample size calculation (section 6.1)
- Added that patients who withdraw consent will not be replaced (section 6.1)
- Clarification that the clinician will determine exclusion criteria #6 in real-time (section 4.3)
- Added a definition of the end of the trial (section 9.3.6)
- Section 9.4 regarding "low-intervention trial" has been removed
- Clarification that the sponsor will allow monitoring from relevant authorities (section 10.1)
- Statement regarding publication of the results on the CTIS portal (section 12)
- Clarification that the funding has been paid to an account at Aarhus University (section 14)

1. BACKGROUND

1.1 In-hospital cardiac arrest

1.1.1 Incidence and mortality

In-hospital cardiac arrest (IHCA) is relatively common with approximately 2,000 cases in Denmark[7] and 300,000 cases in the United States[8] each year. Unfortunately, outcomes remain poor with 50-70% achieving return of spontaneous circulation (ROSC) and only 25-30% surviving to hospital discharge.[7,9,10] Furthermore, in initial survivors, there are substantial post-discharge morbidity and early mortality.[11-13]

1.1.2 An understudied entity

Clinical trials are sparse in cardiac arrest[14,15], and especially in IHCA[9,16], relative to the burden of the condition. In a systematic review of all randomized clinical trials involving cardiac arrest from 1995 to 2014, Sinha et al. found that 81 (88%) were exclusively in out-of-hospital cardiac arrest (OHCA), 7 (8%) involved OHCA and IHCA, and only 4 (4%) involved exclusively IHCA. The total number of included patients were 83 times higher in OHCA studies as compared to IHCA studies.[17] A systematic search conducted in 2018 identified only 23 trials that included patients with IHCA published within the last 30 years.[9] Of these, only two trials included more than 500 patients.[9]

There is a scarcity of evidence-based pharmacological interventions for IHCA.[18,19] The evidence for adrenaline (epinephrine) and amiodarone, the only two drugs currently recommended , is limited and based on extrapolation from OHCA.[20-22] There is therefore a need for additional randomized clinical trials in IHCA in order to advance the science and improve patient outcomes.

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, in which 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.[23-25] Because of this, and since ROSC is a prerequisite for more long-term survival, the goal of most 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.[26-28] 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.[26] Consequently this leads to a clinical state (the post-cardiac arrest syndrome) with global brain injury, impaired myocardial function, macrocirculatory failure, and increased susceptibility to infections.[26] Patients are often hemodynamically unstable following a cardiac arrest and early post-cardiac arrest hypotension is strongly associated with poor outcomes.[29]

1.1.4 Acidosis during cardiac arrest

In a healthy individual, the pH of the blood is tightly regulated to maintain homeostasis. The acid-base status is maintained by intra- and extracellular buffer systems, pulmonary excretion of volatile acids (i.e., CO_2), and by renal excretion of fixed acids. During cardiac arrest, the inability to exhale CO_2 and the production of acids due to decreased perfusion and tissue hypoxia results in a substantial decrease in pH (acidosis). With initiation of chest compressions and ventilation, the excess CO_2 is partly excreted, and the acidosis is therefore often primarily metabolic.[30]

Studies have demonstrated the presence of severe acidosis during and after IHCA[31,32], with many patients also being acidotic prior to the cardiac arrest[33]. In our recent VAM-IHCA trial[34], we found a mean pH after ROSC of 7.05 (standard deviation: 0.18) indicating severe acidosis. 98% of the patients had a pH below 7.35 (defined as acidosis), 35% of the patients had a pH below 7.0 and 21% had a pH below 6.9. A higher pH was strongly associated with better outcomes. For every 0.1 increase in pH, the odds of 30-day survival were increased by 1.33 (95%CI: 1.07, 1.62), while adjusting for potential confounders (age, witnessed status, initial rhythm, duration of the cardiac arrest). The strong relationship between pH and 30-day survival is illustrated in Figure 1. Our findings are consistent with a previous study showing that more severe acidosis is associated with worse outcomes.[31]

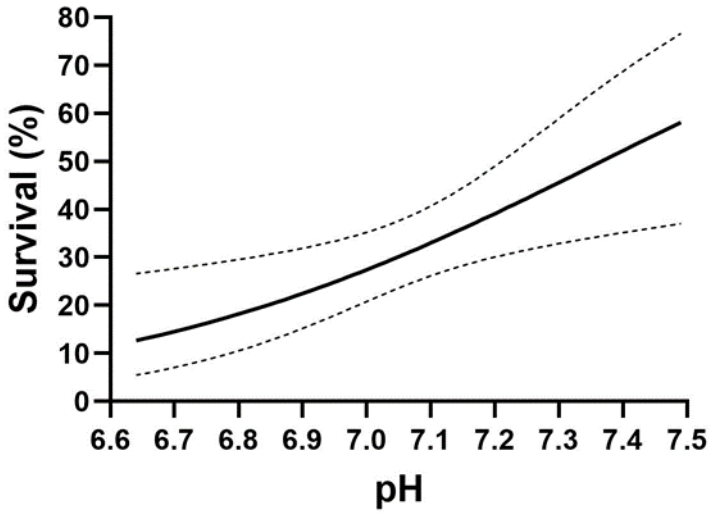


Figure 1. Association between pH and survival

Severe acidosis has a number of important detrimental effects during cardiac arrest: 1) Acidosis decreases cardiac contractility by interfering with almost every step in the excitation–contraction coupling, 2) the effect of catecholamines (e.g., adrenaline) is attenuated by acidosis, and 3) severe cerebral acidosis enhances ischemic brain damage.[30,35] Based on the detrimental effects of acidosis, administration of bicarbonate as a buffering strategy during cardiac arrest is promising.

1.2 Bicarbonate

1.2.1 Mechanism

According to the Henderson–Hasselbalch approach to acid-base status, bicarbonate (HCO_3^-) administration results in an increase in pH (i.e., decrease in H^+) and production of CO_2:

$$H^+ + HCO_3^- \leftrightarrow H_2CO_3 \leftrightarrow CO_2 + H_2O$$

Considering Stewart's approach to acid-base status, sodium bicarbonate administration increases pH by increasing the strong ion difference. Although these different mechanisms are debated, administration of sodium bicarbonate indisputably causes an increase in pH. Given this effect, we postulate, that during cardiac arrest with severe acidosis, the administration of bicarbonate will increase pH and counteract the negative consequences of acidosis (section 1.1.4), improve the chance of ROSC, and ultimately improve more long-term outcomes.

1.2.2 Animal studies

Multiple animal studies have investigated the role of bicarbonate during cardiac arrest. In large animal models (pigs and dogs) published within the last 30 years, results have been inconsistent with some studies

showing harm[36,37], some finding no effect[38-40], and some finding a beneficial effect[41-44]. The results are difficult to interpret for multiple reasons: 1) The animals had no underlying disease, often had short cardiac arrests, and the degree of acidosis was often less severe when compared to the human condition, 2) all of the studies were conducted more than 20 years ago with limited standardization of the methodology and concurrent therapies, and 3) some studies used very large doses of bicarbonate resulting in (severe) alkalosis, which is inconsistent with bicarbonate use in humans.

1.2.3 Human studies

Recent systematic reviews have described the literature related to bicarbonate and outcomes in patients with cardiac arrest.[45-47] A meta-analysis of observational studies found no effect of bicarbonate administration on outcomes.[45] However, these observational studies are at a very high risk of bias due to confounding and "resuscitation time bias". Resuscitation time bias is a unique methodological concept in the setting of cardiac arrest.[48,49] This is a severe bias that occurs when an intervention is compared to no intervention during cardiac arrest without consideration of the timing of the intervention. Briefly, this occurs because patients with longer cardiac arrests are more likely to receive a given intervention and they are also more likely to die irrespective of the intervention. This will bias any comparison against the intervention.[48,49] The results from these observational studies are therefore very difficult to interpret.

Three randomized trials have compared bicarbonate administration to placebo during cardiac arrest.[50-52] An overview of the trials is provided in Table 1 and meta-analytic results for survival to intensive care unit (ICU) admission are provided in Figure 2.

Table 1. Overview of randomized clinical trials of bicarbonate

Trial	Inclusion	Years	Sample size	Intervention	Time to drug
Dybvik, 1995[50]	OHCA, ventricular fibrillation or asystole, cardiac origin	1987-1994	502	250 ml Tribonat*	Not reported
Vukmir, 2005[51]	OHCA, shockable, non-respiratory	1994-1998	874	Mean ≈ 70 mmol bicarbonate	Not reported
Ahn, 2018[52]	OHCA, admitted to ED, pH < 7.1 or bicarbonate < 10 mEq/L	2015	50	50 mmol	31 minutes

* Sodium bicarbonate 160 mmol/l, trometamol 300 mmol/l, disodium phosphate 20 mmol/l, and acetate 200 mmol/l

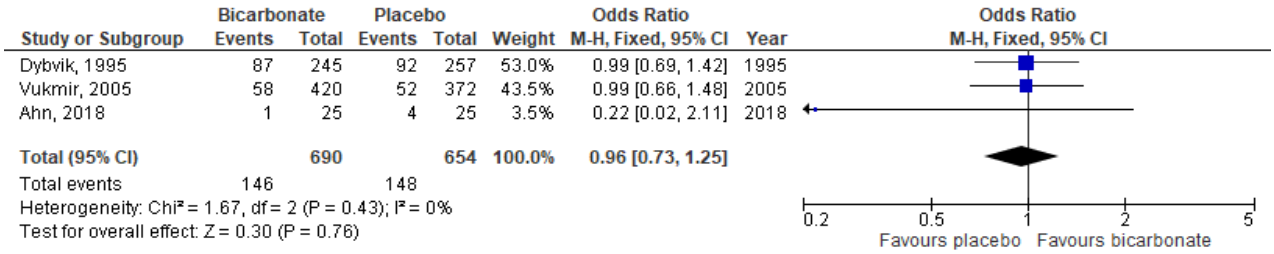


Figure 2. Meta-analysis for survival to ICU admission

As can be seen in Figure 2, these trials found no benefit or harm of bicarbonate administration for patients with OHCA. These results are very difficult to generalize to contemporary IHCA. First, the two largest trials were conducted more than 20 years ago, where cardiac arrest management and outcomes were very different. Second, the trials all included patients with OHCA. As we have described in previous manuscripts, there are important differences between IHCA and OHCA.[9,53] Most notable is the fact that advanced interventions, including drugs, are administered much earlier in the in-hospital setting. For example, in our recent trials, the drug intervention was administered after a median of 8 minutes in the in-hospital setting but after a median of 18 minutes in the out-of-hospital setting.[34,54] Although time to trial drug was not reported in the two larger trials, it was 31 minutes in the trial by Ahn et al.[52] It is highly unlikely that any drug will have an effect when administered this late. Moreover, given that patients with IHCA are often deteriorating prior to the cardiac arrest[33], patients with IHCA are more likely to be severely acidotic. The Dybvik et al. trial reported a mean pH of 7.23 after the cardiac arrest in the placebo group[50], whereas we found a mean pH of 7.05 in our recent trial as described in section 1.1.4.

1.2.4 Recommendations and clinical use of bicarbonate

Current European and American guidelines do not recommend the routine use of bicarbonate for patients with cardiac arrest except in specific circumstances such as hyperkalemia and certain toxicological causes of cardiac arrest.[18,55,56]

Despite these recommendations, bicarbonate is commonly used during cardiac arrest. The best available data comes from a large, multicenter registry of IHCA in the United States. In a publication from 2018 using this registry, we found that bicarbonate was used in approximately 50% of all IHCAs with an increase in use from 2001 to 2016 (Figure 3).[57] This corresponds to approximately 150,000 patients in the United States receiving bicarbonate during IHCA each year.[8,57] We have found similar results for pediatric cardiac arrest, where more than 50% of children with an IHCA in the United States receive bicarbonate.[58]

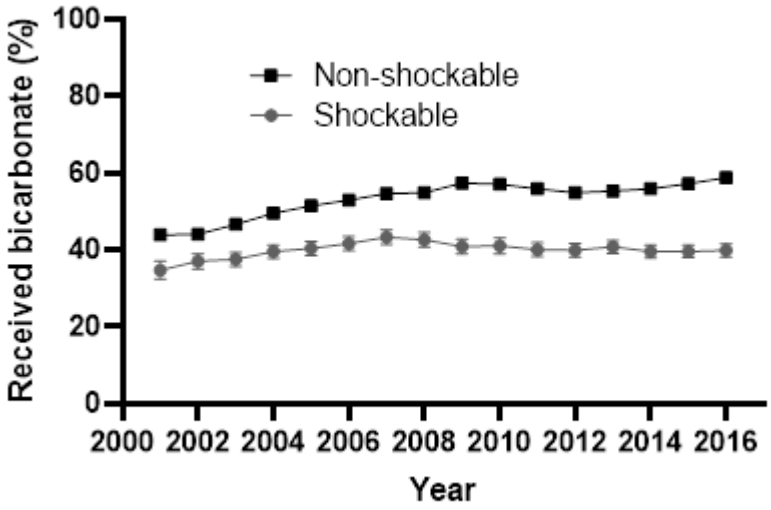


Figure 3. Use of bicarbonate for IHCA in the United States

Data on the use of bicarbonate from outside the Unites States are sparse. In our recently published VAM-IHCA trial, bicarbonate was administered to 9% of all included patients.[34] A recent study from Taiwan found that bicarbonate was administered in 69% of patients with IHCA.[59]

1.2.5 Use of bicarbonate outside of cardiac arrest

Sodium bicarbonate is approved and used for treatment of metabolic acidosis[60] and is commonly administered to acute and critically ill patients for this indication[61,62]. There is limited data from clinical trials to support the use of bicarbonate in the intensive care unit. However, results from a randomized clinical trial suggested that bicarbonate could be beneficial in patients with acute kidney injury and metabolic acidosis (pH < 7.20).[63] Bicarbonate treatment for this indication is included in the Surviving Sepsis Campaign.[64] In contrast, the Surviving Sepsis Campaign suggest against the use of bicarbonate for acidosis related to elevated lactate based on very limited evidence from small cross-over trials showing no benefit of this therapy.[64]

1.2.6 Potential theoretical concerns

Although the positive effects of bicarbonate appear promising, some theoretical concerns have been raised.[65] These primarily include a risk of hypernatremia/hyperosmolarity, decreased coronary and cerebral perfusion pressures, and intracellular acidosis. Many of these concerns are based on a few old animal studies such as a 1991 cardiac arrest study by Kette et al.[36] This study used a very high dose of bicarbonate (2.5 mmol/kg) and did not administer adrenaline making the results difficult to interpret.[36] Multiple subsequent animal and human studies have not reported severe hypernatremia or a decrease in perfusion pressures

with administration of bicarbonate.[38-40,66] The theoretical risk of transient intracellular acidosis is postulated to be caused by a production of excess CO_2, which is freely diffusible into cells and therefore might contribute to intracellular acidosis. However, this is based on studies utilizing very high doses of bicarbonate and providing no ventilation. This theory is not supported by other studies that demonstrate either an increase or no change in intracellular pH.[67,68]

1.3 Standard of care

The standard of care during cardiac arrest is described by guidelines from the European Resuscitation Council.[18] 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.[18] Although the evidence for amiodarone/lidocaine and adrenaline is limited and controversial[20-22], these drugs are currently recommended and are given, when applicable, to most patients with cardiac arrest. The intervention of the present trial (sodium bicarbonate) will therefore be compared to placebo and both groups will receive the established standard of care.

2. TRIAL OBJECTIVES AND HYPOTHESES

Primary objective: To determine whether sodium bicarbonate as compared to placebo, when administered during IHCA, will increase ROSC.

Hypothesis: Sodium bicarbonate administered during IHCA will increase ROSC.

Secondary objective: To determine whether sodium bicarbonate as compared to placebo, when administered during IHCA, will increase survival at 30 days and survival at 30 days with a favorable neurological outcome.

Hypothesis: Sodium bicarbonate administered during IHCA will increase survival at 30 days and survival at 30 days with a favorable neurological outcome.

3. TRIAL DESIGN

3.1 Overview

This is an investigator-initiated, multicenter, randomized, placebo-controlled, parallel group, double-blind, superiority trial of sodium bicarbonate during adult IHCA. There will be 21 enrolling sites in Denmark. 778 adult patients with IHCA receiving at least one dose of adrenaline will be enrolled. The primary outcome is ROSC and 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 sodium bicarbonate or placebo in blocks with random sizes of 2, 4, or 6. The randomization will be stratified according to site.[69] 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, sites will be provided with numbered blinded kits including either sodium bicarbonate or placebo ensuring allocation concealment.

3.3 Interventions

3.3.1 Sodium bicarbonate

The trial drug will consist of 50 ml of 1 mmol/ml sodium bicarbonate (ATC code: B05XA02) given as soon as possible after the first dose of adrenaline. If the patient remains in cardiac arrest, one additional dose of 50 ml of 1 mmol/ml sodium bicarbonate will be administered after the second dose of adrenaline dose for a maximum of two doses.

When sodium bicarbonate is administered during cardiac arrest for special circumstances (e.g., hyperkalemia or tricyclic antidepressant overdose), a dose of 1-2 mmol/kg or 50 mmol is usually recommended.[55,56] It is not feasible to accurately dose sodium bicarbonate based on weight during a cardiac arrest as the weight is often unknown and drugs need to be administered quickly. Therefore, up to two doses of 50 mmol sodium bicarbonate for a total of 100 mmol has been chosen. In our previous VAM-IHCA trial, which had similar inclusion and exclusion criteria[34], the median weight of the included patients was 78 kg (1st and 3rd quartiles: 67, 92). With this weight, a dose of 100 mmol corresponds to 1.3 mmol/kg (1st and 3rd quartiles: 1.1, 1.5). A previous trial found that a dose of 50 mmol sodium bicarbonate increased pH with 0.16 compared to placebo.[52] Based on this, and the severity of acidosis seen during cardiac arrest (see section 1.1.4), we consider a maximum dose of 100 mmol sodium bicarbonate to be appropriate. Given the

urgency of cardiac arrest, it is essential that the medication is administered quickly (i.e., as a bolus). This is consistent with clinical practice and international guidelines.[55,56] We note that some patients might only receive one dose of the trial intervention as resuscitation is terminated or the patient achieves ROSC. In our previous IHCA trial, 28% of the included patients only received one dose of the trial medication.[34]

3.3.2 Placebo

The placebo will consist of 50 mL of 9 mg/mL NaCl ("normal saline") from containers identical to the sodium bicarbonate containers. Normal saline is often administered to critically ill patients and has no known effects or side-effects with these small volumes.

3.3.3 Procedures

The drugs will be produced, managed, and stored according to all relevant guidelines and regulations. The trial drugs will be placed in a blinded trial kit (a small box, see Appendix 1) containing two glass vials each with 50 ml of sodium bicarbonate (1 mmol/ml) or corresponding placebo (0.9% NaCl). The trial kits will be prepared at the Capital Region Pharmacy, a company that specializes in the production of medicine and is approved by the Danish Health authorities and shipped to the participating sites regularly. The trial kit will be stored at room temperature and brought to the IHCA by a designated member of the cardiac arrest team. Once it is anticipated that the patient will receive at least one dose of adrenaline, the trial kit will be opened, and the patient will be considered randomized. A designated member of the cardiac arrest team will then prepare the trial drugs. The cardiac arrest team members will have training in the trial and drug administration procedures (see section 3.5.2). We expect that these procedures will take approximately 1 minute and that they will not interfere with the clinical management of the patient. Once prepared, 50 ml of the trial drug will be administered as soon as possible after the first dose of adrenaline. If the patient is still in cardiac arrest, one additional dose of 50 ml of the trial drug will be administered after the second dose of adrenaline. If a patient achieves ROSC while the drug is being administered, the remaining volume of the drug will be provided. The trial drug can be administered either intravenously or intraosseously.

3.3.4 Overview of trial medication

Trial kits will be produced and labelled centrally. Trial kits will be labelled consecutively with a unique ID. The trial kits and drugs will be clearly labelled according to standard practices for clinical trials (see Appendix 1). Trial kits will be prepared and shipped to the participating sites on a regular basis. Once a trial kit is opened, the site investigator, the research nurse, and the principal investigator will be informed. The central pharmacy will keep a tally of all trial kits and make sure, along with the site investigator and the research

nurse, that sites are always equipped with enough kits. The site investigator at each site will keep track of all delivered and used trial kits. Data on actual drug administration (see section 3.3.3) will be entered in real-time in an electronic case report form (see section 7). This will ensure optimal tracking of trial drug delivery and accountability.

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 kits 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 sodium bicarbonate in that it is colorless and without any identifying features. The normal saline will be stored in containers that are identical to the sodium bicarbonate containers. Furthermore, except for the intended effect (i.e., an increase in pH) and a potential increase in sodium, sodium bicarbonate has no distinctive rapid effects resulting in possible identification. These effects will rarely be identifiable during a cardiac arrest. The risk of unblinding is therefore at an absolute minimum.

A sealed opaque envelope will contain the allocation assignment which will allow for emergency unblinding. These envelopes will be placed at a central location with staff available 24 hours per day. The clinical cardiac arrest team will be able to contact the staff via phone and are therefore able to unblind in real-time. The decision to unblind will be at the discretion of the treating physician and clinical team. However, we do not expect scenarios where emergency unblinding will be necessary. In case unblinding occurs, the reason will be clearly documented in the case report form, and 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 trial-specific case report form, the electronic medical records, and the Danish IHCA registry (DANARREST) (see section 7).

3.5.2 Clinical personnel

Prior to the beginning of patient enrollment and continuously throughout the enrollment period, the clinical teams involved in IHCA resuscitation at the participating hospitals will be informed about the trial. Clinical personnel will be informed about the background and objectives of the trial, 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 trial kits will be included. Online education material will be available throughout the trial.

4. SETTING AND PATIENT POPULATION

4.1 Setting

The trial will be conducted at 21 hospitals in Denmark. All participating sites have clinical experience and expertise in treating IHCA patients.

4.2 Inclusion criteria

Inclusion criteria:

1) IHCA
2) Age ≥ 18 years
3) Received at least one dose of adrenaline during cardiopulmonary resuscitation (CPR)

Cardiac arrest is defined as unconsciousness, abnormal breathing, and a loss of pulses requiring chest compressions and/or defibrillation. IHCA is defined as any individual with a cardiac arrest on hospital grounds, in locations that are covered by the local IHCA team. This will include patients who re-arrest in the emergency department or elsewhere after an OHCA if they, prior to the re-arrest, had sustained ROSC (i.e., spontaneous circulation for at least 20 minutes).

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) Clearly documented “do-not-resuscitate” order prior to the cardiac arrest
2) Prior enrollment in the trial
3) Invasive mechanical circulatory support at the time of the cardiac arrest

4) Known or suspected pregnancy at the time of the cardiac arrest

5) Known objection by the patient to participate in the trial

6) Clinical indication for bicarbonate administration

Occasionally, CPR is inadvertently started in patients with a pre-existing "do-not-resuscitate" order. If a "do-not-resuscitate" order is clearly documented in the electronical medical record prior to the cardiac arrest, the patient will be excluded.

Patients previously included in the trial will be excluded to avoid statistical complexity related to correlated data.

Mechanical circulatory support includes extracorporeal circulation and left ventricular assist devices. Patients having an IHCA while on mechanical circulatory support constitute a very specific patient population with different characteristics and outcomes. They will therefore be excluded.

Patients with known or suspected pregnancy will be excluded. Cardiac arrest during pregnancy is exceedingly rare[70] 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 any harm to the patient or fetus as a result of the trial's intervention or placebo. Guidelines recommend that cardiac arrest in pregnancy is treated according to usual guidelines including intra-cardiac arrest medications.[71] We note that, out of 2,362 patients assessed in our previous IHCA trial, only one was pregnant.[34]

Patients will not be included in the trial if the enrolling investigator is aware that the patient has objected to participating in the trial (see section 9.2.3).

Administration of bicarbonate is recommended in rare occasions when hyperkalemia and certain toxicological causes of cardiac arrest are suspected.[18,55,56] If the treating clinician believes there is a clinical indication for administration of bicarbonate during the cardiac arrest, and prior to randomization, the patient should not be included. This assessment will be made by the clinicians at the time of the cardiac arrest consistent with current clinical care.

4.4 Co-enrollment

There will be no general restrictions on entry into other clinical trials although this will be evaluated on a case-by-case basis.[72] We are not aware of any ongoing or planned trials in this patient population in Denmark.

5. OUTCOMES

5.1 Primary outcome

5.1.1 Definition

The primary outcome will be ROSC. ROSC will be defined as spontaneous circulation with no further need for chest compressions sustained for at least 20 minutes. This definition is consistent with our previous trials[34,54], the *Get With the Guidelines® – Resuscitation* registry[73], the Danish registry for IHCA (DANARREST)[74], and the Utstein guidelines[75]. If a patient is placed on extracorporeal circulation during the cardiac arrest, the patient will only be considered to have ROSC if they are able to be successfully weaned from the extracorporeal circulation with spontaneous circulation for at least 20 minutes.[76]

5.1.2 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[75] and OHCA[76] Utstein guidelines and is suggested as a potential primary outcome measure by the American Heart Association[77].

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 2); 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 2. Modified Rankin Scale (mRS)[78]

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.[77,79,80] All follow-up survival data will be obtained from electronic medical records, the Danish Civil Registration System, or telephone follow-up, which allows for accurate and virtually complete follow-up.[81]

A centrally located, trained, blinded researcher will assess mRS using a standardized telephone interview, which ensures good reliability.[82-84] In case the patient is still hospitalized, the interview might be performed in-person. Assessment of neurological outcome by telephone is valid and reliable.[85] If the patient is not able to participate in the interview, the interview will be conducted with a close relative or secondarily clinical personnel if the patient is admitted. The same standardized interview will be used. The dichotomy with favorable scores of 0-3 and unfavorable scores of 4-6 is widely used in cardiac arrest research and is consistent with recent cardiac arrest trials.[54,86]

In accordance with the recent Core Outcome Set for Cardiac Arrest (COSCA)-initiative, we will also assess the Cerebral Performance Category (CPC).[87] 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 American Heart Association.[77]

Health-related quality of life at 30 and 90 days will be assessed by the EQ-5D-5L questionnaire,[88] which is supported by the American Heart Association[77] as well as the COSCA-initiative[87]. 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.[89] 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 on early cardiovascular function, laboratory values, organ failure, and hospital disposition.

To assess cardiovascular function and organ failure, we will calculate the Sequential Organ Failure Assessment (SOFA)-score[90] 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.[90] 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.[91,92]

Laboratory values, including pH, standard bicarbonate, $PaCO_2$, potassium, calcium, sodium, 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 an acute care hospital.

All outcomes recommended by the recent COSCA initiative (Core Outcome Set for Cardiac Arrest) are included in the present study.[87]

5.4 Harm

5.4.1 General consideration

Patients with IHCA have an in-hospital mortality of 70 to 75% and many patients experience post-cardiac arrest complications such as global brain injury, impaired myocardial function, macrocirculatory failure, acute respiratory distress syndrome, and increased susceptibility to infections.[26,93] Furthermore, patients suffering from IHCA often have multiple underlying conditions including heart failure, myocardial infarction, respiratory insufficiency, diabetes, infections, and renal insufficiency.[94] The immediately preceding cause might be related to circulatory failure (e.g. cardiogenic shock, sepsis), respiratory failure (e.g. pneumonia, chronic obstructive pulmonary disease), arrhythmias (e.g. primary arrhythmias, myocardial infarction), or in in rare instances neurological disorders.[95-98] Given this, it is difficult, if not impossible, to comprehensively report all adverse events and assess their possible relationship with the intervention in this patient population. Sodium bicarbonate is considered safe and is commonly used in clinical practice. The overall benefit and potential harm of the intervention will be captured in our primary and secondary outcomes. Any specific adverse events suspected by the clinical team to be related to the intervention will be documented.

5.4.2 Definitions

The following definitions will be used[99]:

Adverse event: An untoward medical occurrence after exposure to a medicine, which is not necessarily caused by that medicine.

Adverse reaction: A noxious and unintended response to a medicine.

Serious adverse reaction: An adverse reaction that results in death, is life-threatening, requires hospitalization or prolongation of existing hospitalization, results in persistent or significant disability or incapacity, or is a birth defect.

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

Causality with the trial drug will be determined by the site investigator.

5.4.3 Specific adverse events

Sodium bicarbonate is widely used in critically ill patients across the world with limited side effects. After administration, intravenous sodium bicarbonate rapidly dissociates to form sodium and bicarbonate. Thus, the specific adverse and potentially serious adverse events are primarily related to changes in pH and electrolytes. To assess specific adverse and potentially serious adverse events, we will collect data on the following:[60,100,101]

1) Alkalosis (pH > 7.45)
2) Hypernatremia (> 145 mmol/L)
3) Severe hypocalcemia (ionized calcium < 0.9 mmol/L)
4) Hypokalemia (< 3.5 mmol/L)
5) Severely elevated lactate (> 10 mmol/L)

The administration of sodium bicarbonate is known to cause an increase in pH.[102] This could potentially cause pH to increase outside the normal range causing alkalosis. With a normal range for pH of 7.35 to 7.45, alkalosis is defined as pH > 7.45.[103]

The dissociation of sodium and bicarbonate leads to an increase in sodium levels, which potentially could lead to hypernatremia. With a normal range for sodium of 135-145 mmol/L, hypernatremia is defined as > 145 mmol/L.[104]

Hypocalcemia has been observed following sodium bicarbonate administration. This is mediated through an increase in pH which changes the binding between ionized calcium and proteins, and through a direct binding between bicarbonate and calcium.[105] With a normal range for ionized calcium of 1.17-1.33 mmol/L, hypocalcemia is defined as ionized calcium < 0.9 mmol/L.[106,107] This definition of hypocalcemia is based on a previous clinical trial in critically ill patients randomized to sodium bicarbonate or placebo.[63]

A reduction in the serum potassium level has been observed following sodium bicarbonate administration in patients.[100] With a normal range for potassium of 3.5 to 5.0 mmol/L, hypokalemia is defined as < 3.5 mmol/L.[108]

An increase in lactate levels has been observed following sodium bicarbonate administration in experimental studies.[109] Normal lactate levels are 0.6 to 1.4 mmol/L.[110] However, as patients resuscitated from IHCA have elevated lactate levels (the median lactate level in the VAM-IHCA trial was 10 [first and third quartile: 7, 13]), severely elevated lactate is defined as > 10 mmol/L.[111]

Other potential side effects have been described with the administration of sodium bicarbonate, including headache, muscle pain, nausea and vomiting, and vertigo.[60,101] However, given that patients with cardiac arrest are unconscious, these cannot be assessed and are of limited relevance.

Accidental subcutaneous injection of sodium bicarbonate can result in tissue necrosis.[112] However, the trial drug 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.

5.4.4 Collection and timeline

The listed adverse events are assessed using routinely collected data in patients with IHCA. This includes available laboratory values and clinical data. No specific procedures or blood draws will be performed. Based on previous data from the VAM-IHCA trial, the data needed to assess these adverse events are available in all patients achieving ROSC.[34] The specific adverse events will only be collected in patients with ROSC.

The physiological effects of sodium bicarbonate administration during cardiac arrest are likely to be short-lived. After administration, intravenous sodium bicarbonate rapidly dissociates to form sodium and bicarbonate. Bicarbonate anions can consume hydrogen ions (H^+) and subsequently convert to carbonic acid (H_2CO_3, see section 1.2.1). Carbonic acid subsequently converts to water (H_2O) and carbon dioxide (CO_2) for excretion from the lungs. This process occurs within minutes and the concomitant effect on electrolytes

disappear within 24 hours.[113] As such, the specific adverse events listed in section 5.4.3 will only be assessed within the first 24 hours.

5.4.5 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 through EudraVigilance. 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 previous and ongoing trials by our group (EudraCT numbers: 2017-004773-13, 2019-003387-46, and 2021-005922-82). No events, including those outlined in section 5.4.3, will automatically lead to unblinding.

5.4.6 Reporting

Serious adverse events will be reported to the sponsor within 24 hours.

No later than 15 days thereafter, the sponsor will notify the regulatory agencies through Clinical Trials Information System (CTIS) when the trial has started, when the first subject is included, when recruitment has ended, and when the trial has ended. Similarly, the sponsor will notify the regulatory agencies through CTIS in case of a temporary halt of the trial and in case of any serious breach. Once a year, the sponsor will submit a list of all registered adverse events that have occurred during the trial period as a well as a report on safety of the trial subjects to the regulatory agencies through CTIS. The results from the clinical trial, including important adverse events, will be recorded on CTIS no later than one year after the end of the trial.

5.4.7 Drug interactions

Sodium bicarbonate administration is recommended in patients with selected toxic ingestions.[114] The potential mechanisms of sodium bicarbonate in this context is alkalization of urine and subsequent increased urinary excretion of the ingested drug. This increased excretion could potentially result in lower plasma concentrations of selected drugs. However, given the severity of the metabolic acidosis in patients with IHCA, the volume of sodium bicarbonate administered in the current trial is unlikely to result in alkalization of urine and subsequent increased urinary excretion of selected drugs.

5.5 Additional follow-up

The primary trial and publication will be related to the trial outcomes (section 5.1, 5.2, and 5.3). However, extended follow-up at six months and at one year, including overall survival, neurological outcomes, and health-related quality of life, will be collected, and reported in a separate publication. 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 six months and one-year outcomes will be blinded to the treatment assignment.

6. SAMPLE SIZE CALCULATION AND STATISTICAL ANALYSIS PLAN

6.1 Sample size calculation

The trial will be powered to the primary outcome of ROSC. From the VAM-IHCA trial, which had similar inclusion and exclusion criteria, the proportion of patients with ROSC in the placebo group was 33%.[34] Based on an absolute difference of 10% between the placebo and the bicarbonate group, we anticipate that 33% in the placebo group and 43% in the intervention group will obtain ROSC. This corresponds to a relative increase of 30%. With such estimates, an alpha of 0.05, and the use of the Fisher's Exact test, we will need a total of 778 patients to have 80% power to detect a statistically significant difference between groups. Given that the primary analysis will be adjusted for strong prognostic factors (see section 6.2.2 and 6.2.4), we will obtain additional power.[115,116] The trial therefore has a minimum of 80% power.

We anticipate no loss to follow-up for the primary outcome (see section 6.2.7). Patients who withdraw consent and request deletion of data will not be replaced. Of note, no patients withdrew consent in our previous trials.[34,54]

6.2 Statistical analysis plan

6.2.1 General considerations

Details related to the statistical analysis plan are included in the present protocol and there will be no separate document.

Patient inclusion and exclusion will be illustrated in a CONSORT flow diagram (see Appendix 2 for a draft).

All analyses will be conducted on a modified intention-to-treat basis only including patients receiving the first dose of the trial drug and meeting all inclusion criteria and no exclusion criteria. In a double-blind trial, where the inclusion and exclusion criteria are documented (but might not be known by the cardiac arrest team) prior to the cardiac arrest and the intervention, this approach is unbiased while increasing precision.[117]

The two groups will be compared in relation to baseline patient and cardiac arrest characteristics using descriptive statistics (See Appendix 3 for a draft of the Table 1).

6.2.2 Binary outcomes

Binary outcome variables will be presented as counts and proportions in each group. Differences between groups will be presented as risk ratios and risk differences. Risk ratios and risk differences will be estimated using generalized linear models. The risk ratio will be estimated from a log-binomial regression model (i.e., binomial distribution and log link function).[118] If this model fails to converge, a modified Poisson regression model will be used instead (i.e., Poisson distribution and log link function with robust standard errors).[118,119] The risk difference will be estimated using a linear model (i.e., binomial distribution and identity link function). If this model fails to converge, an equivalent modified Poisson approach will be used.[118]

To increase power, all models will include adjustment for strong prognostic factors (see section 6.2.4). If the models are not able to converge with the inclusion of these variables, the adjustment will be done using inverse probability of treatment weighting.[120] In case none of these models are feasible, 95% confidence intervals will be obtained using methods described by Miettinen and Nurmimen.[121]

6.2.3 Continuous outcomes

Continuous data will be presented as means with standard deviations (SD) or medians with first and third quartiles depending on the distribution of the data. Differences between groups in continuous outcomes are presented as mean differences with 95% confidence intervals obtained from a generalized linear model with robust errors with adjustment for prognostic variables (see section 6.2.4). If the data are severely non-normally distributed, other methods (e.g., transformation of the outcome, quantile regression, Hodges–Lehmann median difference) will be considered or the data will be presented descriptively.

6.2.4 Adjustment for prognostic factors

To increase power, we will adjust all outcome comparisons for strong prognostic factors.[115,116] These will include age, whether the cardiac arrest was witnessed, and the initial rhythm. Age will be included as a linear continuous variable[122] and the initial rhythm (shockable [ventricular fibrillation or ventricular tachycardia] or non-shockable [asystole or pulseless electrical activity]) and witnessed status as binary variables. A recent meta-analysis found that these variables are strongly associated with survival after IHCA.[25] To confirm that these variables are also strongly correlated to ROSC and other relevant outcomes in the Danish setting, we performed multivariable logistic regression with age, witnessed status, and initial rhythm as the independent

variables and various outcomes as the dependent variable using data from the VAM-IHCA trial (n = 501).[34] As can be seen in Table 3, these variables were strongly associated with outcomes.

Table 3. Association between various characteristics and outcomes using VAM-IHCA data			
Variable	Odds ratio (95%CI)		
	ROSC	30-day survival	30-day favorable outcome (mRS 0-3)
Age (per 10-year increase)	0.88 (0.70, 0.95)	0.67 (0.54, 0.82)	0.63 (0.49, 0.81)
Non-witnessed vs. witnessed	0.50 (0.32, 0.79)	0.18 (0.06, 0.60)	0.26 (0.06, 1.11)
Non-shockable vs. shockable	0.46 (0.25, 0.83)	0.35 (0.17, 0.72)	0.31 (0.13, 0.75)

6.2.5 Other analyses and considerations

Health-related quality of life and SOFA-scores will only be assessed in those alive at the time of measurement and no imputation will be performed for those not alive at the time of measurement.

Survival until 90 days will be presented graphically with Kaplan-Meier curves,[123] but will otherwise be analyzed as a binary outcome as described in section 6.2.2.

Adverse events and categorical outcomes will only be presented descriptively.

6.2.6 Subgroup analyses

Subgroup analyses will be performed on both the absolute and relative scale using risk ratios and risk differences as described in section 6.2.2.[124] These analyses will not include adjustment for prognostic variables. The analyses will include five pre-defined subgroup analyses for the primary and key secondary outcomes according to 1) first documented rhythm, 2) whether the cardiac arrest was witnessed, 3) patient age, 4) time from cardiac arrest to first trial drug, and 5) known metabolic acidosis prior to the cardiac arrest. The first documented rhythm will be dichotomized as shockable or non-shockable. Patient age and time from cardiac arrest to first trial drug will be dichotomized by the median. As a secondary analysis, these variables will be treated as linear, continuous variables and the results illustrated graphically. Known metabolic acidosis prior to the cardiac will be defined as a pH < 7.35 and a base excess < -2 mmol/L based on the latest laboratory values prior to the cardiac arrest. Only blood samples taken within 6 hours of the cardiac arrest will be considered.

6.2.7 Missing data

Missing data will be reported in the relevant publications for all variables. We do not expect any missing data for the primary outcome or the key secondary outcomes. In our two recent trials including patients with IHCA and OHCA, respectively, we did not have any missing data on these outcomes.[34,54] We do not expect missing data on the SOFA scores or adverse events. There might be some limited missing data for neurological outcomes and health-related quality of life at 90 days (and potentially at 30 days) due to loss to follow-up. Assuming that data are "missing at random", multiple imputation using known risk factors for outcomes after IHCA will be used to impute values for patients with missing data if missing data is substantial (> 5%). In case outcome data are missing on < 5% of patients, a complete case analysis will be performed.

We do not expect missing data for the variables included in the regression models (see section 6.2.4). If data are missing on any of these variables, we will consider imputation or removal of that specific variable from the regression models.

6.2.8 Null-hypothesis testing and multiple comparisons

Null-hypothesis significant testing (and corresponding P values) will be considered for the primary outcome and the two key secondary outcomes in a hierarchical and sequential fashion such that the subsequent outcome will only be tested for statistical significance if the previous outcome had a P value < 0.05 (considered statistically significant). If this is not the case, no P value or test of statistical significance will be provided for the next outcome.[125] The order of the outcomes will be: sustained ROSC, 30-day survival, and 30-day with a favorable neurological outcome. P values will not be provided for other outcomes. All P values will be two-sided.

All confidence intervals will have 95% coverage and will not be adjusted for multiplicity.

6.2.9 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 neutral. Furthermore, since bicarbonate is commonly used during IHCA[57], a neutral trial with an adequate sample size will still be an important finding. There will be no formal stopping criteria for safety (see section 10.2).

6.2.10 Secondary Bayesian analyses

We will perform secondary Bayesian analyses for the primary and key secondary outcomes in order to aid interpretation of the results.[126] Given the limited evidence on bicarbonate use during cardiac arrest, we will primarily use noninformative prior probability distributions and the results obtained from the trial to obtain posterior probability distributions for risk ratios. More skeptical, neutral, and optimistic prior probability distributions will also be used consistent with a recent trial by our group.[54] The posterior probability distributions will be illustrated graphically, and the probability that the true treatment effect is larger than or within various thresholds (e.g., risk ratio above 1.0) 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 research nurse or research assistants, along with the site investigators, will be responsible for data collection and entry. Very limited data will be obtained from the clinical cardiac arrest team in real-time using an electronic case report form that will be accessible through QR codes and URLs. This will include the patient identifier (i.e., Danish Civil Registration System-number ["CPR number"]), timing of the first adrenaline dose, timing of the first trial drug administration, the total doses of trial drug administered, and reasons for not providing all trial drugs if relevant. This, along with the telephone interviews for long-term follow-up, will be the only source data and all additional data will be obtained from the electronical medical records or DANARREST (see section 7.6) and will be based on measurements and assessments made by the clinical team. Data will be entered directly into the database software (see section 7.3).

7.2 Variables

7.2.1 Overview

All IHCA patients at the participating sites will be entered into a screening log. For those not randomized, a specific reason for non-inclusion/exclusion will be documented. All randomized patients who received the trial drug will be entered into the main database.

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 include those outlined in the IHCA Utstein guidelines.[127] 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

Trial related variables

- Trial ID
- Site
- Receipt of trial medication
- Time of trial drug administration
- Doses of trial medication provided
- Requirement for emergency unblinding
- Inclusion criteria
- Exclusion criteria
- Date and time consent for data collection is obtained

Patient demographics and characteristics

- Name
- Unique patient identifier (Danish Civil Registration System-number [“CPR number”]),
- Age
- Sex
- Height
- Weight

Conditions/medications prior to the cardiac arrest

- Co-morbidities (cardiac and non-cardiac)
- Frailty index
- Estimated mRS prior to current hospital admission
- Reason for admission
- Length of stay prior to the cardiac arrest
- Previous IHCA during this admission
- Laboratory values prior to the cardiac arrest

7.2.3 Cardiac arrest characteristics

Location and time

- Location of the cardiac arrest
- Date and time of the cardiac arrest

Interventions in place

- Vasopressors
- Mechanical ventilation
- Intravenous access
- Renal replacement therapy

Cardiac arrest variables prior to the intervention

- Presumed cause of the cardiac arrest
- Initial rhythm
- Monitored
- Witnessed
- Time to first rhythm analysis

Cardiac arrest variables after the intervention

- Date and time of the end of resuscitation (ROSC or termination without ROSC)
- Use of open-label sodium bicarbonate

7.2.3 Post-cardiac arrest characteristics

Laboratory values within the first 24 hours

Targeted temperature management

Temperature at 6, 12, 18, 24, 48, and 72 hours

Cardiac catheterization, percutaneous coronary intervention, and coronary artery bypass grafting

Procedures related to neurological prognostication (e.g., EEG, imaging, biomarkers)

Use of intravenous bicarbonate

Renal replacement therapy

Adverse events (see section 5.4.3)

7.2.4 Outcomes

ROSC

SOFA scores at 2, 24, 48 and 72 hours

Hospital disposition

Survival at 30 days, 90 days, 6 months, and 1 year

CPC score at 30 days, 90 days, 6 months, and 1 year

mRS at 30 days, 90 days, 6 months, and 1 year

EQ-5D-5L at 30 days, 90 days, 6 months, and 1 year

7.3 Data storage and security

The database application will be Research Electronic Data Capture (REDCap, Vanderbilt, Tennessee, USA).[128] 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"), the Data Protection Act ("Databeskyttelsesloven"), and the Danish Health Care Act ("Sundhedsloven"). The project will be registered with the Central Denmark Region's internal list of research projects.

After the last patient follow-up, a copy of the trial master file will be stored securely for 25 years. Hereafter, all records will be anonymized and sent to relevant Danish archives if required.

7.4 Data quality and validity

Data quality and validity will be optimized by having trained researchers enter all data according to a detailed data dictionary. REDCap (see section 7.3) is designed such that data forms contain field-specific validation checks ensuring that mandatory fields are filled out and that continuous as well as ordinal variables are within predefined ranges. Furthermore, REDCap allows for data quality rules warning of potential incorrect data; these data are assessed and, if relevant, corrected continuously throughout the inclusion period.

Given its limited utility, double-data entry will not be performed.[129,130]

7.5 Data access

During the trial, the principal investigator and other relevant research personnel will have access to the entire database, while site investigators will have access to data from their own sites. This will allow for centralized data collection. Once the database is locked, a de-identified 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 entities will have direct access to patients' records and to all relevant trial data including the case report form as applicable.

7.6 DANARREST

For the intra-cardiac arrest characteristics, data are captured in real-time by the clinical cardiac arrest team as part of a nationwide quality improvement registry (DANARREST).[74,131] DANARREST is a quality improvement registry that aims to track the epidemiology of IHCA in Denmark. All hospitals in Denmark are participating and the clinical personnel are required to enter data. A Danish version of the DANARREST case report form is provided in Appendix 4.

8. CLINICAL TREATMENT

The clinical management of included patients will be at the discretion of the treating clinical team 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 European Resuscitation Council[18] and the Danish Resuscitation Council[132] but no specific treatments will be prohibited or mandated. The sites will be informed about the most recent guidelines for intra-cardiac arrest care and will be encouraged to limit premature termination of resuscitation efforts.[133] Sites will also be encouraged to follow European Resuscitation Council post-cardiac arrest guidelines including appropriate neurological prognostication.[134] Use of open-label bicarbonate during cardiac arrest will be recommended against, but will not be prohibited.

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).

9.1.2 Potential harms

Details about the potential harms of the intervention are provided in the background section (section 1.2) and in section 5.4.3.

9.1.3 Risk/benefit ratio

Given the considerations provided in section 1.2 and section 5.4.3, there is clear clinical equipoise for a clinical trial testing sodium bicarbonate in IHCA. The need for high-quality clinical evidence is also highlighted by the high administration rates of sodium bicarbonate to patients with IHCA (see section 1.2.4).

9.2 Research in cardiac arrest

9.2.1 General considerations

Research in cardiac arrest is ethically challenging for two reasons: 1) Patients are unconsciousness 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 designated representative.[135,136] 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 related Danish regulations[137-142]), and the international Good Clinical Practice guidelines[3], clearly support research in such populations.

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

9.2.2 European regulations

The European regulation on clinical trials on medical products for human use 536/2014 states in Article 35 that:[2]

> *"(…) informed consent to participate in a clinical trial may be obtained, and information on the clinical trial may be given, after the decision to include the subject in the clinical trial, provided that this decision is taken at the time of the first intervention on the subject, in accordance with the protocol for that clinical trial and that all of the following conditions are fulfilled:*
>
> *(a) due to the urgency of the situation, caused by a sudden life-threatening or other sudden serious medical condition, the subject is unable to provide prior informed consent and to receive prior information on the clinical trial*

(b) there are scientific grounds to expect that participation of the subject in the clinical trial will have the potential to produce a direct clinically relevant benefit for the subject resulting in a measurable health-related improvement alleviating the suffering and/or improving the health of the subject, or in the diagnosis of its condition

(c) it is not possible within the therapeutic window to supply all prior information to and obtain prior informed consent from his or her legally designated representative

(d) the investigator certifies that he or she is not aware of any objections to participate in the clinical trial previously expressed by the subject

(e) the clinical trial relates directly to the subject's medical condition because of which it is not possible within the therapeutic window to obtain prior informed consent from the subject or from his or her legally designated representative and to supply prior information, and the clinical trial is of such a nature that it may be conducted exclusively in emergency situations

(f) the clinical trial poses a minimal risk to, and imposes a minimal burden on, the subject in comparison with the standard treatment of the subject's condition."

The current trial fulfils all the above criteria as described in section 9.1 for (b) and section 9.2.3 for (a) and (c)-(f). Under these circumstances, research with pharmacological interventions is allowed if 1) informed consent to continue participation in the clinical trial is obtained from the patient or the legally designated representative without undue delay, and 2) the patient or the legally designated representative is informed of the right to object to the use of trial data if consent for continuation in the trial is not provided.[2]

9.2.3 Regulatory conditions in relation to the current trial

The current trial fulfills all criteria listed in section 9.2.2:

Condition (a)

IHCA 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.

Condition (c)

The intervention will be administered as soon as possible after the administration of the first dose of adrenaline. In our previous VAM-IHCA trial, the trial drug was administered after a median of 8 minutes (first and third quartiles: 6, 12).[34] Given these time frames, it would be impossible to obtain informed consent from a legally designated representative.

Condition (d)

IHCA is sudden and often unexpected, and it is unlikely that participants will have objected to participation in a clinical trial should they have a cardiac arrest. In our previous trials involving cardiac arrest patients, all patient and legally designated representatives provided consent for future participation.[34,54] However, in the unlikely event that a participant has clearly objected to participation in the trial prior to their cardiac arrest and the clinician including the patient is aware of this objection, the patient will not be included (see section 4.3).

Condition (e)

The intervention in this trial is specifically targeted for patients with IHCA. Given the high morbidity and mortality of IHCA (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,[143] 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 trial aimed to improve outcomes for cardiac arrest patients can therefore only be conducted in this population. See also condition (a) and (c).

Condition (f)

Given the considerations outlined in section 9.1, the intervention only imposes a minimal risk to and burden on the subject. As noted in section 1.2.4, sodium bicarbonate is already commonly used for patients with IHCA. The intervention, data collection, and the follow-up interviews (see section 5.2, 5.3, and 5.5) will be the only trial-related procedures.

9.3 Procedures and consent

9.3.1 Ethical review committee

The trial will be sent for approval through the European CTIS where the relevant Danish authorities, including the Danish Medicines Agency and the relevant ethics committee, will assess the trial.

9.3.2 Trial-specific procedures

The decision to include and randomize a patient with IHCA will be up to the designated member of the clinical cardiac arrest team, which have been thoroughly educated regarding the trial. This person will assess

inclusion and exclusion criteria and include the patient if relevant. Interventional procedures are described in section 3.3.

For patients who survive to intensive care unit admission, but remain unable to provide consent, written informed consent for continuation in the trial will be obtained as soon as possible from a legally designated representative (in Denmark defined as the closest relative).[2,140] As required by Danish law, this will be supplemented with consent for continuation in the trial given by a "legal guardian" ("forsøgsværge" in Danish). The legal guardian will be a physician that is independent from the principal investigator and the clinical trial.[140]

If and when the patient regains capacity to provide informed consent, written informed consent for continuation in the trial will be obtained from the patient. If the patient is able to provide consent prior to a legally designated representative, Danish law does not require consent from a "legal guardian".[140]

The patient, the legally designated representative, and the legal guardian will, when relevant, be informed verbally and in writing by a physician that is adequately qualified and has knowledge about the trial. If this physician is not an investigator (i.e., a member of the steering committee), there will be a written delegation agreement between the physician and an investigator.[141]

Written and verbal information given prior to consent will include the background and significance of the trial, inclusion criteria, potential risks and benefits, as well as a brief description of the trial protocol. Information about potential de-identified data sharing will also be included. Additionally, information will include 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.

Trial information and the consent request will take place in an undisturbed room, and the patient and/or the legally designated representative 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. The required time for consideration is individual for each case. For our previous trials in cardiac arrest[34,54], the required time has ranged from a few minutes to several hours. Prior to written consent, the patient and/or the legally designated representative will always be asked whether they need more time for consideration.

The patient, the legally designated representative, the legal guardian, and the physician obtaining the consent will sign individual digital or paper consent forms as appropriate. Digital signatures will be written on a smart phone or tablet using REDCap, which has dedicated functionalities for written consent.

9.3.3 Procedures when a patient dies prior to obtainment of any consent

If a patient dies before it is possible to obtain consent from the patient or a legally designated representative, an investigator will attempt to contact a legally designated representative, who is able to give consent. If no legally designated representative is readily available or if it is not possible to obtain contact information for the legally designated representative, the investigators will continue to access the patient's electronic medical records as needed. This approach is allowed by Danish law if the investigator, to a reasonable degree, has tried to contact a legally designated representative.[139] Consent will be obtained from the legal guardian as described in section 9.3.2.

9.3.4 Refusal of consent

If a patient or legally designated representative 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.[142]

In accordance with the European regulations, a patient or legally designated representative can object to the use of all trial data collected and will be informed of this right in the case of refusal of consent.[2]

9.3.5 Included patients who do not speak Danish

The trial might include patients who do not speak Danish, as it is not possible to exclude these patients before inclusion. In the setting of cardiac arrest, data on a patient's language skills are often unavailable, unreliable, and cannot be prioritized over collection of more important clinical information.

In case patients or surrogates do not speak Danish, an authorized written translation of the participant information and the informed consent form will be provided in the patient's or surrogate's native language. The oral information will be translated into the participant's or surrogate's native language by a certified interpreter.

9.3.6 Insurance

The patients in the trial are covered by the Danish patient insurance.[144]

9.3.7 End of trial

The trial will be considered finished when the last surviving patients have completed 1-year follow-up.

10. MONITORING

10.1 Good Clinical Practice monitoring

The sites will be monitored by the regional Good Clinical Practice monitoring units affiliated with the participating sites. A detailed monitoring plan will be developed prior to trial commencement.

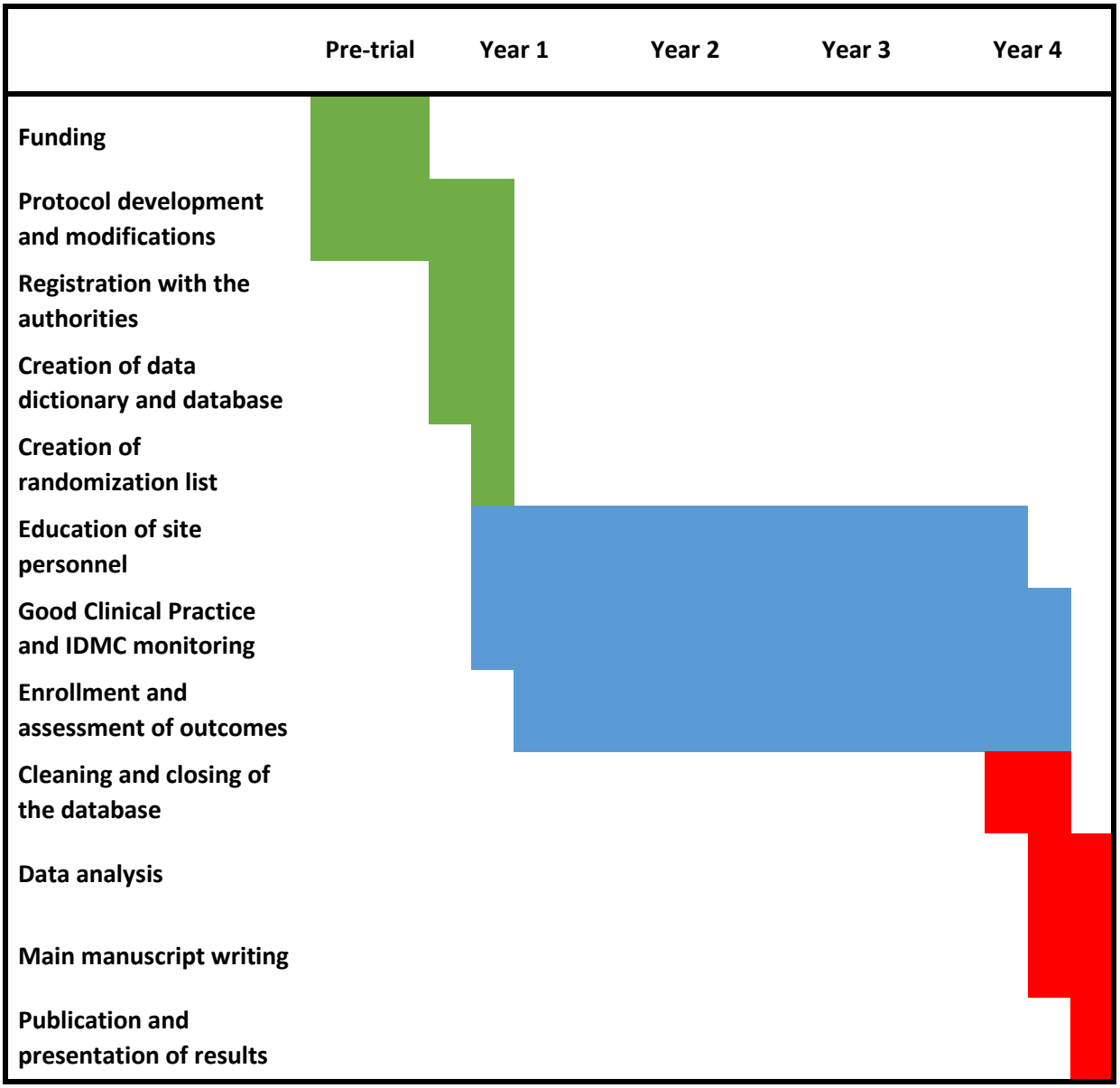
The sponsor will allow monitoring, revision, and inspection from relevant authorities.

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/trialists with expertise in research within acute and critically ill patients. 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 de-identified data for safety at two pre-defined milestones (after 200 and 400 included patients); unless there are group differences necessitating unblinding (as determined by the IDMC), the IDMC will be blinded to treatment groups. The IDMC can request review of the data at other timepoints as well. 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. As noted in section 6.2.9, there will be no formal stopping criteria for efficacy, futility, or safety. Criteria for recommending termination will be at the discretion of the IDMC. 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 5.

11. TIMELINE AND ENROLLMENT

11.1 Timeline



11.2 Feasibility

The VAM-IHCA trial, which had similar inclusion and exclusion criteria as the present trial, included 501 patients from October 15, 2018 to January 21, 2021 corresponding to 220 patients per year.[34] The VAM-IHCA trial included 10 hospitals, whereas the present trial will include 22 hospitals (section 4.1). We ancipate that we will be able to include approximately 300 patients per year and therefore anticipate that enrollment will take 2,5 to 3 years.

11.3 Enrollment

Enrollment at each site will be continuously monitored by the site investigator, the research nurse, and the principal investigator. Formal reports outlining the number of IHCAs and the proportion of those enrolled at each site will be shared with the steering committee when appropriate. In case multiple eligible IHCAs 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 IHCA, we do not expect 100% enrollment of eligible IHCA. In case a site continuously underperforms despite troubleshooting and feedback, the steering committee will evaluate whether enrollment will continue at that site.

12. PUBLICATION PLAN

Three manuscripts are planned from the current trial. The first and primary manuscript will include the main results including pre-defined primary, secondary, and tertiary outcomes. The manuscript will adhere to the CONSORT guidelines.[145,146] The principal investigator will be the last and corresponding author. Additional authorship will follow authorship guidelines from the International Committee of Medical Journal Editors[147] and will include members of the steering committee. In addition, as a guideline, sites enrolling > 50 patients will be entitled one additional author and sites enrolling > 100 patients two additional authors in addition to the site investigators and members of the steering committee. The trial results will be shared with participating sites and via press releases but not directly with the participating patients. The second manuscript will include long-term follow-up at six months and 1 year (see section 5.5). The third manuscript will include a detailed description of early cardiovascular function and acid-base status. Trial findings will be published irrespective of the results. Trial results, including a layperson version, will be made public on the CTIS portal one year after the end of the trial at the latest.

13. DATA SHARING

Six months after the publication of the last results, all de-identified individual patient data will be made available for data sharing.[148] Procedures, including re-coding of key variables, will be put in place to allow for complete de-identification 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[147] and might or might not include authors from the steering committee depending on the nature of their involvement.

14. FUNDING

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15. TASKS AND RESPONSIBILITIES

Principal investigator and sponsor: 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.

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

Site investigators: Responsible for site-specific enrollment, evaluation of eligible patients not enrolled, education of personnel at participating sites, reporting of site-specific issues or challenges to the principal investigator, participant consent.

Research nurse/assistants: Daily management, education of personnel at participating sites, contact to pharmacy, contact to Good Clinical Practice monitoring unit, data dictionary development, trial registration, data entry and management, patient follow-up, budget overview.

Clinical team: Administration of the trial drug, limited data entry, participant consent for data collection.

Good Clinical Practice-unit: See section 10.1.

Data and safety monitoring board: See section 10.2.

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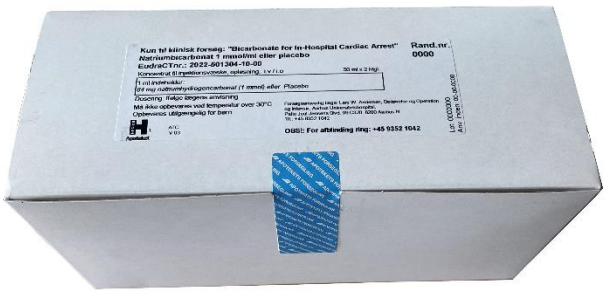
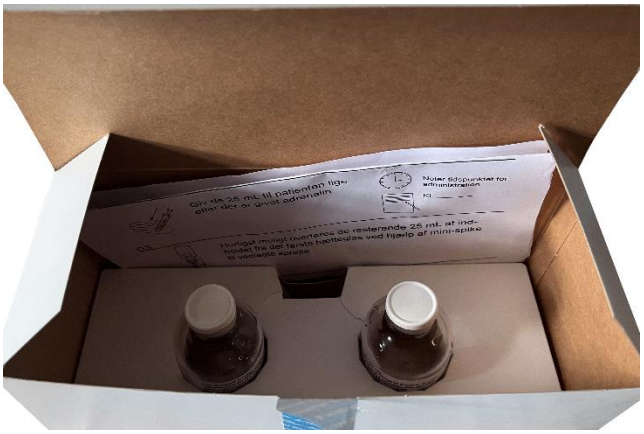
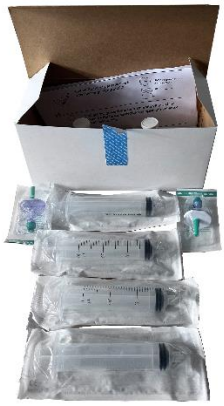
Appendices

Appendix 1: Trial kit and drug labeling (Danish)







Label on the glass vials:

V.nr.: XXXXXX

Kun til klinisk forsøg:
"Bicarbonate for In-Hospital Cardiac Arrest"
Natriumbicarbonat 1 mmol/ml eller placebo
EU CT.: 2022-501304-10-00
Koncentrat til infusionsvæske, opløsning i.v./i.o. (50 ml)

1 ml indeholder
84 mg natriumhydrogencarbonat (1 mmol) eller Placebo

Rand.nr.
0000

Dosering: Ifølge lægens anvisning
Forsøgsansvarlig læge: Lars W. Andersen,
Bedøvelse og Operation og Intensiv, Aarhus Universitetshospital
Palle Juul Jensen Blvd. 99C320, 8200 Aarhus N, Tlf.: +45 9352 1042
Må ikke opbevares ved temperatur over 30°C
Opbevares utilgængelig for børn

ATC:
V03

Lot: 0000000
Anv. Inden: 00-00-0000

Region H
Logo 1.

Label for the trial kit:

Kun til klinisk forsøg: "Bicarbonate for In-Hospital Cardiac Arrest"
Natriumbicarbonat 1 mmol/ml eller placebo
EU CT.: 2022-501304-10-00
Koncentrat til injektionsvæske, opløsning, i.v./i.o. 50 ml x 2 htgl.

1 ml indeholder:
84 mg natriumhydrogencarbonat (1 mmol) eller Placebo

Rand.nr.
0000

Dosering: ifølge lægens anvisning

Må ikke opbevares ved temperatur over 30°C

Opbevares utilgængelig for børn

Forsøgsansvarlig læge: Lars W. Andersen, Bedøvelse og operation og intensiv, Aahus Universitetshospital,
Palle Juul Jensens Blvd. 99 C320, 8200 Aarhus N
Tlf.: +45 9352 1042

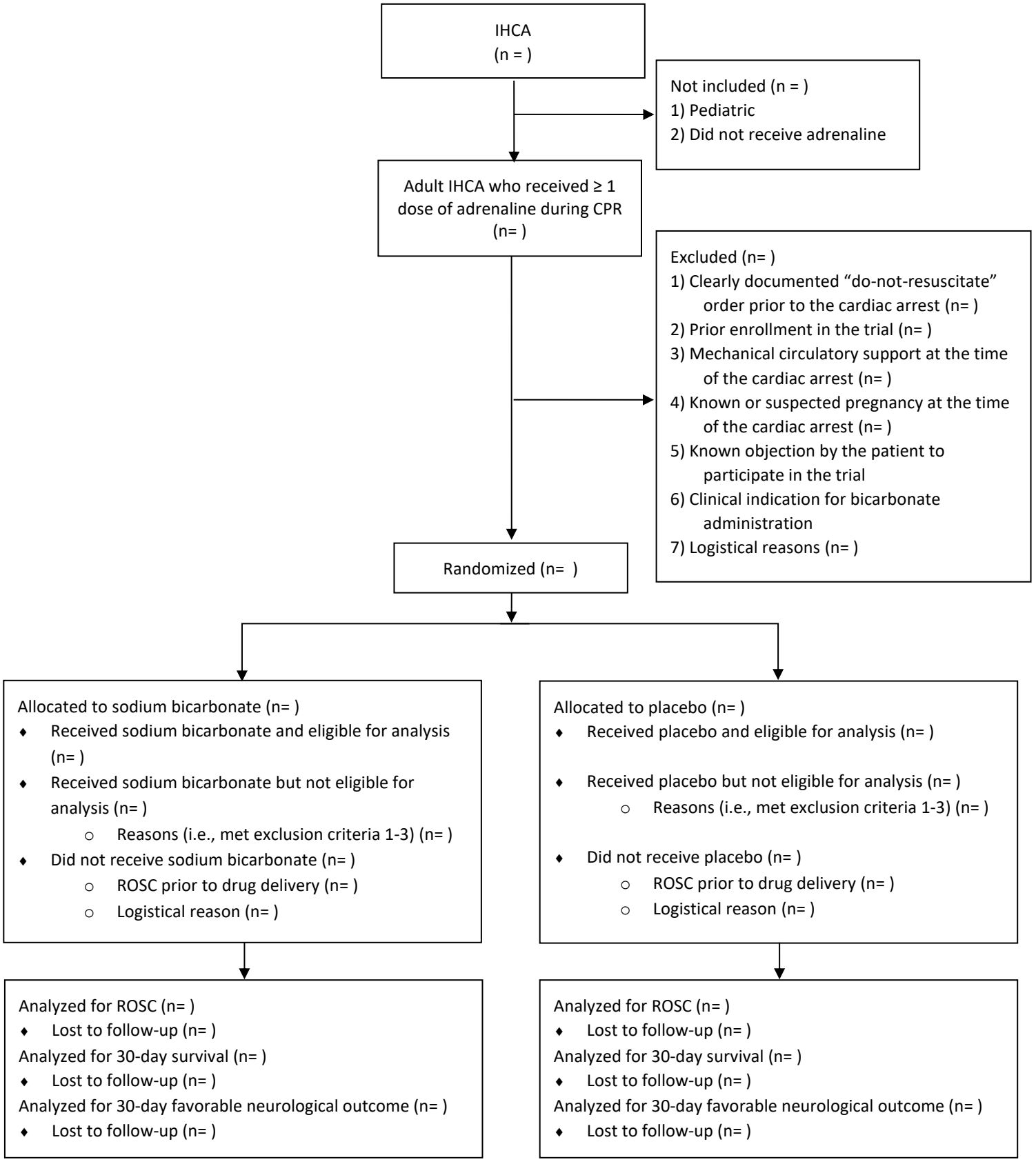
OBS!: For afblinding ring: +45 9352 1042

Lot: 0000000
Anv. Inden: 00-00-0000

Region H
Logo 1.

ATC:
V03

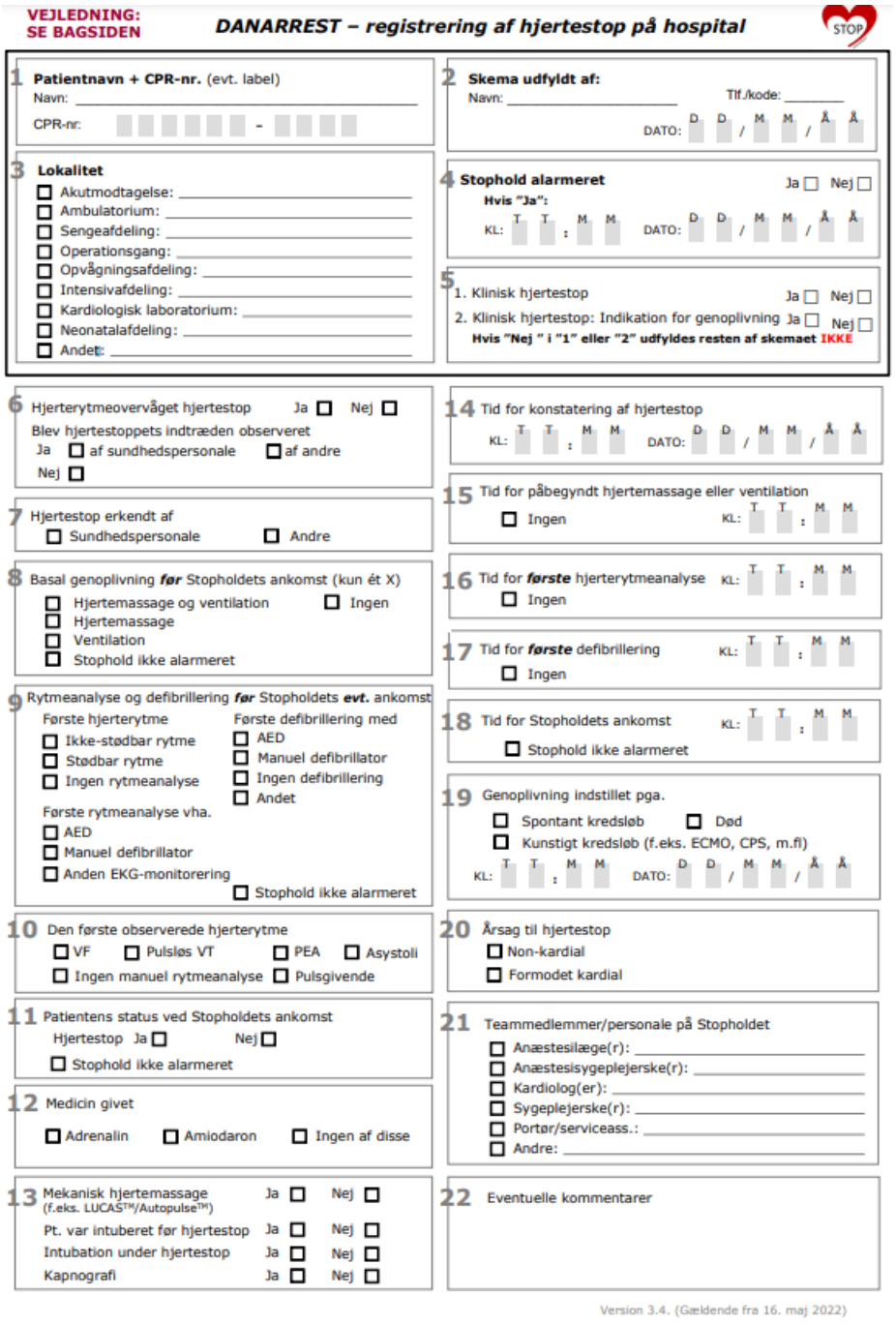
Appendix 2: Draft of CONSORT flow diagram



Appendix 3: Draft of Table 1 for the main publication

Table 1. Baseline characteristics according to treatment assignment		
	Sodium Bicarbonate (n =)	**Placebo (n =)**
Patient Characteristics		
Age – years		
Male sex – no. (%)		
BMI – kg/m^2		
Past medical history – no. (%)		
Arterial hypertension		
Coronary artery disease		
Atrial fibrillation		
Diabetes		
Pulmonary disease		
Cancer		
Kidney disease		
Chronic heart failure		
Stroke		
Venous thromboembolism		
Liver disease		
Dementia		
Known metabolic acidosis prior to cardiac arrest – no. (%)		
Interventions prior to cardiac arrest – no. (%)		
Kidney replacement therapy		
Invasive mechanical ventilation		
Vasopressor infusion		
Cardiac Arrest Characteristics		
Location – no. (%)		
Hospital ward		
Intensive care unit		
Emergency department		
Other		
Cardiac catheterization laboratory		
Operating room		
Monitored – no. (%)		
Witnessed – no. (%)		
Initial rhythm – no. (%)		
Pulseless electrical activity		
Asystole		
Ventricular fibrillation		
Ventricular tachycardia		
Time from cardiac arrest recognition to …		
Epinephrine administration - minutes		
Trial drug administration - minutes		

Appendix 4: DANARREST case report form (Danish)



VEJLEDNING: SE BAGSIDEN

DANARREST – registrering af hjertestop på hospital

STOP

1 Patientnavn + CPR-nr. (evt. label)
Navn: _____
CPR-nr: _____ - _____

2 Skema udfyldt af:
Navn: _____ Tlf./kode: _____
DATO: D D / M M / Å Å

3 Lokalitet
- ☐ Akutmodtagelse: _____
- ☐ Ambulatorium: _____
- ☐ Sengeafdeling: _____
- ☐ Operationsgang: _____
- ☐ Opvågningsafdeling: _____
- ☐ Intensivafdeling: _____
- ☐ Kardiologisk laboratorium: _____
- ☐ Neonatalafdeling: _____
- ☐ Andet: _____

4 Stophold alarmeret Ja ☐ Nej ☐
Hvis "Ja":
KL: T T : M M DATO: D D / M M / Å Å

5
1. Klinisk hjertestop Ja ☐ Nej ☐
2. Klinisk hjertestop: Indikation for genoplivning Ja ☐ Nej ☐
Hvis "Nej " i "1" eller "2" udfyldes resten af skemaet IKKE

6 Hjerterytmeovervåget hjertestop Ja ☐ Nej ☐
Blev hjertestoppets indtræden observeret
Ja ☐ af sundhedspersonale ☐ af andre
Nej ☐

7 Hjertestop erkendt af
☐ Sundhedspersonale ☐ Andre

8 Basal genoplivning ***før*** Stopholdets ankomst (kun ét X)
- ☐ Hjertemassage og ventilation
- ☐ Hjertemassage
- ☐ Ventilation
- ☐ Stophold ikke alarmeret
- ☐ Ingen

9 Rytmeanalyse og defibrillering ***før*** Stopholdets ***evt.*** ankomst

Første hjerterytme
- ☐ Ikke-stødbar rytme
- ☐ Stødbar rytme
- ☐ Ingen rytmeanalyse

Første defibrillering med
- ☐ AED
- ☐ Manuel defibrillator
- ☐ Ingen defibrillering
- ☐ Andet

Første rytmeanalyse vha.
- ☐ AED
- ☐ Manuel defibrillator
- ☐ Anden EKG-monitorering
- ☐ Stophold ikke alarmeret

10 Den første observerede hjerterytme
☐ VF ☐ Pulsløs VT ☐ PEA ☐ Asystoli
☐ Ingen manuel rytmeanalyse ☐ Pulsgivende

11 Patientens status ved Stopholdets ankomst
Hjertestop Ja ☐ Nej ☐
☐ Stophold ikke alarmeret

12 Medicin givet
☐ Adrenalin ☐ Amiodaron ☐ Ingen af disse

13 Mekanisk hjertemassage (f.eks. LUCAS™/Autopulse™) Ja ☐ Nej ☐
Pt. var intuberet før hjertestop Ja ☐ Nej ☐
Intubation under hjertestop Ja ☐ Nej ☐
Kapnografi Ja ☐ Nej ☐

14 Tid for konstatering af hjertestop
KL: T T : M M DATO: D D / M M / Å Å

15 Tid for påbegyndt hjertemassage eller ventilation
☐ Ingen KL: T T : M M

16 Tid for ***første*** hjerterytmeanalyse KL: T T : M M
☐ Ingen

17 Tid for ***første*** defibrillering KL: T T : M M
☐ Ingen

18 Tid for Stopholdets ankomst KL: T T : M M
☐ Stophold ikke alarmeret

19 Genoplivning indstillet pga.
☐ Spontant kredsløb ☐ Død
☐ Kunstigt kredsløb (f.eks. ECMO, CPS, m.fl)
KL: T T : M M DATO: D D / M M / Å Å

20 Årsag til hjertestop
☐ Non-kardial
☐ Formodet kardial

21 Teammedlemmer/personale på Stopholdet
- ☐ Anæstesilæge(r): _____
- ☐ Anæstesisygeplejerske(r): _____
- ☐ Kardiolog(er): _____
- ☐ Sygeplejerske(r): _____
- ☐ Portør/serviceass.: _____
- ☐ Andre: _____

22 Eventuelle kommentarer

Version 3.4. (Gældende fra 16. maj 2022)

DANARREST – registrering af hjertestop på hospital

Vejledning til udfyldelse af registreringsskema

Registrering af hjertestop er vigtig for at dokumentere og forbedre behandlingen. Stopholdet er derfor som helhed ansvarlig for udfyldelse af skemaet. Skemaet udfyldes af lederen af Stopholdet, evt. med assistance fra et medlem af Stopholdet. Hvis Stopholdet ikke bliver tilkaldt, f.eks. på intensiv afdeling, operationsgang eller kardiologisk laboratorium, udfyldes skemaet af den for genoplivningen ansvarlige læge.

ALLE TIDSPUNKTER ANGIVES EFTER BEDSTE SKØN

1. Anfør navn og CPR-nr. på person med hjertestop.
2. Anfør navn og telefon/personsøger på den person der har udfyldt skemaet. Angiv endvidere tidspunkt (dag, måned, år) for udfyldelse af skemaet.
3. Afkryds lokalitet, hvor hjertestoppet er indtrådt. Herudover anføres navn på lokaliteten. Ved kryds i "Andet" anføres lokalitet.
4. Angiv tidspunkt (time, minut, dag, måned, år) for hvornår Stopholdet alarmeres. Det tidspunkt der anføres, er det, hvor Omstillingen eller andet personale videreformidler alarmeringen til Stopholdet. Hvis Stophold ikke tilkaldes, sættes kryds i "Nej" og tidspunkt udfyldes ikke.
5. Skemaet skal udfyldes til alle med hjertestop på hospital, og til alle hvor Stopholdet tilkaldes. Skemaet skal således også udfyldes i fald patienten er blevet genoplivet INDEN Stopholdets ankomst. I fald patienten IKKE har eller har haft hjertestop eller der ikke er indikation for genoplivning, udfyldes kun punkt 1-5. Hvis en patient er genoplivet efter hjertestop uden for hospital (= ROSC > 20 min.), men får nyt hjertestop efter ankomst til hospital, skal skemaet ligeledes udfyldes. Der skal udfyldes et nyt skema, hvis en patient får et nyt hjertestop efter ROSC > 20 min. Hvis der forud for hjertestop foreligger en beslutning om "ingen genoplivning" afkrydses "Nej" i punkt 2.
6. Afkryds hvorvidt hjertestop er observeret af sundhedspersonale, andre eller er ubevidnet. "Observeret" indebærer, at man har set eller hørt personen få hjertestop, eller identificeret ventrikelflimren på EKG-overvågning. Afkryds hvorvidt hjertestoppet var hjerterytmeovervåget. Med hjerterytmeovervåget menes monitoreret med EKG-overvågning (telemetri eller lignende).
7. Afkryds hvorvidt hjertestoppet er erkendt af sundhedspersonale eller af andre. Erkendelsen af hjertestop beror på bevidstløshed og ikke normal vejrtrækning. For den trænede og erfarne behandler indgår pulsløshed ligeledes i diagnosen.
8. Afkryds hvilken form for hjertelungeredning, der er ydet før Stopholdets ankomst. Hvis Stophold ikke tilkaldes, afkryds "Stophold ikke alarmeret", og undlad at udfylde den øvrige del af punktet.
9. Hjerterytmeanalyse før Stopholdets evt. ankomst. Hvis Stopholdet ikke er alarmeret, kan der ikke være noget før, derfor "evt." Afkryds hvorvidt det drejer som en stødbar rytme, en ikke-stødbar rytme eller der ingen hjerterytmeanalyse er udført. Anvendes en AED, oplyses om der er stødbar rytme eller ikke-stødbar rytme. Ved brug af manuel defibrillator aflæses rytmen på apparatets skærm. Afkryds med hvilket apparatur rytmeanalyse er foretaget. Afkryds om der er foretaget defibrillering før Stopholdets evt. ankomst (med AED, manuelt, eller andet, f.eks. med ICD) eller om der ingen defibrillering er foretaget. Hvis Stophold ikke tilkaldes, afkryds "Stophold ikke alarmeret", men øvrige punkter udfyldes.
10. Afkryds den først observerede hjerterytme relateret til hjertestop, uanset om denne er observeret af afdelingens personale eller af Stopholdet. Er der ikke gjort manuel rytmeanalyse ved at vurdere hjerterytmen på EKG-overvågning eller med manuel defibrillator afkrydses "Ingen manuel rytmeanalyse".
11. Afkryds hvorvidt patienten har klinisk hjertestop ved Stopholdets ankomst. Hvis Stophold ikke tilkaldes, afkryds "Stophold ikke alarmeret", og undlad at udfylde den øvrige del af punktet.
12. Afkryds hvilken medicin der er givet (sæt om nødvendigt flere krydser).
13. Afkryds om der er givet mekanisk hjertemassage (f.eks. LUCAS® eller Autopulse®), om patienten var intuberet inden hjertestoppet eller om det er sket i forbindelse med hjertestopbehandlingen, og om der er anvendt kapnografi.
14. Angiv tidspunkt for konstatering af hjertestop (time, minut, dag, måned, år).
15. Angiv tidspunkt for påbegyndt hjertemassage eller ventilation (time, minut).
16. Angiv tidspunkt for første hjerterytmeanalyse (time, minut) (hjerterytmeanalyse med AED, manuel defibrillator, EKG monitorering eller andet).
17. Angiv tidspunkt for første defibrillering (time, minut) uanset hvornår stødet er afgivet.
18. Anfør tidspunkt for Stopholdets ankomst (time, minut). Hvis Stophold ikke tilkaldes, afkryds "Stophold ikke alarmeret", og undlad at udfylde den øvrige del af punktet. Ankomst af Stopholdet defineres ved ankomsten af lederen af Stopholdet.
19. Afkryds om genoplivningen er indstillet grundet genvundet spontant kredsløb, etablering af kunstigt kredsløb (ekstrakorporal cirkulation eller tilsvarende) eller om yderligere forsøg på genoplivning vurderes udsigtsløs ("Død"). Angiv tidspunkt (time, minut, dag, måned, år).
20. Afkryds om der er en oplagt ikke-kardial årsag til hjertestoppet (f.eks. traumatisk, hypoxisk, forgiftning, drukning/hængning), og hvis det ikke er tilfældet – er årsagen formodet kardial.
21. Personnavne eller personhenførbare data indtastes ikke i DANARREST, men anføres på papirskemaet (til opfølgning, debriefing o.lign). Den enkelte region/institution tager stilling til lokal praksis.
22. Indberettes ikke. Kan anvendes på papirskemaet til lokale kommentarer til genoplivningsforløbet.

Definitioner	Aflevering af udfyldte skemaer
Stophold = hospitalets udrykningshold til behandling af hjertestop **Sundhedspersonale** = læge, sygeplejerske, social- og sundhedsassistent, fysio- og ergoterapeut, serviceassistent og portør **Stødbar rytme** = Ventrikelflimren og pulsløs ventrikulær takykardi **Ikke-stødbar rytme** = Asystoli og pulsløs elektrisk aktivitet **VF** = Ventrikelflimren **Pulsløs VT** = Pulsløs ventrikulær takykardi **PEA** = Pulsløs elektrisk aktivitet **AED** = Automatisk Ekstern Defibrillator ("Hjertestarter") **ICD** = Implanterbar Cardioverter Defibrillator	

Version 3.4. (Gældende fra 16. maj 2022)

Appendix 5: Charter for the independent data-monitoring committee (IDMC)

Charter for the Independent Data-Monitoring Committee (IDMC) for the BIHCA trial

Trial name: Bicarbonate for In-Hospital Cardiac Arrest (BIHCA) – A Randomized, Double-Blind, Placebo-Controlled Trial

Principal investigator and sponsor: Lars W. Andersen, Aarhus University

EU Clinical Trials number: 2022-501304-10-00

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 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 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 stop 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 group consisting of physicians that, collectively, have 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:

Anders Perner, M.D., Ph.D. (chairman)

Professor

Department of Intensive Care, Rigshospitalet

University of Copenhagen, Copenhagen, Denmark

Gavin Perkins, M.D.
Professor
Warwick Clinical Trials Unit
University of Warwick, Coventry, United Kingdom

Giuseppe Ristagno, M.D., Ph.D.
Associate Professor
Department of Pathophysiology and Transplantation
University of Milan, Milan, Italy

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 that 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 de-identified data for safety at two predetermined milestones (after approximately 200 and 400 enrolled patients have obtained 30-day follow-up, 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, futility, or safety. Criteria for recommending termination will be at the discretion of the IDMC.

Raw data will be provided to the IDMC chair in an Excel file 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:

Trial related:

1: id: A number that uniquely identifies the patient.

2: group: The randomization code (group A or B)

3: received_drug: Whether the patient received at least one dose of the trial drug (1 for yes, 0 for no)

4: time_drug: Time to first trial drug administration in minutes

Baseline characteristics:

5: age: Age continuous in years

6: rhythm: Initial rhythm (1 for shockable, 0 for non-shockable)

7: witness: Witnessed status (1 for yes, 0 for no)

Outcomes:

8: rosc: The primary outcome return of spontaneous circulation (ROSC) (1 for ROSC, 0 for no ROSC)

9: surv_30: Survival at 30 days (1 for survival at 30 days, 0 for death prior to 30 days)

10: mrs_30: Modified Rankin Scale score at hospital discharge (0 to 6)

Specific adverse events (see section 5.4.3 in the protocol for definitions):

11: adverse_event: Any of alkalosis, hypernatremia, hypocalcemia, hypokalemia, severely elevated lactate (1 for yes, 0 for no)

The adverse events will be combined to limit the opportunity for unblinding.

Variables #1 and #3-11 will be provided by the steering committee and item #2 will be provided by the pharmacy or the person who created the randomization list. Missing data will be coded as ".".

The IDMC chair will be responsible for creating aggregate data for each of the variables #3-11 stratified by treatment group (variable #2), which will then be reviewed 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 IHCA at participating sites), number of patients included in the trial, 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 (see section 4.2 and 4.3 in the protocol).

All data will be provided to the IDMC at least 5 days prior to their meeting. The IDMC can request additional data if relevant.

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 trial overview provided by the principal investigator. This will include an overview of recruitment and potential challenges 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 sites including patients in the trial about the recommendation of the IDMC and the steering committee's 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 is obligated to keep all patient-level data confidential.